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<th>Name: Dr G Jones</th>
<th>Organisation: Newcastle Hospitals NHS FT</th>
<th>Date Agreed: 15.06.16</th>
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Haematology NSSG members agreed the Guidelines on:
Date Agreed: Emailed to group 15.06.16 for endorsement at the next meeting.
Review Date: May 2017
CONTENTS
NEHODS- Northern England Haematological Diagnostic Service.......................................................... 5
GUIDELINES FOR CYTOGENETIC ANALYSIS IN HAEMATOLOGICAL MALIGNANCIES ..... 18
NORTH OF ENGLAND CANCER NETWORK GUIDELINES AND INDICATIONS for PETCT.... 21
GUIDELINES FOR MANAGEMENT OF ACUTE MYELOID LEUKAEMIA (AML)......................... 24
GUIDELINES FOR MANAGEMENT OF MYELOIDYSPLASTIC SYNDROMES ................................ 30
GUIDELINES FOR MANAGEMENT OF ACUTE LYMPHOBLASTIC LEUKAEMIA ....................... 39
GUIDELINES FOR THE MANAGEMENT OF CHRONIC MYELOID LEUKAEMIA .......................... 45
GUIDELINES FOR MANAGEMENT OF MYELOPROLIFERATIVE DISORDERS .......................... 48
POLYCYthaEMIA VERA (PRV) ............................................................................................................. 50
ESSENTIAL THROMBOCYthaEMIA.................................................................................................... 54
MYELOFIBROSIS (MF)..................................................................................................................... 57
NOTES RELEVANT TO MANAGEMENT OF ANY MPD ................................................................. 60
GUIDELINES FOR MANAGEMENT OF CHRONIC LYMPHO CYTIC LEUKAEMIA (CLL) AND
LYMPHOPROLIFERATIVE DISORDERS......................................................................................... 63
GUIDELINES FOR MANAGEMENT OF CHRONIC LYMPHO CYTIC LEUKAEMIA (CLL) AND
LYMPHOPROLIFERATIVE DISORDERS......................................................................................... 63
Hairy cell leukaemia .......................................................................................................................... 74
T-PROLYMPHO CYTIC LEUKAEMIA.............................................................................................. 75
Waldenström macroglobulinaemia................................................................................................. 76
GUIDELINES FOR THE MANAGEMENT OF LOW-GRADE NON-HODGKIN LYMPHOMA ...... 78
FOLLICULAR LYMPHOMA ..................................................................................................................... 79
MARGINAL ZONE B CELL LYMPHOMA ............................................................................................ 82
MANTLE CELL LYMPHOMA ............................................................................................................... 86
GUIDELINES FOR THE MANAGEMENT OF HIGH GRADE B CELL NON-HODGKIN
LYMPHOMA (NHL) ............................................................................................................................ 89
DIFFUSE LARGE B CELL LYMPHOMA (DLBCL) ........................................................................ 89
BURKITT LYMPHOMA ...................................................................................................................... 95
PRIMARY MEDIASTINAL LARGE B CELL LYMPHOMA (PMLBCL) ............................................ 96
NEHODS- Northern England Haemato- Diagnostic Service
Solid lymphoreticular specimens

Northumbria/Cumbria/Durham/Darlington/North Tees/SOT
Local report (+/- minimal IHC)
Suggestive / possibility of lymphoma
Sample sent to NEHODS

Newcastle NEHODS
Morphological and immunohistochemical assessment

- Molecular testing
- Cytogenetics
- Additional IHC / ISH (Newcastle)

Weekly consensus meeting with NEHODS pathologists (MDT cases & difficult cases)

Confected or revised local report

Integrated final report
Cytopenias 1

PB: Slides, EDTA

Morphology

? Blasts
Flow: AST; ALP if significant blast population present
Consider TCR Clonality Testing

? LGLs

? Hairy Cells
Flow: LPD

Consider PNH Panel

Report
Cytopenias 2

Bone Marrow Aspirate: Slides/EDTA/Cytogenetics Trephine

Aspirate: Morphology + Perls Stain

? Blasts
Flow: AST; ALP if significant blast population present
Cytogenetics: Karyotype +/- Appropriate FISH panels

? Lymphoid Cells
Flow: LPD
See LPD Pathway for any supplementary tests
Consider Spliceosome Mutation Analysis

? MDS
Flow: LPD
Karyotype +/- Fish for 5 and 7 abnormalities
Advise PNH Screen on PB

Trephine: H&E + Retic
IHC as appropriate

Aplastic Anaemia
Other Haemopoietic Malignancy
Supplementary Tests as per Appropriate Pathway
Non-Haemopoietic Malignancy
Refer to Histopathology
Further report in Pathosys?

Report
MPN 2

Bone Marrow
Aspirate: Slides/EDTA/Cytogenetics

? ET/Myelofibrosis
- BMA Morphology + Perls Stain
- BMT H&E + Retic +/- IHC
- Cytogenetics: FISH for BCR-ABL +/- Karyotype

Eosinophilia
- BMA Morphology
- BMT H&E + Retic +/- IHC
- Flow: LFD (e.g., CD3/CD4+)
- FISH for BCR-ABL, PDGFRα, PDGFRβ, +/- Karyotype

? MPN/MDS
- BMA Morphology + Perls Stain
- BMT H&E + Retic +/- IHC
- BMA flow: AST/ALP
- FISH for BCR-ABL +/- Karyotype
- Consider CSF3R

? Mastocytosis
- BMA Morphology
- BMT H&E + Retic +/- IHC
- Molecular: CKIT D816V

Report
Lymphoproliferative and Lymphoma 2

BMT

IHC

Clear Diagnosis

Diagnostic uncertainty

Molecular

Molecular clonality studies

FISH

Diagnosis

Follow Up

PB/BMA/BMT

Flow

IHC (If frank relapse not clearly demonstrated)
SECTION 2

GUIDELINES FOR CYTOGENETIC ANALYSIS IN
HAEMATOLOGICAL MALIGNANCIES

Genetic analysis of haematological malignancies

The following is the single Cytogenetics / Molecular Genetics Laboratory for the Haematology Site-Specific Group of the North of England Cancer Network:

Northern Genetics Service,
Cytogenetics Laboratory,
Institute of Genetic Medicine,
Central Parkway,
Newcastle upon Tyne,
NE1 3BZ.

telephone: 0191 241 8703
email: cancer.cytogenetics@nuth.nhs.uk

Key Personnel:

Mr Gavin Cuthbert, FRCPath, Head of Cancer Cytogenetics
Dr Nick Bown, FRCPath, Head of Cytogenetics Laboratory.

Core service:

Chromosome analysis, FISH, MLPA, sequencing and RT-PCR to identify translocations / gene fusions and chromosome copy number abnormalities in haematological malignancies, including

AML: PML-RARA [t(15;17)], PLZF-RARA [t(11;17)], RUNX1-RUNX1T1 [t(8;21)],
       CBFB-MYH11 [inv(16)], MECOM [3q27], MLL [11q23],
       FLT3-ITD and NPM1 mutation analysis.

ALL: ETV6-RUNX1 [t(12;21)], PAX5-ETV6 [t(9;12)], TCF3-PBX1 [t(1;19)],
       MLL-AF4 [t(4;11)], CALM-AF10 [t(10;11)], SIL-TAL1 [del(1p)], TCR A/B/G/D

CML: BCR-ABL1 [t(9;22)]

MPN: FIP1L1-PDGFR [del(4q)], PDGFRB, FGFR1, CSF3R mutation analysis

Lymphoma: IGH-CCND1 [t(11;14)], IGH-MYC [t(8;14)], IGH-BCL2 [t(14;18)],
           IGK [2p11], IGL [22q11], BCL6 [3q27], ALK [2p23], MALT1 [18q21],
           BCL10 [1p22], MYD88 mutation analysis

Myeloma: FGFR3-IGH [t(4;14)], IGH-MAF [t(14;16)], 1q gain, TP53 deletion

MDS: karyotype complexity, 5q and 7q loss

CLL: deletions of TP53, 11q,13q and trisomy12.

Notes
Bone marrow and Blood samples for Genetic study should be sent to the NEHODS specimen reception using a NEHODS Diagnostic Kit. These are distributed from NEHODS Centralised Specimen Reception.

**NEHODS Specimen Reception**
Flow Laboratory, Blood Sciences
Level 3 Leazes Wing
Royal Victoria Infirmary
Richardson Road
Newcastle upon Tyne
NE1 4LP
NEHODS Office tel: 0191 282 5028
email: tnu-tr.nehods@nhs.net

To maximise the chance of a successful result, samples should ideally be transported to Cytogenetics on the same day that they are taken.

Advance telephone or email warning of samples – particularly from high priority cases – is extremely helpful. The laboratory is open between 08.30 and 17.00. Special arrangements can be made for receipt and analysis of urgent samples outside these hours.

To manage workload and optimise reporting times, we may contact referring Haematologists by email to confirm the need for analysis and assess priority for individual samples.

Available on request – further details of test repertoire.

Please contact us to discuss requirements for new test development.

The laboratory is CPA accredited – no. 2212

****************************************

**Monitoring of allo-BMT by DNA microsatellite analysis** (Molecular Genetics Laboratory, Northern Genetics Service)

Contact Tony Jackson   tel. 0191 241 8775
Dr David Bourn, FRCPath.

email: molecular.genetics@nuth.nhs.uk

****************************************

**Molecular Diagnostics - Newgene**

The following specific assays are provided by Newgene:
BCR-ABL quantitation
CML mutation screening
JAK2,MPL and CALR mutation screening
BRAF Mutation testing

Further details can be found on the website: www.newgene.org.uk
Contact:

NewGene Ltd., Bioscience Building
International Centre for Life
Newcastle upon Tyne
NE1 4EP

Tel: 0191 242 1923

Key personnel: Dr Ann Curtis, Scientific Director

email: info@newgene.org.uk
website: www.newgene.org.uk

JAK2/MPL/CALRSamples for Newgene should be sent to:-

Department of Haematology
Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne
NE1 4LP

CML follow-up samples (transcript monitoring and kinase mutation screening) should be sent to:-

NewGene
Institute of Genetic Medicine,
Central Parkway,
Newcastle upon Tyne,
NE1 3BZ.

NB. samples for Diagnostic BCR/ABL1 testing and all other Haem-Onc Genetics studies – send to NEHODS Specimen Reception
SECTION 3

NORTH OF ENGLAND CANCER NETWORK GUIDELINES AND INDICATIONS for PETCT

NECN Policy Statement

The North East Strategic Health Authority (SHA) and the associated Network PCTs have committed to the provision of a local PET CT scanning service for the Network population from October 2007.

It should be noted that in this instance the Network population does not include North Cumbria as they have elected to provide PET CT from a facility based in Preston hence the guidelines in this policy will not include those patients from North Cumbria.

Author:

The principal authors of these guidelines are Dr John Wilsdon and Dr George Petrides with contribution and support from the Network Radiology Clinicians and Managers.

Referral for PET CT has to be within the guidelines listed below. If requests are not within the guidelines they must be discussed with the ARSAC holder or delegated authoriser.

The PET CT request form can be obtained from your local hospital Radiology dept. For Newcastle upon Tyne referrals, requests must be sent to Kerry Morton the PET CT secretary (Kerry.Morton4@nuth.nhs.uk). For all other hospitals, requests should be sent to the local ARSAC holder or delegate (see list at end), for legal authorisation. Radiology will then refer on to Alliance.

The Agreement with Alliance is that a patient will be offered an appointment within 5 working days following receipt of a correctly filled in request form. This may be at James Cook or Freeman Hospitals. The report and images should be back on the referring hospitals RIS/PACS 48 hours following the day of the scan.

Delays may be due to patient choice or the submission of inadequately completed referral forms (either the clinical or demographic aspects).

Date: 12/12/12
NECN PET CT Guidelines

Below are the current guidelines. The test is funded only for cancer patients who fall into the categories below. These are agreed as a basis for referral by The North of England Cancer Network and the ARSAC holder.

PET CT is to a certain extent non-specific and will often turn up other abnormalities not necessarily related to the malignant process which may need investigating.

Both Radiotherapy and Chemotherapy can influence the PET CT result. Therefore the treatment dates of these are important to the reporter. Generally we would like to wait at least 3 months between the end of radiotherapy and scanning and at least 3 weeks post chemotherapy. Scans after a couple of cycles of chemotherapy are increasingly used for clinical decision making (see Hodgkin’s disease below).

Haematological Indications.

This is an evolving area but a review of current guidelines from elsewhere would suggest:

Lymphoma

a) Staging of Hodgkin’s disease and aggressive non-Hodgkin lymphoma (NHL) and as a baseline for comparison with treatment response scan. Where there is a high index of suspicion that a biopsy will reveal either of the diagnoses above, it would be reasonable to request a PET CT scan before the definitive histological diagnosis is available in order to minimise delays in the patient pathway.

b) PET CT can be used to assess treatment response if the initial scan is positive. The scan should be performed after 2 cycles. Risk adapted studies are in progress and it is recommended that publication of these studies is awaited before PET CT is ROUTINELY used to guide therapy. Participation in relevant studies is encouraged.

c) End of treatment response assessment of Hodgkin’s Disease and aggressive NHL.

d) Assessment of response to second line treatment and subsequent treatments for FDG avid lymphoma.

e) Evaluation of suspected relapse for FDG avid lymphomas in symptomatic patients. PET CT can detect recurrent disease before it is clinically apparent and this can be useful to direct early salvage therapy rather than waiting for overt relapse.

f) Staging of presumed early stage follicular lymphoma in patients considered for radiotherapy treatment.

g) Staging of suspected post transplant lymphoproliferative disorder (PTLD).

h) Prior to bone marrow transplant to assess volume of disease and suitability for transplant.

i) To determine extent and identify a suitable biopsy site in patients with low grade lymphomas in whom there is suspected high grade transformation.
Myeloma

j) Assessment of patients with apparently solitary plasmacytoma or patients with ambiguous lytic lesions on skeletal survey.

k) Suspected relapse in patients with non secretory myeloma or predominantly extra-medullary disease.

References

- The Intercollegiate Standing Committee on Nuclear Medicine 2003
- Yorkshire Cancer Network PET CT guidelines September 2007
- Evidence-based indications for the use of PET-CT in the United Kingdom 2012. Royal College of Physicians & Royal college of Radiologists.

Further Information

George Petrides – CLINICAL LEAD FOR PET-CT IN THE NORTH EAST

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<thead>
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GUIDELINES FOR MANAGEMENT OF ACUTE MYELOID LEUKAEMIA (AML)

Patients with AML should be managed in accordance with BCSH guidelines (2006). Where eligible, patients should be offered the chance of randomisation into an NCRI-badged study where available – currently AML18, AML 19 and AML LI-1 study.

Diagnostic Criteria

- WHO classification system 2008 is used to confirm and classify cases of AML
- AML is diagnosed when the blast content of the marrow, defined morphologically or immunophenotypically, is ≥20% of nucleated cells.
- In the presence of a balanced translocation; t(8;21) or inv(16) the diagnosis can be made when the blast count is 5-19%

Essential Investigations

Blood

- FBC
- Clotting screen including fibrinogen and D-dimers
- Urea and electrolytes
- Liver function tests
- Urate
- CMV serology (in those patients who may be transplant candidates)
- HLA class 1 and 2 tissue typing for potential allogeneic stem cell transplant candidates

Marrow

- Marrow aspirate and trephine where possible for morphological assessment
- EDTA sample for immunophenotyping
- Cytogenetic and molecular analysis

Principles of Management

Intensive vs Non-intensive Therapy

Intensive chemotherapy is central to management if patients are to be offered potentially curative therapy. In general such treatment is offered to patients up to the age of 70 years but clearly not every patient is fit enough to tolerate intensive therapy and some patients older than 70 years may be considered suitable candidates. There are no validated criteria upon which the fitness of patients can be objectively assessed in AML. This decision is therefore at the discretion of the treating physician who will discuss this issue with individual patients and with the MDT.

Non-intensive therapy is given with palliative intent.
Risk Stratification

A number of factors are known to affect prognosis of patients with AML including:

- age
- peripheral white cell count
- marrow cytogenetics
- response to induction chemotherapy
- molecular studies

To date cytogenetic abnormalities have been most widely used to stratify risk in AML.

**Good risk:** Any patient with favourable genetic abnormalities – t(8;21), inv(16), t(16;16), t(15;17) irrespective of other genetic abnormalities or marrow status after Course 1.

**Standard:** Any patient not in either good or poor risk groups.

**Poor risk:** Any patient with more than 15% blasts in the bone marrow after Course 1 and without favourable genetic abnormalities, or with adverse genetic abnormalities: -5, -7, del(5q), abnormal (3q) or complex (5 or more abnormalities).

**Risk Stratification in Normal Karyotype AML**

Most patients diagnosed with AML have a normal karyotype and thus are included in the standard cytogenetic risk group. Several molecular markers are now available which attempt to improve prognostication for this group of patients. The 2 most promising molecular markers are FLT3 mutation–internal tandem duplication (ITD) and NPM1 mutation.

The following subgroups can be demonstrated:

- **FLT3-ITD +, NPM1 -** Poor Risk
- **FLT3-ITD +, NPM1+** Intermediate Risk
- **FLT3-ITD -, NPM1 -** Intermediate Risk
- **FLT3-ITD -, NPM1 +** Good Risk

**CKIT mutation**

In patients with t(8;21) the presence of a cKIT mutation confers a poorer prognosis, higher relapse risk and lower overall survival, than would be expected in this normally good risk group.

**The Role of Haematopoietic Stem Cell Transplantation (HSCT)**

As for any haematological malignancy, the potential benefits of transplantation must be balanced against the morbidity and mortality associated with the procedure.
The following patients should be considered for allografts in the absence of significant co-morbidities:

- those in 2\textsuperscript{nd} or subsequent CR
- those in CR1 with poor risk cytogenetics
- those in CR1 with FLT3-ITD mutation and no mutation in NPM1.
- those aged >40 and considered to be in a standard risk group and for whom there is a matched sibling donor

When patients are transplanted in CR1, myeloablative transplants should be offered as course 3 of therapy and non-myeloablative transplants as course 4.

**Management of Patients Aged <60 Years (non-APL)**

All eligible patients up to age 60 and suitable for intensive therapy, with de novo or secondary AML should be considered for entry to NCRI AML 19 study.

Non-trial patients fit for intensive chemotherapy should receive standard DA induction chemotherapy x 2 followed by consolidation with high-dose cytarabine.

Patients not considered suitable for intensive chemotherapy should be offered entry into AML 18 or NCRI AML LI-1 trial

Non-trial patients, not considered suitable for intensive chemotherapy, should be treated with a palliative regimen (see later).

**Management of Patients Aged ≥60 Years (non-APL)**

Eligible patients aged >60 and suitably fit for intensive chemotherapy can be offered entry into AML 18 clinical trial. For patients not suitable for intensive chemotherapy should be considered for entry to NCRI AML LI-1 trial (contact ThomasIF@cardiff.ac.uk for details).

Non-trial patients fit for intensive chemotherapy should receive standard DA induction chemotherapy (DA 3+10 then DA 3+8) followed by consolidation with either DA (2+5) or high-dose cytarabine (1.5g/m2 outside of a trial) if the patient can tolerate a more intensive approach.

Non-trial patients not considered fit for intensive chemotherapy should be treated with a palliative regimen (see later).

**Management of Fitter Patients with Refractory or Relapsed Disease**

- Refractory disease or relapse should be treated with FLAG-Ida.
- All suitable patients should be discussed with a transplant specialist to consider HSCT.
- Clofarabine is approved from the Cancer Drug Fund as a bridge to transplant in those patients who have failed FLAG or FLAG-Ida. Clofarabine in combination with cytarabine, is the preferred treatment option
Potential Palliative Options as First Line Treatment or For Refractory/Relapsed Disease

**Low Dose Ara-C**
Ara-C 20 mg twice daily, SC x 10 days

**Hydroxycarbamide**
Hydroxycarbamide 1g daily PO, titrated to cell count response

**Etoposide**
Etoposide 50mg alternate days PO initially, titrated to cell count response

**Idarubicin/Etoposide**
This is a more myelosuppressive regimen than those outlined above but has been shown to induce temporary remissions
Idarubicin 20mg/m² days 1-3 PO
Etoposide 80mg/m² days 1-3 PO

In fitter patients the above regimen may be used to consolidate remission after an idarubicin/cytarabine induction (Riverside schedule).

**Riverside Schedule**
Idarubicin 12mg/m² IV days 1-3
Cytarabine 100mg/m² over 12 hours IV, once daily days 1-7

**Azacitidine**
This hypomethylating agent is now licensed for the treatment of adult patients with AML with 20-30 % blasts and multi-lineage dysplasia, who are not eligible for haematopoietic stem cell transplantation (see Guidelines on Myeloidysplastic Syndromes).

The recommended starting dose for the first treatment cycle, for all patients regardless of baseline haematology laboratory values, is 75 mg/m² of body surface area, injected subcutaneously, daily for 7 days. Each 7-day treatment is followed by a rest period of 21 days (28-day treatment cycle). It is recommended that patients be treated for a minimum of 6 cycles. Treatment should be continued as long as the patient continues to benefit or until disease progression.

The use of azacitidine in MDS/AML has been approved by NICE.

**Appendix of Regimens**

**Daunorubicin+Ara-C (DA: 2+5)**
Daunorubicin 50 mg/m² IV days 1, 3 (2 doses)
Ara-C 100 mg/m² IV 12-hourly on days 1-5 inclusive (10 doses)

**Daunorubicin+Ara-C (DA: 3+10)**
Daunorubicin 50 mg/m² IV days 1, 3, 5 (3 doses)
Ara-C 100 mg/m² IV 12-hourly on days 1-10 inclusive (20 doses)

**Daunorubicin+Ara-C (DA: 3+8)**
Daunorubicin 50 mg/ m² IV days 1, 3, 5 (3 doses)
Ara-C 100 mg/m² IV 12-hourly on days 1-8 inclusive (16 doses)

**Daunorubicin+Ara-C infusion (DA: 3+7)**
Daunorubicin 50 mg/m² IV days 1, 3, 5 (3 doses)
Ara-C 100 mg/m² IV over 24 h daily for 7 days
[This may be used for non-trial patients and approved by BCSH. It may be given as day case chemotherapy if the patient is well.]

**High-dose cytarabine**
Ara-C 3 g/m² IV over 4 h 12-hourly days 1,3,5

**Cytarabine 1.5g/ m²**
Ara-C 1.5 g/m² IV over 4 h 12-hourly days 1,3,5

**Fludarabine + Ara-C (FLA)**
Fludarabine 30 mg/m² IV days 1-5 inclusive (5 doses)
Ara-C 2 g/m² IV over 4 h days 1-5 inclusive (5 doses) commencing 4 h post-fludarabine

**Fludarabine, Ara-C and Idarubicin (FLAG-Ida)**
Fludarabine 30mg/m² IV days 2-6
Cytarabine 2g/m² IV days 2-6
Idarubicin 8mg/m² IV days 4, 5, 6
GCSF sc days 1-7

**Management of Patients with Acute Promyelocytic Leukaemia (APL)**

Eligible patients with APL should be offered entry into the NCRIAML 19 study.

APL patients in complete remission (CR) should have molecular monitoring every 3 months for at least 2 years to look for signs of early relapse (contact Professor D Grimwade, Guys Hospital, London).

Non-trial patients should be offered an ATRA and idarubicin-based regimen (AIDA).

Where patients are not considered fit enough for such treatment they should be offered a palliative regimen with the addition of ATRA.

**AIDA (ATRA + idarubicin based treatment for APML)**

**Induction**

- All-transretinoic acid (ATRA), 45 mg/m²/day orally in two equally divided doses and rounded to the nearest 10 mg increment, starting on day 1. ATRA treatment will be continued until haematologic CR and for a maximum of 60 days. If haematological CR is not achieved by day 60, consider the “High Risk” APL protocols of AML 17.
- Idarubicin, 12 mg/m² on days 2, 4, 6 and 8 by short (20 minute) intravenous infusion. Idarubicin doses should be brought forward by one day in patients presenting with WBC>10x10⁹/L, with first dose given within a few hours of starting ATRA.

**First consolidation cycle**

- Idarubicin, 5 mg/m²/d by short (20 minute) intravenous infusion on days 1, 2, 3, 4.
- ATRA, 45 mg/m²/day, will be administered orally in two equally divided doses from day 1 to day 15.
Second consolidation cycle

- Mitoxantrone, 10 mg/m²/d as 30 minute intravenous infusion on days 1, 2, 3, 4, and 5.
- ATRA, 45 mg/m²/d will be administered orally in two equally divided doses from day 1 to day 15.

Third consolidation cycle

- Idarubicin, 12 mg/m²/d as short (20 minute) intravenous infusion only on day 1.
- ATRA, 45 mg/m²/d will be administered orally in two equally divided doses from day 1 to day 15.

Relapsed APL

For relapsed APL, ATRA should not be used as single agent therapy due to significant possibility of acquired secondary resistance. Arsenic trioxide (ATO) should only be used in patients with confirmed PML-RARA positive APL. Relapse therapy in APL aims to induce molecular remission. At relapse, patients with APL are considered to be at high risk for CNS disease and a lumbar puncture should be performed.
SECTION 5

GUIDELINES FOR MANAGEMENT OF MYELODYSPLASTIC SYNDROMES

Key points
- The diagnosis of Myelodysplastic syndromes (MDS) must be made according to the WHO classification (2008).
- A bone marrow aspirate and trephine including an iron stain should be performed. An EDTA and unstained slides should be sent to NEHODS for flow cytometric analysis and cytogenetic analysis. Bone marrow trephine immunohistochemistry can be considered.
- All MDS patients must have risk stratification according to the International Prognostic Scoring System (IPSS) and the revised IPSS (IPSS-R).
- All MDS patients must be discussed at the haematology multidisciplinary team meeting (MDT). Transplant eligible patients should be discussed with the bone marrow transplant team.
- It is important to note that for asymptomatic patients, a period of observation to determine the rate of progression can be helpful before formulating a management plan.
- Patients should be managed in line with the BCSH Guidelines on the management of Myelodysplastic Syndromes (2013).

Diagnosis
See NEHODS cytopenias and myelodysplasia pathways

Classification

<table>
<thead>
<tr>
<th>WHO Classification of the Myelodysplastic Syndromes</th>
<th>Blood</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anaemia with unilineage dysplasia (RCUD)</td>
<td>Uni or bicytopenia</td>
<td>Unilineage dysplasia: 10% of affected cells are dysplastic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;5% blasts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;15% erythroid precursors are ring sideroblasts</td>
</tr>
<tr>
<td>Refractory anaemia with ring sideroblasts (RARS)</td>
<td>Anaemia</td>
<td>Erythroid dysplasia only &lt;5% blasts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥15% erythroid precursors are ring sideroblasts</td>
</tr>
<tr>
<td>Refractory cytopenia with multi lineage dysplasia (RCMD) +/- ring sideroblasts (RCMD-RS)</td>
<td>Bi or pancytopenia</td>
<td>Dysplasia in ≥10% cells in two or more lineages</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;5% blasts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No auer rods</td>
</tr>
<tr>
<td></td>
<td></td>
<td>±15% ring sideroblasts</td>
</tr>
<tr>
<td>Refractory anaemia with excess blasts-1 (RAEB-)</td>
<td>Cytopenia(s)</td>
<td>Unilineage or multilineage dysplasia</td>
</tr>
<tr>
<td></td>
<td>&lt;5% blasts</td>
<td></td>
</tr>
</tbody>
</table>
1) No auer rods
<1 x 10⁹/l monocytes
5-9% blasts
No auer rods

Refractory anaemia with excess blasts-2 (RAEB-2)
Cytopenia(s)
5-19% blasts ±Auer rods
<1 x 10⁹/l monocytes
Unilineage or multilineage dysplasia
10-19% blasts ±Auer rods

Myelodysplastic syndrome – unclassified (MDS-U)
Cytopenias
Unequivocal dysplasia
<10% one/more lineages but typical cytogenetic abnormality
RCUD plus pancytopenia

MDS with isolated del(5q)
Anaemia
Usually normal or raised platelet count
No or rare blasts
Megakaryocytes with hypolobated nuclei
<5% blasts
No auer rods

Risk stratification
• The International Prognostic Scoring System (IPSS) (1997) is an important tool designed to assess the outcome of patients with untreated adult MDS
• The revised IPPS (IPSS-R) (2012) further refined the parameters of the IPSS (cytogenetic groups, marrow blast % and cytopenias)
• The IPSS-R should be the preferred scoring system for determining prognosis

IPSS-R
• Is not a dynamic scoring system and can only provide prognosis at diagnosis
• Recognises 5 cytogenetic groups with differing prognostic significance
• Demands finer distinction between % blasts at the lower end of the scale. The distinction between 2% and 5% is now regarded as having prognostic significance
• Each cytopenia is individually weighted in the algorithm
• Five prognostic groups are now recognised and are deemed as carrying: very low, low, intermediate, high and very high risk. The low and very low risk categories map to low risk and INT-1 risk in the IPSS. Similarly the high and very high risk patients map most closely to the INT-2 and high risk IPSS groups. The clinical significance of the newly described intermediate risk group remains to be determined in terms of treatment recommendations.

IPSS prognostic score values

<table>
<thead>
<tr>
<th>Score value</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM blast %</td>
<td>&lt;5</td>
<td>5-10</td>
<td>-</td>
<td>11-20</td>
<td>21-30</td>
</tr>
<tr>
<td>Karyotype*</td>
<td>good</td>
<td>intermediate</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopenias**</td>
<td>0-1</td>
<td>2-3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Good = normal, -Y, del(5q), del(20q), Poor = complex (>3 abnormalities) or Ch 7 abnormalities, Intermediate = all other

** Hb <100, Neutrophils <1.8x10⁹/L and platelets <100x10⁹/L
Risk stratification of MDS using IPSS

<table>
<thead>
<tr>
<th>IPSS score</th>
<th>Risk group</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>Low</td>
</tr>
<tr>
<td>0.5-1.0</td>
<td>Intermediate 1 (INT-1)</td>
</tr>
<tr>
<td>1.5-2.0</td>
<td>Intermediate 2 (INT-2)</td>
</tr>
<tr>
<td>≥2.5</td>
<td>High</td>
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</tbody>
</table>

IPSS-R prognostic score values

<table>
<thead>
<tr>
<th>Score value</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>Very good</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>Very poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM blast %</td>
<td>≤2</td>
<td>&gt;2-&lt;5</td>
<td>5-10</td>
<td>&gt;10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb concentration</td>
<td>≥100</td>
<td>80-&lt;100</td>
<td>&lt;80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td>≥100</td>
<td>50-&lt;100</td>
<td>&lt;50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>≥0.8</td>
<td>&lt;0.8</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

IPSS-R Cytogenetic prognostic subgroups

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Good</td>
<td>-Y, del (11q)</td>
</tr>
<tr>
<td>Good</td>
<td>Normal, del(5q), del(12p), del(20q), double including del 5q</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Del(7q), +8, +19, i(17q), any other signele or double independent clones</td>
</tr>
<tr>
<td>Poor</td>
<td>-7, inv(3)/t(3q), double incl -7/del(7q), complex: 3 abnormalities</td>
</tr>
<tr>
<td>Very Poor</td>
<td>Complex &gt;3 abnormalities</td>
</tr>
</tbody>
</table>

IPSS-R prognostic risk scores and outcomes

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Score</th>
<th>Survival (median – years)</th>
<th>25% AML evolution (median – years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>≤1.5</td>
<td>8.8</td>
<td>NR</td>
</tr>
<tr>
<td>Low</td>
<td>&gt;1.5-3</td>
<td>5.3</td>
<td>10.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt;3-4.5</td>
<td>3.0</td>
<td>3.2</td>
</tr>
<tr>
<td>High</td>
<td>&gt;4.5-6</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Very High</td>
<td>&gt;6</td>
<td>0.8</td>
<td>0.73</td>
</tr>
</tbody>
</table>
Management

General points
- Supportive care is the mainstay of treatment for patients with MDS and symptomatic cytopenias
- Red blood cell (RBC) transfusions should be considered for symptomatic anaemia
- Platelet transfusions are not routinely indicated for stable, non-bleeding patients with MDS

Low risk MDS
- Includes patients defined by IPSS as Low or INT-1 and by IPSS-R as Very Low and Low
- These patients have a more favourable prognosis and often present with anaemia
- Supportive care with RBC transfusion remains important but is associated with risks of alloimmunisation and iron overload
- Consideration should be given to treatments that reduce transfusion requirements
- Iron chelation is not routinely recommended for patients with transfusional iron overload but should be considered in those with a very good prognosis (RA, RARS and del(5q)). Potential triggers are ferritin >1000ng/l and transfusion of >20 units of red cells.

Erythroid Stimulating Agents (ESAs)
- Consider a trial of erythropoietin for patients with low risk MDS who score ≤1 in the predictive algorithm below

| Model for predicting response to ESA (Predicted response: Score 0 = 74%, Score 1 = 23%, Score 2 = 7%) |
|-----------------------------------------------|-----------------------------------------------|
| Transfusion requirement | Point | S-EPO | Point |
| <2 units RBC/month | 0 | <500 u/l | 0 |
| ≥2 units RBC/month | 1 | ≥500 u/l | 1 |

- Non-sideroblastic phenotypes: Consider erythropoietin or darbopoietin alone. Erythropoietin dose is 30,000 units per week for 8 weeks. If no response double to 60,000 units once per week or 30,000 units twice per week for 8 weeks. Darbopoietin dose is either 150mcg every 7 days or 300mcg every 14 days. The dose is doubled in non-responders for a further 8 weeks at a dose of 300mcg per week.
- Sideroblastic phenotypes: The guidance with respect to erythropoietin and darbopoietin is the same but treatment should be combined with GCSF from the outset at a starting dose of 300mcg in 2/3 divided doses per week rising to 300mcg three times weekly in non-responders. The aim is to double the white cell count if it starts below 1.5x10^9/l or to keep the count between 6-10 x 10^9/l in other patients.
- Maximum trial period should be 16 weeks
- Patients who respond should continue on long term therapy until response is lost
- Care should be taken if the HCT rises rapidly. The target Hb is <12g/dl in view of the 2% incidence of thrombosis associated with ESAs.
Anti thymocyte globulin (ATG) and Ciclosporin
- Consider antithymocyte globulin (ATG) and ciclosporin therapy for patients who are considered able to tolerate the treatment (typically age <60) in those with low-risk MDS (IPSS ≤ INT-1) with normal karyotype or trisomy 8.
- Ciclosporin alone may have a role for patients with a hypocellular marrow or autoimmune phenomena.
- ATG should only be administered at level 2b/3 centres.
- Corticosteroids as an immunosuppressive therapy to improve cytopenias are not recommended.

Ciclosporin alone may have a role for patients with a hypocellular marrow or autoimmune phenomena.

Lenalidomide (Revlimid)
- Is licensed for use for the treatment of anaemia in IPSS ≤ INT-1 MDS with isolated del(5q) (NICE approved).
- Can be used for the treatment of transfusion dependent anaemia in IPSS ≤ INT-1 MDS with isolated del(5q) plus one other cytogenetic abnormality (CDF approved).
- Lenalidomide dose is 10mg daily for 21 days, repeated every 28 days.

High risk MDS – Transplant eligible

Intensive chemotherapy
- Patients with >10% BM blasts and a hypercellular bone marrow should be considered for intensive AML induction chemotherapy (see Guidelines for Management of Acute Myeloid Leukaemia). NCRN AML 19 trial is available. The use of azacitidine in this setting is experimental and should only be given in the context of a clinical trial.
- Patients with <10% BM blasts are at risk of chemotherapy complications such as prolonged hypoplasia and upfront HSCT should be considered.

The Role of Allograft
- In patients considered fit for transplant, HSCT can offer the only chance of long term disease free survival and early discussion with the transplant unit should be undertaken. Allogeneic SCT from a voluntary unrelated donor should be considered if there is no HLA matched sibling. Generally there is no place for SCT in those who do not achieve complete remission with induction chemotherapy.

Other indications for SCT
- Selected patients with low risk MDS should be considered for allogeneic SCT on individual grounds. Examples include young patients with platelet refractoriness, or heavy red cell transfusion requirement in the absence of an alternative cause for anaemia. Chemotherapy prior to SCT will be necessary in this group only in the rare patient with blasts 5-10% or an adverse karyotype.
- Autologous SCT should be offered only in the context of clinical trials.

High risk MDS – Transplant ineligible

Intensive chemotherapy
- Patients aged >60 years with >10% blasts in marrow, considered fit to tolerate intensive chemotherapy and lacking a high risk karyotype, should be offered therapy intensive AML-style treatment and consideration of allograft. NCRN AML 18 trial is available.

Non-intensive chemotherapy
- Azacitidine is recommended as a treatment option for adults who are not eligible for HSCT and have:
1. **INT-2 and high-risk MDS according to the IPSS**
2. Chronic myelomonocytic leukaemia (CMML) with 10–29% marrow blasts without myeloproliferative disorder
3. Acute myeloid leukaemia with 20–30% blasts and multilineage dysplasia, according to the World Health Organization classification
   (And if the manufacturer provides azacitidine with the discount agreed as part of the patient access scheme)

The recommended dose of azacitidine is 75 mg/m² daily subcutaneously for 7 days. An acceptable alternative regimen is azacitidine daily Monday to Friday, a break over a weekend then 2 further doses Monday and Tuesday (termed 5-2-2). Treatment is given as a 28 day cycle. It is recommended that patients be treated for a minimum of 6 cycles. Treatment should be continued as long as the patient continues to benefit or until disease progression.

   - **Oral low dose melphalan** should be considered for a select group of patients with >5% blasts in a hypocellular marrow with a normal karyotype

**The Role of Iron Chelation in MDS**

- The benefit of iron chelation in MDS is unproven
- Despite this, it is widely felt that iron chelation should be considered for selected low MDS patients and those in whom HSCT is being planned

**Patient Selection**

Patients should fulfil criteria in point A with consideration of point B.

A. Patients diagnosed with MDS with a very good prognosis, specifically those with RA, RARS and isolated del(5q)

B. Iron chelation may be withheld at the discretion of the Haematologist in patients with significant organ damage (not due to iron overload) likely to reduce the above survival figures.

**When to start**

- Trigger for consideration of treatment is a serum ferritin consistently above 1000 ng/mL or >20 units of red cells transfused. When on chelation, serum ferritin should be checked every 3 months to allow assessment of trends.
- In practice, iron load is monitored by changes in serum ferritin concentrations, but reliance on serum ferritin alone may lead to inaccurate assessment of body iron burden in individual patients.
- Liver biopsy with samples sent for dry iron weight (liver iron content - LIC) remains the “gold standard” in patients in whom serum ferritin is unreliable. Iron chelation is recommended if there is evidence of moderate iron overload. Negotiation with local hepatologist/histopathologist will be required in advance since this test is not routinely available in most labs.
- MRI techniques such as T2* are non-invasive and reliable for assessment of both hepatic and cardiac iron load. Discuss with local imaging experts as the test may require referral to a tertiary centre. Iron chelation is recommended if there is evidence of at least moderate iron overload. Myocardial iron overload has a much longer latency than hepatic iron overload. Currently, T2* imaging is available at Freeman Hospital.
  - LIC <2 mg Fe/g dry weight (or equivalent T2*) no iron overload
  - LIC 2-5 mg Fe/g dry weight (or equivalent T2*) mild iron overload
  - LIC 5-10 mg Fe/g dry weight (or equivalent T2*) moderate iron overload
  - LIC >10 mg Fe/g dry weight (or equivalent T2*) severe iron overload
Recommendation
- An annual T2* MR scan is indicated when serum ferritin is >1000 ng/mL.
- If there is mild iron overload, T2* MR scan should be repeated at 6 months.
- Initiate chelation when there is moderate liver iron overload, i.e. LIC>5 (or equivalent T2*).
- Initiate chelation if the heart shows any evidence of iron overload.

Treatment

**Deferasirox**
- Contraindicated if estimated creatinine clearance is <60 mL/min.
- Dose: Recommended initial daily dose is 20 mg/kg. Consider 30 mg/kg for those who receive >4 units of red cells/month.
- Monitoring:
  - Renal: use of this agent is associated with a rise in serum creatinine in about 36% of patients. It is recommended that serum creatinine should be measured twice before starting therapy then weekly for the first month or after a dose increase and monthly thereafter. Dose should be reduced by 10mg/kg if creatinine levels rise by >33% of pre-treatment levels. Testing for proteinuria should be performed monthly.
  - Hepatic: Increases in transaminases have been observed in trials. LFTs should be performed at baseline and monthly. Deferasirox is not recommended in patients with severe hepatic impairment.
  - Auditory and ophthalmic testing is recommended before the start of treatment and annually thereafter.
- Interruption of deferasirox should be considered if serum ferritin levels fall consistently below 500 ng/mL.

**Desferrioxamine (DFO)**
- DFO may be used if there is intolerance and/or refractoriness to deferasirox.
- Administration: DFO may be administered in a variety of ways:
  - Via a SC “Graseby” infusion pump over 8-12 hours (preferably overnight).
  - Via a Balloon infuser (Baxter or similar) SC over 12-24 hours. Balloon infusers delivering DFO over several days are also available.
  - IV ambulatory DFO administered via balloon infusers through implantable venous access ports or Hickman lines are associated with rapid reduction of iron burden and improvement in cardiac function in severe iron overload.
- There is no role for infusing DFO concomitantly with a blood transfusion.
- Iron excretion induced by DFO is enhanced by vitamin C given at a maximal dose of 200mg daily and should be started 4 weeks after initiation of DFO. It should be given separately from food and is contraindicated in patients with cardiac failure.
- Dose: Start at the lowest effective dose, usually between 20-50mg/kg daily SC infusion. Usual starting dose is 2g/day 3-5 days/week.
- Monitoring:
  - Baseline and annual ophthalmic examination, early retinal and optic nerve disturbances are reversible. Diabetic patients are at greater risk and may require monitoring and more frequent intervals.
  - Baseline and annual audiometry to detect high frequency sensorineural deafness.
  - Ophthalmic and audiometric assessments should be more frequent in patients on intensive continuous chelation or in patients where a rapid fall in iron load is achieved.
  - Cautious use on renal impairment.
  - Greater risk of Yersinia infections. DFO should be stopped in febrile patients until Yersinia infection is ruled out.
  - 24 hour urine collection for iron excretion is not generally required.
  - The majority of patients on regular transfusion will require regular chelation though...
dosage or frequency may need to be reduced according to the DFO toxicity index. DFO toxicity increases in well-chelated patients. The DFO therapeutic index should be kept <0.025.

- Therapeutic index = mean daily dose (mg/kg) / serum ferritin (ng/mL) 42
Myelodysplastic/myeloproliferative neoplasm

WHO classification of Myelodysplastic/myeloproliferative neoplasms
- Chronic myelomonocytic leukaemia (CMML)
- Atypical chronic myeloid leukaemia, BCR-ABL1 negative (aCML)
- Juvenile myelomonocytic leukaemia (JMML)
- Myelodysplastic/myeloproliferative disease unclassifiable (including refractory anaemia with ring sideroblasts and thrombocytosis as a provisional entity)

WHO diagnostic criteria

**CMML**
- Persistent peripheral blood monocytosis >1x10^9/L
- No Philadelphia chromosome or BCR-ABL1 fusion gene
- No rearrangement of PDGFRA or PDGFRB (should be specifically excluded in cases with eosinophilia)
- Fewer than 20% blasts in the peripheral blood and BM
- Dysplasia in one or more myeloid lineages; if myelodysplasia is absent or minimal, the diagnosis of CMML may still be made if the other requirements are met and an acquired, clonal cytogenetic or molecular genetic abnormality is present in haemopoietic cells, or the monocytosis has been persistent for at least 3 months and other causes of monocytosis have been excluded

**CMML-1**
- Blasts (including promonocytes) are <5% in the peripheral blood and <10% in BM

**CMML-2**
- Blasts (including promonocytes) are 5%-19% in the peripheral blood or 10%-19% in the BM or Auer rods are present irrespective of the blast plus promonocyte count

Prognosis of CMML
Both prognostic scoring systems below have value:
- **Düsseldorf score** which takes into account BM blast %, LDH, Hb concentration and platelet count.
- **CPSS** which takes into account WHO subtype, FAB subtype, CMML specific cytogenetic risk classification and RBC transfusion dependency

Treatment of CMML
- Transplant eligible patients should be considered for an allogeneic SCT
- Supportive care +/- hydroxycarbamide remains the mainstay of care for the majority of patients with CMML
- Azacitidine is approved for use in non-proliferative CMML-2 with 10-29% marrow blasts.
GUIDELINES FOR MANAGEMENT OF ACUTE LYMPHOBLASTIC LEUKAEMIA

Overview

The Network Site-Specific Group recommends that all adult patients with acute lymphoblastic leukaemia (precursor B-lineage and T-lineage ALL) are invited for entry into the UKALL 14 trial if eligible.

The main inclusion criteria of UKALL14
1. age ≥ 25 and ≤ 65
2. newly diagnosed, previously untreated ALL (a steroid pre-phase of 5-7 days is acceptable and can be started prior to registration)

The main exclusion criteria of UKALL14
1. known HIV infection
2. pregnant or lactating women
3. blast transformation of chronic myelogenous leukaemia
4. mature B-cell leukemia i.e. Burkitt’s disease t(8,14)(q24;q32) and all disorders with amplification of c-myc e.g. t(2;8)(p12;q24),t(8;22)(q24;q11)

Patients of age between 18 and 24 must be referred to the Teenage and Young Adult MDT and should be considered to be entered into UKALL2011 study

For patients who are not entered into these trials, the following protocols are recommended as the standard of care.

• UKALL 2011 for 24 years and under (discuss at the Teenage and Young Adult MDT), and
• UKALL 14 “standard treatment” arms for adults of age ≥ 25 and ≤ 65
• UKALL60 for adults >60 if unfit for UKALL14 study – treatment pathways are dependent on cytogenetics, co-morbidities and performance status

NHS England has nationally approved PEG-asparaginase instead of L-asparaginase for induction ALL therapy

1. Adults 16-24 years - UKALL2011 trial

Refer to UKALL2011 for guidance on treatment schedules, supportive care and details of MRD testing.

All patients aged > 10 are classified as NCI high risk and will receive regimen B.

MRD monitoring is done at day 29 and further treatment is stratified based on MRD results at day 29 or tumour volume if LBL. Patients with MRD risk (>0.005%) and MRD No results but slow early responder on day 8 marrow will be switched to regimen C.

Allogenic transplantation is not recommended in patients with CR1 independent of cytogenetics.

2. Adults 25-60 years as well as adults >60 fit enough to be considered for an allograft - UKALL14 trial

It is recommended to refer to the UKALL 14 protocol for treatment schedules MRD testing and supportive care.

- Patients who are not entered into the UKALL14 trial, should receive treatment according to the “standard” arms of the UKALL 14 protocol.
- See the treatment algorithm for adults with acute lymphoblastic leukaemia : age ≥ 24 years. (UKALLL 14 standard treatment arm).
- Refer to the UKALL 14 protocol for details of phase 1 induction; phase 2 induction, intensification, consolidation and maintenance therapy.
- Patients with Philadelphia positive disease (Ph+ ALL) should also receive continuous daily imatinib, orally, starting at 400mg daily, aiming to escalate to 600mg daily within 2 weeks, if tolerated. This should be continued until transplant wherever possible.
- **Important:** Patients with Philadelphia positive ALL should not receive PEG-asparaginase at any timepoint.
- Patients who achieve complete remission have risk assessment at the end of phase 2 of induction. Any one of the factors below makes the patient high-risk.

1. Age over 40 years
2. WBC ≥30 x 10⁹/L (precursor-B), ≥100 x 10⁹/L (T-lineage)
3. Cytogenetics – any one or more of the abnormalities below
   - t(4;11)(q21;q23)/MLL-AF4
   - low hypodiploidy/near triploidy (30-39 chromosomes / 60-78 chromosomes)
   - complex karyotype (five or more chromosomal abnormalities)
   - Philadelphia chromosome t(9;22) (q34;q11)/BCR-ABL1 (detected by cytogenetic or molecular methods)
4. High Risk Minimal Residual Disease (MRD) post phase 2 of induction.

- If the MRD result is not available (failed or specimen not sent) patient should be considered standard risk in the absence of any other high risk features.

TREATMENT ALGORITHM FOR ADULTS WITH ACUTE LYMPHOBLASTIC LEUKAEMIA : Age ≥ 24 years. (UKALL 14 Standard Treatment Arm)
Refer to the UKALL 14 protocol for details.

Steroid pre-phase (5-7 days); dexamethasone 6 mg/m²/day orally for 5-7 days

Phase 1 induction (4 weeks): pegylated asparaginase (PEG-ASP) + standard phase 1 induction therapy

Phase 2 induction (4 weeks): standard phase 2 induction therapy

Patients in complete remission: risk assessment performed on all patients at this point.

Sibling donor present

Over 40 years old
- Intensification with high-dose methotrexate + PEG-ASP
- Conditioning regimen with fludarabine + melphalan + alemtuzumab
- Allo-SCT (sibling)

40 years old and under
- Myeloablative conditioning regimen (e.g. etoposide) + TBI
- Allo-SCT (sibling)

Continue methotrexate intensification, consolidation and maintenance

Over 40 years old
- Intensification with high-dose methotrexate + PEG-ASP
- Conditioning regimen with fludarabine + melphalan + alemtuzumab
- Allo-SCT (MUD)

40 years old and under
- Myeloablative conditioning regimen (e.g. etoposide) + TBI
- Allo-SCT (MUD)
SCHEDULE OF TESTING FOR MINIMAL RESIDUAL DISEASE (MRD) FOR RISK ASSESSMENT

*Recovery is defined as neutrophils >0.75 x 10⁹/L, platelets >75 x 10⁹/L.

<table>
<thead>
<tr>
<th>At Diagnosis</th>
<th>Specimens for local assessment</th>
<th>Specimens to be sent to central laboratory**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics/molecular assessment of BCR-ABL and MLL on bone marrow.</td>
<td>Bone marrow 3-5ml in EDTA (OR peripheral blood 30-50ml in EDTA if WCC &gt; 30x 10⁹/L). BCR-ABL status will also be checked.</td>
<td></td>
</tr>
</tbody>
</table>

**All samples should be sent by courier or by 1st class post to arrive the same day or overnight to the following address:

Minimal Residual Disease Laboratory
URGENT UKALL14 STUDY SAMPLE (FAO Adele Fielding, Rachel Mitchell or Krisztina Alapi)
UCL Cancer Institute
Paul O’Gorman Building
72 Huntley Street
London UK
WC1E 6DD

MRD Lab email: ALLMRDlab@ucl.ac.uk

Adults > 60 years - UKALL60 trial

It is recommended to refer to the UKALL60 protocol for treatment schedules and supportive care.

UKALL60+ - Protocol - v3.0 21.05.2015.pdf

Four different treatment pathways are suggested depending on cytogenetics, co-morbidities and performance status of patient. The treatment pathway will be chosen by local clinician after discussion with patient.
1.2 Study Schema

PH +ve

PHILADELPHIA POSITIVE

Induction Phase 1

PHILADELPHIA NEGATIVE (INTENSIVE)

Induction Phase 2

PHILADELPHIA NEGATIVE (INTENSIVE+)

Consolidation 1

PHILADELPHIA NEGATIVE (NON-INTENSIVE)

Consolidation 2

Consolidation 3

Maintenance (2 years)

REGISTRATION ONLY

Data Collection only

Follow Up: Patients to be followed up annually from completion of maintenance for 5 years

*Treatment pathway to be chosen by local investigator after consultation with patient and taking into account performance status, co-morbidities and personal preference. Reason for choice will be documented.

Bone marrow samples sent to central lab for MRD

Diagnostic bone marrow*
All patients with Philadelphia positive ALL will be treated as per pathway A. Patients with Ph-neg ALL need to be carefully assessed and depending on clinical status can either be offered, an intensive arm (pathway B), an intensive + arm (pathway C) or a non-intensive arm (pathway D).

MRD assessment is experimental and should only be undertaken if patient is participating in the study. Intent is potentially curative but although remission is often achieved, relapses frequently occur and relapsing patients would not normally be offered salvage chemotherapy. This protocol can also be used for patients aged 60 or younger deemed unfit for standard arm of UKALL14.

4. **Relapsed ALL**

Patients treated on UKALL 2011 and UKALL14 and not transplanted owing to perceived ‘low risk’ may relapse. Other options for reinduction include FLAG-Ida, clofarabine (via CDF) and nelarabine (via CDF). Patients should proceed to transplantation if remission is achieved.
GUIDELINES FOR THE MANAGEMENT OF CHRONIC MYELOID LEUKAEMIA

Where *** indicated, please see notes overleaf
Suspected CML


Initial management. If typical CML morphology and WBC >50x10^9/L then start treatment whilst definitive diagnosis awaited. Perfectly reasonable to start HU whilst Ph and/or BCR-ABL status awaited. Start definitive treatment. Once diagnosis confirmed by BM Ph or BCR-ABL please consider the SPIRIT 2 trial for all patients before starting imatinib. (www.spirit-cml.org/spirit-2-home.aspx)*. In non-trial patients: imatinib 400mg (CP), 600mg (AP/BP) daily. Allopurinol at individual discretion but rarely required for more than one month. No necessity to use hydroxyurea rather than imatinib initially but HU can be used pending definitive diagnosis. Very few, if any, patients should be allografted ‘up front’. Leucopheresis not essential but useful for research or if transplant might be considered.

Who to refer/discuss?* Consider: possible SPIRIT trial patients; patients under 50 to discuss potential allograft strategy; advanced disease at presentation or on treatment; drug resistance and/or difficult patients; use of 2nd generation TKI drugs; difficult toxicity; children (rare); pregnancy.

3 months. Response assessment. FBC. PCR EVERY 3/12*

CHR* at 3/12

No

6 months. Response assessment
Bone marrow cytogenetics, PCR*

Ph- positivity

0% (CCR*)

>95%

1-95%: continue treatment

0% (CCR*)

Ph positivity

>35% (i.e. NO MCR*)

<=35% (MCR*)

0% (CCR*)

Ph positivity

>0% (i.e. NO CCR*)

0% (CCR*)

Continue imatinib

3 monthly PCR. No further BMs unless loss of response.

Loss of response**?

No

Yes

Mutation analysis.
Consider alternative therapy: 2nd generation TKI* or transplant.
(Consider repeat BM if loss of response)
NOTES
This algorithm is based on evidence from the IRIS/0106 trial which has been described and referenced in more detail in the European Leukaemia Net and forthcoming BCSH guidelines documents. The tables below are modified from these documents and the reader is referred to these sources for further detail.

Investigations at diagnosis. FBC, differential esp. blast %, biochem screen inc. LFTs, urate.
Bone marrow (or blood if BM difficult) for cytogenetics or PCR for BCR-ABL. Trophine not necessary. There is no absolute requirement to perform a BM examination. At individual discretion the diagnosis can be made on PCR detection of BCR-ABL alone but baseline marrow may be useful for future comparison and to define additional chromosomal abnormalities.
Possible additional investigations. HLA type patient and any sibs if less than 60.

Monitoring. FBC (look out for early neutropenia and thrombocytopenia (10-15% on imatinib 400mg); LFTs probably at every visit - occasional patients develop late liver tox (1-2 years+ out): bone marrow cytogenetics, PCR and mutation testing as per algorithm.

Loss of response. Obvious: loss of CHR or significant increase in BM Ph (e.g. 10% @6/12, 80% at 12/12). More subtle: Failure to achieve MMR (<0.1% BCR-ABL/ABL ratio) or sustained increase in previously low PCR result. See table below for ELN summary – by no means ‘set in stone’ as yet, a work in progress.

Managing toxicity is beyond the scope of this document, please contact Anne or Steve to discuss.

Samples. PCR for BCR-ABL: 2.5 ml in PAXgene™. Send to Molecular Pathology Service, Department of Haematology, RVI, Newcastle NE1 4LP. Contact details below.
ABL tyrosine kinase domain mutation analysis (available Autumn 2007): same as PCR sample and send to the same address. PCR and mutation analysis can be done on same sample if need be. Samples can be sent by 1st class post, courier or taxi as you wish. If posting, please avoid posting on thursdays/fridays as samples likely to languish over the weekend and be useless. Sample ‘freshness’ important: to arrive within 24 hours if possible. Please discuss with Steve O’Brien or Andy Hall before dispatch of samples.

Contacts
Clinical advice & PCR, mutation interpretation
Steve O’Brien: 0191 282 0605, 07789 200525, s.g.o'brien@ncl.ac.uk
Anne Lennard: 0191 282 9408, 07801 443516, anne.lennard@nuth.nhs.uk
PCR/mutation service
Ann Curtis 0191 2418772, ann.curtis@nuth.nhs.uk
Andy Hall: 0191 246 4411 a.g.hall@ncl.ac.uk
Spirit-2
Wendy Banks 0191 282 0904 wendy.banks@ncl.ac.uk

2nd generation Tyrosine Kinase Inhibitors (TKIs)
Nilotinib 400 mg twice daily or Dasatinib 100mg daily is standard dose. NOTE: dasatinib and nilotinib don't work against the T315I mutation. Nilotinib use is approved by NICE and dasatinib should be used only in cases of nilotinib intolerance
Bosutinib (Ski606), MK0457 (T315I inhibitor) and others not available as yet.

Definitions of response to treatment

<table>
<thead>
<tr>
<th>Haematological response (HR)</th>
<th>Cytogenetic response (CR)</th>
<th>Molecular response (MR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete (CHR)</td>
<td>Complete (CCR)</td>
<td>Complete (CMR)</td>
</tr>
<tr>
<td>Platelets &lt;450 x 10^9/L</td>
<td>0% Ph-positive metaphases</td>
<td>No detectable BCR-ABL</td>
</tr>
<tr>
<td>WBC &lt;10 x 10^9/L</td>
<td>or BCR-ABL FISH positivity</td>
<td>transcripts</td>
</tr>
<tr>
<td>Differential: No immature</td>
<td>Major (CMR) is combination</td>
<td>&lt;0.1% BCR-ABL to ABL</td>
</tr>
<tr>
<td>granulocytes and &lt;3%</td>
<td>of complete and partial</td>
<td>ratio</td>
</tr>
<tr>
<td>basophils</td>
<td>Minor</td>
<td>(Sample must be of</td>
</tr>
<tr>
<td></td>
<td>Minimal</td>
<td>good quality and have</td>
</tr>
<tr>
<td></td>
<td>No cytogenetic response</td>
<td>adequate BM)</td>
</tr>
</tbody>
</table>

Definitions of failure or sub-optimal response to imatinib based on ELN guidelines

<table>
<thead>
<tr>
<th>Time</th>
<th>Failure</th>
<th>Suboptimal response</th>
<th>Warnings</th>
<th>Phase of disease. Based on European Leukaemia Net guidelines, not WHO.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chronic phase</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Warnings at diagnosis: high risk ( Sokal/Halsted); del 9q; additional chromosome abnormalities in Ph-positive cells.</td>
<td></td>
<td></td>
<td>Blast cells 15-25% in PB or BM</td>
</tr>
<tr>
<td>3 months</td>
<td>No HR</td>
<td>No CHR</td>
<td>None of the criteria for AP or BP have been met</td>
<td>Additional cytogenetic abnormalities alone do not indicate accelerated phase</td>
</tr>
<tr>
<td>6 months</td>
<td>No CHR</td>
<td>No CCR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>No MCR</td>
<td>No CCR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 months</td>
<td>No CCR</td>
<td>No MMR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any time</td>
<td>Loss of CHR</td>
<td>Loss of CCR</td>
<td>Chromosomal abnormalities in Ph+ cells</td>
<td>Any rise in PCR level Chromosome abnormalities in Ph- negative cells</td>
</tr>
</tbody>
</table>
GUIDELINES FOR MANAGEMENT OF MYELOPROLIFERATIVE DISORDERS

DEFINITIONS

Proposed Diagnostic Criteria for Myeloproliferative Diseases (MPD) with JAK2 Mutation

**JAK2-positive thrombocythaemia** (diagnosis requires the presence of all threecriteria)
A1. Platelet count >450×10⁹/L
A2. Mutation in JAK2
A3. No other myeloid cancer, especially JAK2-positive polycythemia, myelofibrosis, or myelodysplasia

**JAK2-positive polycythemia** (diagnosis requires the presence of both criteria)*
A1. High hematocrit (>52% in men or >48% in women) or an increased red cellmass (>25% above predicted value)
A2. Mutation in JAK2

*Dual pathology (secondary erythrocytosis or relative erythrocytosis) might rarely coexist with a JAK2-positive myeloproliferative disorder. In this situation, it would be prudent to reduce the hematocrit to the same targets as those for polycythemia vera.

**JAK2-positive myelofibrosis** (diagnosis requires the presence of A1 and A2 and any two B criteria)
A1. Reticulin grade 3 or higher (on a 0–4 scale)
A2. Mutation in JAK2
B1. Palpable splenomegaly
B2. Otherwise unexplained anaemia (haemoglobin <11.5 g/dL for men; <10 g/dL for women)
B3. Teardrop red cells on peripheral blood film
B4. Leukoerythroblastic blood film (presence of at least 2 nucleated red cells or immature myeloid cells in peripheral blood film)
B5. Systemic symptoms (drenching night sweats, weight loss >10% over 6 months, or diffuse bone pain)
B6. Histologic evidence of extramedullary haematopoiesis

**JAK2 positive clinically occult MPD**
Patient present with thrombotic problems but without abnormal blood counts and are JAK2 positive. There is limited evidence to guide treatment in this group though it is increasingly recognised. Some consider anticoagulation sufficient and some groups recommend a reduction in platelet count.
Proposed Diagnostic Criteria for MPD without JAK2 Mutation.

**JAK2-negative polycythaemia vera** (diagnosis requires the presence of A1, A2, and A3, plus either another A or two B criteria)

- A1. Increased red-cell mass (>25% above predicted value) or a haematocrit ≥60% in men or >56% in women
- A2. Absence of mutation in JAK2
- A3. No causes of secondary erythrocytosis (normal arterial oxygen saturation and no elevation of serum erythropoietin)
- A4. Palpable splenomegaly
- A5. Presence of acquired genetic abnormality (excluding BCR-ABL) in haematopoietic cells

**JAK2-negative essential thrombocythaemia** (diagnosis requires the presence of all five criteria)

- A1. Platelet count >600×10^9/L on two occasions at least 1 month apart*
- A2. Absence of mutation in JAK2
- A3. No reactive cause for thrombocytosis
- A4. Normal ferritin (>20 μg/L)
- A5. No other myeloid disorder, especially chronic myeloid leukaemia, myelofibrosis, polycythaemia vera, or myelodysplasia

* The platelet threshold is preferred in patients without the JAK2 mutation, given the difficulty in ruling out reactive thrombocytosis and the fact that 2.5% of persons without a myeloproliferative disorder have a platelet count above the normal range.

**JAK2-negative idiopathic myelofibrosis** (diagnosis requires the presence of A1, A2, A3, and any two B criteria)

- A1. Reticulin grade 3 or higher (on a 0–4 scale)
- A2. Absence of mutation in JAK2
- A3. Absence of BCR-ABL fusion gene

**B1. Palpable splenomegaly**

**B2. Otherwise unexplained anaemia (haemoglobin <11.5 g/dL for men or <10 g/dL for women)**

**B3. Teardrop red cells on peripheral blood film**

**B4. Leukoerythroblastic blood film (presence of at least 2 nucleated red cells or immature myeloid cells in peripheral blood film)**

**B5. Systemic symptoms (drenching night sweats, weight loss >10% over 6 months, or diffuse bone pain)**

**B6. Histologic evidence of extramedullary haematopoiesis**

*From UK BCSH amended guidelines for diagnosis of Polycythaemia Vera (McMullin, M.F et al BJH and BCSH website) and from Campbell and Green N Engl J Med 2006;355:2452-66*
POLYCYTHAEMIA VERA (PRV)

INVESTIGATION OF POLYCYTHAEMIA (ERYTHROCYTOSIS)

Persistently raised haematocrit: 52% (≈17g/dL) – adult male
48% (≈ 16 g/dL) – adult female

Causes

1. JAK 2 V617F-positive MPD
2. JAK2 exon 12-positive polycythaemia
3. JAK 2-negative MPD
4. Hypoxia
   a) Right to left cardiac shunt
   b) Lung disease / smoking / nocturnal sleep apnoea
5. Inappropriate erythropoietin (Epo) secretion
   a) Renal, uterine, cerebellar or other tumour
   b) Post-renal transplant polycythaemia/polycystic kidney disease
   c) Self-administered erythropoietin
6. Hypoxia sensing disorder (eg. VHL-Chuvash Erythrocytosis, HIF2a abnormalities) - High or normal Epo levels
7. Epo sensing disorder (eg. EpoR) - Low Epo levels
8. High oxygen affinity haemoglobin
9. Red cell membrane or enzyme disorder with low 2,3 DPG
10. Spurious or apparent polycythaemia due to reduced plasma volume
11. Idiopathic erythrocytosis

First line investigations

If there is a clear and sufficient cause of polycythaemia, eg. cyanotic heart disease or significant respiratory disease, investigate and refer for that condition as appropriate. If the cause is not apparent consider investigation as follows at the first visit.

- FBC, serum vitamin B₁₂, red cell/serum folate and serum ferritin
- Biochemistry profile including LDH
- JAK2V617F mutation analysis (1 x EDTA to Molecular Diagnostics, Haematology RVI)
- Epo level (1x EDTA to Haematology, FreemanHospital or 1x clotted sample to JamesCookUniversityHospital)
  - Normal Epo levels using a typical assay range from 3.1 to 16 mIU/mL with a geometric mean of about 8 mIU/mL.
  - An Epo level below 2 IU/mL is nearly always due to PV, however 50% of PV cases will have a level between 2 and 12 IU/mL.
  - A high Epo level >16 IU/mL in a patient with a high Hb indicates secondary polycythaemia.
  - Patients with secondary polycythaemia rarely have Epo levels below the normal range despite the high Hb.
  - Epo levels in between are less helpful.
  - Epo levels must be interpreted with concurrent Hb concentration.
  - Epo does show daily variation by as much as 60% of the lowest value with the lowest values typically being found in the morning and early afternoon, and higher values in the later afternoon and evening. Peak levels in those with respiratory disease are often in the early hours of the morning.
Further investigations

A. If JAK2 mutation is positive, the diagnosis is of JAK2+ve polycythaemia vera (PV).
   - Consider ultrasound of spleen as baseline investigation.

B. If JAK2 mutation is negative and EPO level low, the diagnosis could be JAK2-negative PV, apparent/spurious polycythaemia or Epo receptor abnormality
   - Red cell mass (RCM) is recommended, but is not necessary if Hct is >0.60 in males and >0.56 in females.
   - If raised RCM is confirmed or Hct above these limits, proceed to bone marrow examination and ultrasound scan of abdomen.
   - If bone marrow is suggestive of primary polycythaemia, request, via haematology at the RVI, a test for Exon 12 mutations that can be done by Newgene on stored DNA following a negative JAK2 v617f assay. A new sample should not be required.
   - If still no cause found, and especially if there is a family history of polycythaemia, consider Epo receptor mutation analysis.
   - Exon 12 mutation PV typically reported to have ‘normal platelet count and marrow showing moderate hypercellularity with erythroid hyperplasia but without megakaryocytic or granulocytic changes seen in other MPD.’ (JAK2 exon 12 mutations in PV and Idiopathic erythrocytosis. Scott LM et al NEJM 2007; 356: 459-68.)
   - It may be worth repeating the Epo level if overall picture does not fit with PV.

C. If JAK2 mutation is negative and Epo level high, the diagnosis is secondary polycythaemia
   - CXR, blood gasses, SaO2, sleep study if necessary
   - Ultrasound scan of abdomen for renal tumours/cysts
   - Hb HPLC or Hb NMR studies at Leeds (may be arranged via Haematology Specials Laboratory RVI),
   - Hb-O2 saturation studies if altered affinity Hb suspected, eg familial polycythaemia
   - von Hippel Lindau gene analysis, ?PHD2 mutation analysis (Arrange via the Department of Haematology, Belfast University, see below)

D. If JAK2 mutation is negative and Epo normal, the diagnosis of either PV or secondary polycythaemia cannot be excluded.
   - Consider repeating Epo level.
   - RCM and plasma volume studies are recommended if Hct males <0.60, females <0.56 to exclude apparent polycythaemia.
   - If raised RCM is confirmed and secondary polycythaemia is still a possible diagnosis, especially with Epo at high end of normal range, investigate as for JAK2 mutation negative and high Epo initially (see C above).
   - If Epo level is low normal, investigate as for JAK2 negative and low Epo (see B above). It may be necessary to investigate both possibilities.
TREATMENT OF POLYCYTHAEMIA VERA

Venesection

• Venesection to Hct of 0.45.
  - Hct of 0.45 equates to a Hb of 15 g/dL, 0.50 to Hb 16.6g/dL. It is possible that the Hb is more reliable than Hct.
• Blood should be venesected over 15 min or more to a maximum of 7mL/kg, i.e. 400 mL in < 60 kg, ≈ 500 mL in 70 kg, ≈ 650mL in 90 kg using likely lean body weight.
• Isovolaemic dilution (500 mL of 0.9% sodium chloride either concurrently or immediately after venesection) may be preferable if
  - the aim is to produce rapid reduction of Hb (equilibration after venesection takes 36-48 hrs and in patients with PV with a markedly raised total blood volume there may be little reduction in Hct until several venesections have been performed).
  - the patient is considered to be at relatively high risk of thrombosis, eg. recent thrombosis or ischaemic cardiac history.
• In new cases blood may be venesected daily or on alternate days to reach a ‘safe’ Hb. Isovolaemic dilution is recommended when intensive venesection is undertaken.

Hydroxycarbamide (HC)

Indications to start HC according to BCSH Guidelines are
• poor tolerance of venesection,
• symptomatic or progressive splenomegaly,
• weight loss or night sweats suggesting disease progression, and
• thrombocytosis.

Finzzi & Barbui* suggested dividing patients into risk categories and treating with HC if high risk as for ET.
• High risk = previous thrombosis, age > 60
• Intermediate risk = age < 60 with cardiovascular risk factors e.g. diabetes, smoking etc.

This would probably lead to more patients being treated with HC.

ELN and IWG-MRT criteria for Hydroxycarbamide resistance and intolerance (Ref: Barbui T et al –JCO, 2011;29:761-770)

HU resistance is defined as anyone of the following criteria- (after 3 months of >2g/d of HU)
Need for phlebotomy to keep Hct <45% or
Uncontrolled Myeloproliferation i.e platelet count >400 and WBC count > 10 x 10^9/L or
Failure to reduce massive splenomegaly by >50% as measured by palpation or failure to relieve symptoms related to splenomegaly

HU intolerance is defined as either of the following criteria -
ANC less than 1.0 x 10^9/l or platelet count < 100 x 10^9 or Hb < 100 at the lowes dose of HU required to achieve complete or partial clinicohaemtological response or
Presence of leg ulcers or other unacceptable HU related non haematological toxicities such as mucocutaneous manifestations, GI symptoms, pneumonitis or fever at any dose of HU.

Treatment Options:
- Interferon-Alpha
- Busulphan (Increased risk of leukemic transformation)
- Adding anagrelide?
- JAK 2 inhibitor – if fulfils CDF criteria

TREATMENT OF OTHER FORMS OF POLYCYTHAEMIA

Apparent or spurious erythrocytosis
- Confirm raised Hct with two counts at least 3 months apart
- Advise reduction of ethanol, smoking cessation, avoidance of diuretics, avoidance of excessive caffeine intake and control of hypertension.
- Consider venesection if Hct >0.54, recent history thrombosis, strong risk factors for thrombosis. If thrombotic events occur despite this target, venesection to 0.45.
- Monitor untreated patients.

Idiopathic erythrocytosis
- Treat as for apparent erythrocytosis

High oxygen affinity Hb
- Venesection if symptoms possibly due to high Hb. eg. dizziness, dyspnoea, angina (?to Hct 0.6).
- Venesection if one or more previous thrombotic episodes (?to Hct 0.6).
- If symptoms or events at Hct < 0.6 consider venesection to 0.52.
- Consider partial red cell exchange for major surgery if Hct >0.6.

Hypoxic pulmonary disease
- Refer to respiratory physicians for consideration O2 therapy
- If there are hyperviscosity symptoms or Hct > 0.56, venesection to 0.5-0.52
- Consider ACE or angiotensin inhibitors.

Cyanotic heart disease
- Isovolaemic venesection when the patient has symptoms of hyperviscosity (dizziness, headache, etc.).
- Target Hb should be individualised to the patient.
- Avoid excessive venesection with iron deficiency which may increase viscosity while compromising O2 delivery.

Post Renal transplant erythrocytosis
- Avoid dehydration.
- Treat with ACEI or angiotensin II receptor antagonist
- Venesection to Hct of 0.45.
ESSENTIAL THROMBOCYthaemia

BCSH 2015 - Proposed diagnostic criteria for essential thrombocythaemia.

Diagnosis requires A1–A3 or A1 + A3–A5

A1 - Sustained platelet count ≥450 x 10⁹/l

A2 - Presence of an acquired pathogenetic mutation (e.g. in the JAK2, CALR or MPL genes)

A3 - No other myeloid malignancy, especially PV, PMF, CML or MDS

A4 – No reactive cause for thrombocytosis and normal iron stores

A5 - Bone marrow aspirate and trephine biopsy showing increased megakaryocyte numbers displaying a spectrum of morphology with predominant large megakaryocytes with hyperlobated nuclei and abundant cytoplasm. Reticulin is generally not increased (grades 0–2/4 or grade 0/3)

- Polycythaemia vera; excluded by a normal haematocrit in an iron-replete patient.
- Primary myelofibrosis; indicated by presence of significant marrow bone marrow fibrosis (greater or equal to 2/3 or 3/4 reticulin) AND palpable splenomegaly, blood film abnormalities (circulating progenitors and tear-drop cells) or unexplained anaemia (Barosi, 1999; Mesa et al, 2007).
- Chronic myeloid leukaemia; excluded by absence of BCR-ABL1 fusion from bone marrow or peripheral blood.
- Myelodysplastic syndrome; excluded by absence of dysplasia on examination of blood film and bone marrow aspirate

Check history, Hb, ESR, CRP and fibrinogen. If inflammatory markers (especially fibrinogen) are not raised and if Hb is normal or high normal, essential thrombocythaemia (ET) is likely. Molecular tests: Peripheral blood JAK2 V617F mutation, MPL W515L mutation, CAL-R, BCR-ABL.

The following are considered atypical features for the diagnosis of ET.
- Anaemia without iron deficiency
- Poikilocytosis
- Leucocytosis
- Monocytosis
- Blasts
- Marked splenomegaly

A. JAK2-positive or MPL mutation positive with no atypical features

This is diagnostic of ET and bone marrow biopsy is not necessary.
B. **JAK2-positive or MPL mutation positive with atypical features**

Possible diagnoses are myelofibrosis (MF), JAK2-positive RARS with thrombocytosis, and JAK2-positive CMML. Bone marrow examination with or without cytogenetics is indicated.

C. **JAK2-negative and MPL mutation negative and platelets >600 x10^9/L**

If inflammatory markers are negative and Hb are normal, ET is likely/possible. Please note that ET is not necessarily excluded even if inflammatory markers are positive.

**JAK2 and other conditions with thrombocytosis**

- RARS with thrombocytosis: 30-50% of these patients will also be found to have the JAK2 mutation.
- CMML with JAK2 mutation: 5-10% of CMML will have the JAK2 mutation.
- AML: <5% of AML cases will have the JAK2 mutation. The majority will have a known pre-existing MPD.

**RISK STRATIFICATION IN ET**

- High risk: Age > 60, previous thrombosis or platelets >1500x10^9/L
- Intermediate risk: Age 40-60. No high risk features
- Low risk: Age <40. No high risk features

Diabetes mellitus, hypertension, renal failure, hyperlipidaemia, smoking, family history and known thrombophilia may all be considered as risks likely to interact. Given the uncertainty about the need for or benefit of cytoreductive treatment in the intermediate risk group (see MRC-PT1 trial), the presence of 2 or more of these factors may be considered enough to raise the intermediate-risk patient into the high risk group.

**TREATMENT OF ESSENTIAL THROMBOCYTHAEMIA**

**Low risk**
- Aspirin 75mg od alone.
- Reassess at age 40.

**Intermediate risk**
- Consider for PT1 trial intermediate risk arm (hydroxycarbamide (HC) + aspirin vs aspirin alone).
- Non-trial patients should be treated with aspirin alone until 60 years of age.
- If there are one major or 2 or more minor vascular risk factors, consider treatment with HC plus aspirin.
- Italian consensus guidelines (Barbui et al. 2004. Haematologica, 89;215-32) suggest platelets >1000x10^9/L plus another vascular risk factor as indications for cytoreductive treatment plus aspirin.

**High risk**
- Cytoreductive treatment plus aspirin. HC (start 0.5-1 g daily depending on patient size) is the preferred cytoreductive treatment.
- If HC is not tolerated (see side-effects) or platelet count is inadequately controlled, try:
  - Anagrelide*
  - anagrelide plus HC
  - interferon alfa in younger patients
  - busulfan or $^{32}$P in patients >75years
  - aspirin alone (if there are no history of and no additional risk factors for thrombosis, thrombocytosis is longstanding, and platelets < 1000x10^9/L)

*Anagrelide was less effective at preventing arterial events, chiefly TIAs in the PT-1 trial, and was associated with more progression to MF, greater withdrawal due to side-effects (35% vs 20% for HC). However, it was associated with fewer venous thrombotic events though more gastrointestial bleeds, perhaps due to the antiplatelet effect of anagrelide in addition to aspirin.

If using Anagrelide perform baseline marrow biopsy and repeat 2-3 yearly for assessment of reticulin fibrosis. If fibrosis is increasing then stop anagrelide and seek alternative agents.

Aspirin and bleeding risk: If the platelet count is >1500X10^9/L do not start aspirin unless there is active or recent thrombosis. Bleeding may be a greater risk due to acquired von Willebrand disease from adsorption of HMW vWF multimers by the platelet mass. Once the platelet count is <1500x10^9/L, aspirin should be started unless there have been bleeding complications.

Treatment aim: The target platelet count should be <450x10^9/L. Some suggest <600x10^9/L may be adequate especially given that there is no clear relationship between platelet count and thrombotic episodes. Once a stable platelet count has been achieved, follow-up FBC should be not less than 3 to 4 monthly.

Young patients: Patients of age <40. Most authorities recommend interferon alfa or anagrelide due to the uncertainty about the very longterm effects of hydroxycarbamide and residual concern regarding leukaemogenicity.

Pregnancy and family planning: Advise against conception on HC or any alkylating agent. Use interferon alfa instead. If further advice is required, contact Dr Claire Harrison at St Thomas's Hospital.
Table II. Diagnostic criteria for primary myelofibrosis: diagnosis requires A1 + A2 and any two B criteria.

<table>
<thead>
<tr>
<th>A1</th>
<th>Bone marrow fibrosis $\geq 3$ (on 0–4 scale).</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2</td>
<td>Pathogenetic mutation (e.g. in JAK2 or MPL), or absence of both BCR-ABL1 and reactive causes of bone marrow fibrosis</td>
</tr>
<tr>
<td>B1</td>
<td>Palpable splenomegaly</td>
</tr>
<tr>
<td>B2</td>
<td>Unexplained anaemia</td>
</tr>
<tr>
<td>B3</td>
<td>Leuco-erythroblastosis</td>
</tr>
<tr>
<td>B4</td>
<td>Tear-drop red cells</td>
</tr>
<tr>
<td>B5</td>
<td>Constitutional symptoms*</td>
</tr>
<tr>
<td>B6</td>
<td>Histological evidence of extramedullary haematopoiesis</td>
</tr>
</tbody>
</table>

*Drenching night sweats, weight loss $>10\%$ over 6 months, unexplained fever ($>37.5^\circ C$) or diffuse bone pains.

Table III. Diagnostic criteria for post-PV and post-ET myelofibrosis: diagnosis requires A1 + A2 and any two B criteria.

<table>
<thead>
<tr>
<th>A1</th>
<th>Bone marrow fibrosis $\geq 3$ (on 0–4 scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2</td>
<td>Previous diagnosis of ET or PV</td>
</tr>
<tr>
<td>B1</td>
<td>New palpable splenomegaly or increase in spleen size of $\geq 5$ cm</td>
</tr>
<tr>
<td>B2</td>
<td>Unexplained anaemia with 20 g/l decrease from baseline haemoglobin</td>
</tr>
<tr>
<td>B3</td>
<td>Leuco-erythroblastic blood film.</td>
</tr>
<tr>
<td>B4</td>
<td>Tear-drop red cells</td>
</tr>
<tr>
<td>B5</td>
<td>Constitutional symptoms*</td>
</tr>
<tr>
<td>B6</td>
<td>Histological evidence of extramedullary haematopoiesis.</td>
</tr>
</tbody>
</table>

*Drenching night sweats, weight loss $>10\%$ over 6 months, unexplained fever ($>37.5^\circ C$) or diffuse bone pains.
Bone marrow biopsy is an essential test.
- Testing for JAK2, CAL-R, MPL gene mutations
- BCR-ABL should be routinely tested.
- In the presence of significant eosinophilia, PDGFRα and PDGFB rearrangements should be tested to exclude chronic eosinophilic leukaemia (see below).

RISK STRATIFICATION IN MYELOFIBROSIS

Historically the Lille scoring system was widely used: Hb <10 g/dL score 1. WCC<4 x10⁹/L or >30 x10⁹/L score 1

<table>
<thead>
<tr>
<th>Score</th>
<th>Risk group</th>
<th>Cases (%)</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>47</td>
<td>93 months</td>
</tr>
<tr>
<td>1</td>
<td>Intermediate</td>
<td>45</td>
<td>26 months</td>
</tr>
<tr>
<td>2</td>
<td>High</td>
<td>8</td>
<td>13 months</td>
</tr>
</tbody>
</table>


The Lille score has been superseded by several more scoring systems: the International Prognostic Scoring System (IPSS, 2009), Dynamic IPSS (DIPSS, 2010) and DIPPS Plus (2011).

<table>
<thead>
<tr>
<th>Variable</th>
<th>IPSS</th>
<th>DIPSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 years</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Constitutionals symptoms</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Hb &lt;100g/l (or 10g/dl)</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>WBC &gt;25</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Circulating blasts &gt;=1%</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>1 point each</td>
<td></td>
<td>1 point each but Hb=2</td>
</tr>
</tbody>
</table>

DIPSS=plus add 1 point to the DIPSS risk group in addition for:
- Platelet count <100
- RBC transfusion need
- Unfavourable karyotype +8, -7/7q-, i(17q), inv(3), -5/5q-, 12p-, 11q23 rearrangement

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>IPSS</th>
<th>DIPSS</th>
<th>DIPSS-plus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of factors</td>
<td>Med survival (yrs)</td>
<td>No of factors</td>
</tr>
<tr>
<td>Low</td>
<td>0</td>
<td>11.3</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate 1</td>
<td>1</td>
<td>7.9</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Intermediate 2</td>
<td>2</td>
<td>4.0</td>
<td>3 or 4</td>
</tr>
<tr>
<td>High</td>
<td>&gt;=3</td>
<td>2.3</td>
<td>5 or 6</td>
</tr>
</tbody>
</table>
TREATMENT OF MYELOFIBROSIS

Options

Supportive care: with red cell transfusion

Cytoreductive agents:

Hydroxycarbamide – If does not fulfil criteria for use of Ruxolitinib. (Please note that in the MRC-PT1 trial anagrelide was associated with more rapid progression in marrow fibrosis compared to HC.)

Ruxolitinib: The JAK1 and JAK2 inhibitor, Ruxolitinib (marketed in the UK by Novartis as Jakavi) has been compared against placebo, or best available therapy in the COMFORT 1 and COMFORT2 studies, respectively. The BCSH guidelines 2015 - currently recommend Ruxolitinib as

First line therapy for symptomatic splenomegaly and/or myelofibrosis-related constitutional symptoms regardless of JAK2 V617F mutation status (evidence grade 1A).

Ruxolitinib is currently available via the Cancer Drug Fund (CDF) for the following population:

The first or second line treatment of symptomatic splenomegaly in primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis where the following criteria are met:

a) Intermediate / high risk primary myelofibrosis, OR
b) Post-polycythaemia myelofibrosis, OR
c) Post-essential thrombocytosis myelofibrosis

AND the patient has symptomatic splenomegaly and/or constitutional symptoms AND is unsuitable for a stem cell transplant.

‘Thal-Pred’ regime: (thalidomide 50 mg o.d. for 6 months PLUS prednisolone 0.5 mg/kg o.d. tapering over 3 months) from the Mayo Clinic may be associated with moderate responses in the platelet count (75%), Hb (60%) and spleen size (20%).

Splenectomy: is indicated for mechanical symptoms affecting the gastrointestinal tract, pain from distension or infarction, portal hypertension, and cytopenias especially transfusion-dependant anaemia. Splenectomy does not appear to improve survival but may improve quality of life.

- The largest published series of 223 patients from the Mayo Clinic reported a 9% early mortality and 30% post-operative morbidity. 16% of patients went on to develop significant hepatomegaly but this did not appear to affect overall survival and was not predictable. 22% developed platelet counts of >600x10^9/L and 6% >1000x10^9/L. Of these, 19% (4% of total) died of bleeding or thrombosis. Hypo- or normo-cellular bone marrow correlated with poorer survival. Marked thrombocytopenia’ (not defined) preoperatively was associated with a short survival.
• Relative contra-indications to splenectomy are marked preoperative thrombocytopenia (<20x10^9/L) or thrombocytosis (>2500x10^9/L) and bone marrow that is not hypercellular.

• Before operation repeat bone marrow biopsy to assess cellularity and perform doppler ultrasound to check for intrahepatic thrombosis (Budd-Chiari syndrome) before proceeding as this preferentially requires porto-systemic shunt instead or as well (refer to the Liver Team at Freeman Hospital for assessment in this case). Try to bring platelets well within normal range if raised.

**Splenic irradiation:** can produce temporary alleviation of symptoms. It does not prevent future splenectomy but is reported to increase operative bleeding. It may be followed by prolonged cytopenia.

**Allogeneic Haemopoietic Stem Cell Transplant:** See Indications for Haemopoietic Stem Cell Transplantation.

**New Drugs: Jak2 inhibitors.** Centres in Sheffield (Professor John Reilly), Cambridge (Professor Anthony Green) and Belfast (Professor Mary-Francis MacMullin) may offer advice/trial treatment to patients with progressive MF.

**NOTES RELEVANT TO MANAGEMENT OF ANY MPD**

**Side-effects of HC**

• Patients should be counselled that HC is unlikely to be leukaemogenic and that the risk of secondary acute leukaemia is very small.

• Drug fever with abnormal LFTs is uncommon but indicates stopping of the drug.

• Dry skin, mild non-specific skin rash, mouth ulcers (2% in MRC-PT1 trial) may occur. If not severe, HC can be continued.

• Ankle ulcers. (5% in PT1 trial) are nearly always on the external malleolus and are deep and painful. A red reticular rash over the toes, also with pain, is a common accompaniment. The features are often mistaken for vascular insufficiency. Stopping HC causes resolution of the ulcer(s) over a few months but the pain usually settles first. The lesions on the toes may be slower to remit. The mechanism of this is not known. It has also been rarely reported in patients on anagrelide. Patients often are referred to vascular surgeons before the problem is brought to the attention of the haematologist.

• There is an increased risk of skin cancers in patients treated with HC. Appropriate minimisation of sun exposure should be recommended along with increased vigilance for skin changes.

**Side-effects of anagrelide**

• Cardiovascular events: chiefly palpitations (16%) and less commonly cardiac failure (3.5% vs 1.75% for HC in PT1 trial)

• Gastrointestinal effects: bleeding (3%), diarrhoea, abdominal pain

• Headaches, bloating, fluid retention, ‘constitutional’ symptoms.
**Thrombosis and JAK2**

- Splanchnic vein thrombosis is an increasingly recognised complication of MPD which is often occult at the time of diagnosis. It occurs in younger patients especially women. 50% or more of patients with Budd-Chiari syndrome are associated with JAK2-positive MPD, usually with erythroid and platelet involvement rather than plain ET. JAK2-negative MPD is relatively infrequent. The prognosis after Budd-Chiari syndrome is surprisingly good if patients are treated with HC plus warfarin or plus aspirin or both.

- A number of cases of cerebral sinus vein thrombosis (≈6%) are similarly associated with JAK2-positive MPD.

**Systemic Mastocytosis**

- The diagnosis should be suspected if if there are dermatographism and/or recurrent or unusual anaphylactic reactions. Measure serum tryptase and repeat serum tryptase after recovery from anaphylaxis if suspicious. Levels of > 20 μg/L are suspicious and warrant further investigation. Enquire Immunology at RVI for this test (serum sample). Bone Marrow trephine (including stains for mast cell tryptase) should show diagnostic features. C-KIT mutation analysis may be performed via Cytogenetics/Newgene at the Centre for Life on bone marrow aspirate or on trephine section recovered DNA. Patients negative for the common c-KIT mutation may be effectively treated with low dose tyrosine kinase inhibitor (Imatinib).

**Eosinophilia**

- Moderate eosinophilia = 1.5-5x10⁹/L
- Severe eosinophilia = >5 x 10⁹/L

Eosinophilia may be a reactive, familial or acquired clonal disorder.

**Reactive causes**: Worms and flukes, toxoplasmosis, borreliosis, HIV infection, atopic/allergic conditions including drug reactions, Churg-Strauss syndrome, Wegener’s granulomatosis, polyarteritis nodosa and sarcoidosis, Hodgkin lymphoma, or solid cancers, may produce extreme eosinophilia.

**Familial eosinophilia**: is very rare.

**Acquired clonal disease**: Chronic eosinophilic leukemia is associated with platelet-derived growth factor receptor alpha (PDGFRA) or beta (PDGFRB) abnormalities, c-kit mutations and 8p11 syndrome with rearrangement of fibroblast growth factor receptor-1 gene. PDGFRA abnormalities frequently arise from an interstitial deletion of chromosome 4 (4q12) which produces a constitutionally activated tyrosine kinase. These particular patients may be effectively treated with imatinib at doses much smaller than those normally used in the treatment of chronic myeloid leukaemia.

**Patient websites and associations**

MPD-support website [www.mpdvoice.org.uk](http://www.mpdvoice.org.uk)

**Addresses/contacts**

- JAK2V617F mutation, JAK2 exon 12 mutation and ML gene analysis (1 x EDTA to Newgene via the Haematology laboratory at the RVI)
- Epo level (1x EDTA to Haematology, FreemanHospital or 1x clotted sample to JamesCookUniversityHospital)
- VHL gene, Epo receptor gene and other inherited causes of polycythaemia. Professor Mary-Francis MacMullin, Consultant Haematologist, or Dr Melanie Percy, ClinicalScientist,(melanie.percy@belfasttrust.hscni.net) Department of Haematology, C Floor, Tower Block, Belfast City Hospital Lisburn Road, Belfast BT9 7AD (phone: 028 90 263733)

References


SECTION 9

GUIDELINES FOR MANAGEMENT OF CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL) AND LYMPHOPROLIFERATIVE DISORDERS

GUIDELINES FOR MANAGEMENT OF CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL) AND LYMPHOPROLIFERATIVE DISORDERS
Investigation of asymptomatic lymphocytosis

- Routine requesting of immunophenotyping for the investigation of asymptomatic lymphocytosis should only be requested when the total lymphocyte count is greater than 10x10^9/L.
- Full blood count monitoring every 3-6 months should be recommended for those who are asymptomatic and have a total lymphocyte count < 10x10^9/L.
- Symptomatic patients or patients with lymphocytosis and associated cytopenias or patients with lymphadenopathy/hepatosplenomealy should be investigated as clinically indicated following clinical assessment.

CHRONIC LYMPHOCYTIC LEUKAEMIA

Diagnostic Criteria

A definitive diagnosis of CLL is based on the combination of a lymphocytosis and characteristic lymphocyte immunophenotype.

Scoring system for the diagnosis of CLL

<table>
<thead>
<tr>
<th>marker</th>
<th>score: 1</th>
<th>score: 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD5 positive</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>CD23 positive</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>FMC7 negative</td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td>SmIg weak</td>
<td>strong</td>
<td></td>
</tr>
<tr>
<td>membrane CD22/CD79b weak</td>
<td>strong</td>
<td></td>
</tr>
</tbody>
</table>

Scores for CLL range from 3 to 5 and non-CLL cases from 0 to 2.

Prognostic factors

<table>
<thead>
<tr>
<th>factor</th>
<th>low risk</th>
<th>high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic abnormalities</td>
<td>▪ None</td>
<td>▪ loss/ mutation of p53*</td>
</tr>
<tr>
<td></td>
<td>▪ del 13q (sole)</td>
<td>▪ del 11q23</td>
</tr>
<tr>
<td>ZAP-70</td>
<td>▪ negative</td>
<td>▪ positive</td>
</tr>
<tr>
<td>IgVH gene status</td>
<td>▪ mutated</td>
<td>▪ unmutated</td>
</tr>
<tr>
<td>CD23</td>
<td>▪ -</td>
<td>▪ negative</td>
</tr>
<tr>
<td>Richter’s transformation</td>
<td>▪ -</td>
<td>▪ present</td>
</tr>
</tbody>
</table>

*p53 abnormalities predict a poor response to alkylating agents, purine analogues and rituximab monotherapy but not to high-dose steroids or alemtuzumab.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Frequency (stage A patients)</th>
<th>Median time to treatment (years)</th>
<th>Median survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>&gt;50%</td>
<td>&gt;5-10</td>
<td>&gt;15-20</td>
</tr>
<tr>
<td>17p deletion</td>
<td>4-7%</td>
<td>&lt;1</td>
<td>2-4</td>
</tr>
<tr>
<td>11q deletion</td>
<td>10-15%</td>
<td>1-2</td>
<td>6-9</td>
</tr>
<tr>
<td>Germline IgV_{H} (&gt;98%)</td>
<td>25-40%</td>
<td>&lt;4</td>
<td>8-9</td>
</tr>
<tr>
<td>ZAP-70 expression</td>
<td>20-50%</td>
<td>3-4</td>
<td>8-10</td>
</tr>
<tr>
<td>CD38 expression</td>
<td>25-40%</td>
<td>&lt;4</td>
<td>8-10</td>
</tr>
</tbody>
</table>
Investigations

Baseline investigations

1. Full blood count
2. Immunophenotyping of peripheral blood lymphocytes
3. Renal and liver biochemistry (including urate level)
4. Calculation of Binet/ Rai stage

Other recommended investigations

1. Serum Immunoglobulins – consideration of IVlg replacement
2. Pneumococcal and HiB immunity testing with vaccination in those not immune
3. Direct antiglobulin test (DAT) and reticulocyte count are essential in all anaemic patients and before starting treatment.
4. Bone marrow aspirate and trephine biopsy if:
   - phenotypically atypical CLL (atypical morphology and low CLL score)
   - for investigation of cytopenias
5. Lymph node biopsy is indicated if:
   - the diagnosis is uncertain from the peripheral blood and bone marrow examinations.
6. CT-scans/US is indicated:
   - where the finding of intrathoracic or bulky intra-abdominal disease would influence the need for, or choice of, therapy
   - if the presence of splenomegaly is uncertain on physical examination
   - to determine remission status following treatment in patients with bulky nodes prior to therapy
7. FISH cytogenetics on peripheral blood for 17p (p53) loss/mutation, 11q23 abnormality (ATM), chromosome 12/ trisomy 12 and del 13q.
   - at time of requiring treatment as a minimum in patients fit for intensive treatment.
   - Consider performing at diagnosis in young patients to help advise on likely prognosis

Staging of CLL

Binet stage

A  < 3 lymphoid areas*
B  > 3 lymphoid areas
C  Hb < 10 g/dL or platelet < 100x10^9/L

*The five lymphoid areas comprise unilateral or bilateral cervical, axillary and inguinal lymphadenopathy, hepatomegaly and splenomegaly.
Management of CLL

All newly diagnosed patients with CLL should have their management defined by a formal Multi-Disciplinary Team Meeting.

Monoclonal B-lymphocytosis (CLL phenotype) – MBL-CLL

MBL-CLL is defined as the presence of a CLL immunophenotype with lymphocyte count <5x10^9/L and no lymphadenopathy or organomegaly.

These patients should have their blood counts, constitutional symptoms, lymph node enlargement, liver and spleen size monitored every 3 to 6 months in the first year and, if stable, annually thereafter. The regular follow-up can be performed in the local haematology clinic or by the patient’s general practitioner.

Early stage (Binet A) CLL

Treatment is not indicated for patients with early stage CLL regardless of the prognostic markers at presentation.

Patients with low risk CLL (see Prognostic factors) are monitored as MBL-CLL.

Patients with high risk CLL should be monitored every 3 months in the haematology clinic. Only after a period of time with stable disease, should the intervals between patient’s follow-up visits be extended.

Advanced stage CLL requiring therapy (Binet B and C) = WCLL2008 criteria used for trials

- Progressive marrow failure due to bone marrow infiltration by CLL
  - Haemoglobin <10 g/dL
  - Platelets <100 x 10^9/L
- Massive or progressive lymphadenopathy (cluster >10 cm diameter)
- Massive (>6cm below costal margin) or progressive splenomegaly
- Progressive lymphocytosis >50% increase over 2 months or lymphocyte doubling time <6 months
- Systemic symptoms:
  - Weight loss >10% in previous 6 months
  - Fever >38°C for >2 weeks in the absence of infection
  - Extreme fatigue – cannot work or unable to perform usual activity = ECOG 2 or worse
  - Severe night sweats in the absence of infection
- Autoimmune cytopenias which are poorly controlled by corticosteroids
**Recommendations for initial therapy in CLL**

The choice of therapy should be judged according to the performance status, co-morbidities and desires of the patient. Patients known to have p53 mutation/deletion in >20% of cells are unlikely to respond to following standard therapies and should be considered for treatments recommended for fludarabine-refractory disease. All patients should be screened for HIV/Hep B and Hep C and appropriate supportive therapy initiated if positive prior to commencing therapy. Advice from Infectious disease/hepatologist as indicated.

Options:

1) Gold standard first line therapy for those adequately fit to receive it. German CLL8 trial has demonstrated improved Progression free survival, overall survival and early evidence suggests that some patients with mutated immunoglobulin gene (low risk) CLL may be cured of their disease (Fischer et al, Blood, Jan 2016, Thompson et al, Blood, Jan 2016)

    Fludarabine 24 mg/m² oral for 5 days (breakfast time)
    Cyclophosphamide 150 mg/m²oral for 5 days (lunchtime)
    Rituximab 500 mg/m² IV infusion (375 mg/m² for cycle 1)

28 Day cycle, aim to give 6 cycles. Blood products must be irradiated.
If WCC >30, then rituximab dose should be split over 2 days (100mg on day1, the rest on day 2)

2) Bendamustine is recommended in patients for whom fludarabine combination chemotherapy is not appropriate. Effects can be enhanced by the addition of rituximab (funded by standard commissioning). Outcomes of BR not far behind FCR. May be more beneficial for patients to receive full dose BR which is associated with less toxicity rather than abbreviated/attenuated FCR although this has not been tested in a direct head to head clinical trial.

    Bendamustine 100 mg/m² IV infusion, over 30–60 mins on days 1,2
    28 day cycle, aim to give 6 cycles. Blood products must be irradiated.

    Bendamustine/ Rituximab combination
    Bendamustine 70-90mg/m² IV infusion over 30-60 mins on days 1,2
    Rituximab 500mg/m² IV infusion (375mg/m² for cycle 1)

28 day cycle, aim to give 6 cycles. Blood products must be irradiated

3) Chlorambucil is indicated for elderly patients and those with significant co-morbid conditions considered inappropriate for fludarabine combination or bendamustine therapy.

    Chlorambucil 10mg/m² od orally for 7 days
    28 day cycle, continue up to 12 cycles according to response/tolerance. Prolonged treatment is associated with longer PFS – median about 12 months.

4) Addition of anti-CD20 immunotherapy to chlorambucil therapy as above improves responses and PFS.
Options:  a) add IV Rituximab 500mg/m² day 1 of each cycle (375mg/m² in cycle 1)

    • 6 to 12 cycles as tolerated
• Median PFS 15-23 months trials (Hillmen et Al phase 2 trial, German CLL 11 trial – NB chlorambucil dose different)
• Minimal additional toxicity

b) add Ofatumumab 300mg IV day 1, 1000mg day8 of cycle 1, then 1000mg day 1 of each subsequent cycle
• 6 to 12 cycles as tolerated
• Median PFS 23 months (Complement 1 trial)
• Minimal additional toxicity, well tolerated

c) add Obinutuzumab 1000mg – type 2 anti-CD20 antibody
• IV cycle 1 days 1/2(dose divided), day 8, day 15, then day 1 for subsequent cycles
• 6 cycles as per German CLL 11 trial
• Median PFS 29 months (NB lower dose of chlorambucil used)
• Time to next treatment may 42.7 months in Feb 15 but data still immature – may offer prolonged treatment free interval to frail population
• Increased infusion reactions seen in CLL 11 trial – can be managed by stopping BP medication and use of Methylpred or dexamethasone because reactions do not respond to hydrocortisone as used for other anti-CD20 agents
• Well tolerated in the frail elderly trial population

Relapsed but not refractory CLL (fludarabine-sensitive relapse) – patients fit for further chemoimmunotherapy

• Patients who relapse more than 24 months after completion of fludarabine based therapy should be considered for repeat chemoimmunotherapy if they are fit enough to receive it
• Patients who relapse more than 12 months after completion of Bendamustine or chlorambucil therapy should be considered for repeat chemoimmunotherapy treatment if they are fit enough to receive it.
• Bendamustine is no longer funded by the CDF for second or subsequent line therapy – removed from CDF in November 2015
• Therefore options for second line chemoimmunotherapy are FCR or chlorambucil/ rituximab
• Currently Obinutuzumab and Ofatumumab are only funded as first line therapy. Therefore rituximab should be considered for second line and subsequent therapies which is funded through standard commissioning.
• Patients relapsing less than 24 months after fludarabine-combination therapy should be considered for alternative therapies recommended for fludarabine-refractory CLL.
• all patients at relapse should have cytogenetic testing to test of p53 mutation/ deletion and considered for appropriate therapy if positive
• Patients who are considered eligible for either conventional myeloablative or reduced intensity conditioning allogeneic stem cell transplantation should be discussed with the Newcastle Transplant team after initial therapy (if they have adverse prognostic features) or following second-line therapy.

Relapsed CLL – Patients not fit for further chemoimmunotherapy
See options of Idelalisib/ Ibrutinib below
Fludarabine-refractory CLL or TP53 deleted/ mutated CLL

Fludarabine-refractory/ p53 deleted CLL has a poor prognosis of 12 to 24 months. Patients who are eligible for allogeneic transplantation should be discussed with Newcastle Transplant centre and attempts initiated to find a suitable donor. Patient should only proceed to transplant if remission can be achieved with clearance of the disease from the bone marrow by morphological assessment (complete response), otherwise disease has high risk of relapse.

Treatment options to induce remission:

1) Alemtuzumab in combination with high dose methylprednisolone (1g/m2).

Alemtuzumab is now only available through a compassionate use programme from Genzyme. Subcutaneous administration is equally effective as IV administration and more convenient for the patient

Alemtuzumab 3 mg on day 1, 10 mg on day 2, 30 mg on day 3, and 30 mg three times weekly thereafter, up to a maximum of 16 weeks. Methylprednisolone 1g/m2 IV, days 1-5 repeated every 4 weeks

- Prophylaxis against Pneumocystis jiroveci pneumonia and herpesvirus infection should be initiated during therapy and continued following the completion of treatment for four months.

- Blood products must be irradiated lifelong.

- A weekly blood test for CMV by PCR is recommended until 2 months after completion of treatment. If CMV becomes detectable by PCR, alemtuzumab must be withheld and treatment with ganciclovir or valganciclovir be considered, especially when there are clinical features suggestive of active CMV infection, and/or a high (>1x10⁴), persistent or increasing viral load. Guidance from a Virologist is recommended. Alemtuzumab may be restarted using an incremental dosing schedule when CMV becomes undetectable.

2) Ofatumumab is no longer funded for treatment of refractory CLL

3) Idelalisib/ Rituximab

- Idelalisib was approved for the treatment of 17p deleted or TP53 mutated CLL in October 2015
  - An interim analysis of trials in front line CLL and indolent lymphomas by Gilead in March 2016 identified a toxicity signal – increased mortality from infection in the idelalisib arms. This has precipitated a review of the idelalisib EMA drug licence. Gilead have stopped all front line CLL and indolent lymphoma trials
  - Following the above, first line idelalisib treatment is not recommended pending an EMA review of the licence
  - Patients who are already receiving idelalisib are recommended to receive PCP prophylaxis and CMV PCR monitoring because of an increase of these infections seen in the trials
- Idelalisib/ Rituximab is recommended for CLL patients who require second or subsequent treatment within 24 months of previous treatment – NICE approved
- Treatment
  - Idelalisib is continued longterm until disease progression – standard dose 150mg bd
  - Rituximab IV 375mg/m2 week1, 500mg/m2 weeks 3, 5, 7, 9, 11, 15, 19
• Risk of autoimmune side-effects in addition to increased infections—rashes, colitis, pneumonitis which tend to occur in the first 6-12 months. Early diarrhoea common and may settle through dose interruption and reintroduction

4) Ibrutinib

• Currently funded by the cancer drug fund pending further NICE appraisal

• Indications
  o Considered not appropriate for treatment or retreatment with purine analogue based therapy due to
    ▪ Failure to respond to chemoimmunotherapy OR
    ▪ Disease free interval of less than 3 years OR
    ▪ Age 70 years or more OR
    ▪ Age 65 years or more plus presence of comorbidities
    ▪ 17p deletion or TP53 mutation
  o Performance status ECOG 0-2
  o Neutrophils >= 75 x10 9/L
  o Platelets >= 30 x 10 9/L
  o Patient not on warfarin (or other anticoagulant) because ibrutinib associated with impaired platelet function or CYP3A4/5 inhibitors
  o No prior treatment with idelalisib unless idelalisib has had to be stopped within 6 months because of toxicity and in the clear absence of disease progression

• Further NICE assessment of Ibrutinib is CLL is expected in June 2016

Allogeneic haemopoietic stem cell transplantation (allo-HSCT)
See Transplantation section for indications/ recommendations of when to perform in CLL

• A significant graft-versus-CLL effect with long-term disease free survival is achievable following allo-HSCT but transplant-related morbidity and mortality are high.

• Patients who are possible candidates for allo-HSCT should be referred to transplant team in Newcastle.

• Allo-HSCT may be considered only if the patient has poor-risk disease either according to biological characteristics of the disease or because it is refractory to fludarabine.

Clinical Trials

The UK has an excellent reputation for the delivery of high quality clinical trials overseen by the UK CLRN CLL Clinical trials committee. The trial portfolio is constantly evolving.

Please contact Dr Scott Marshall to discuss current availability of trials in the Northeast scott.marshall3@nhs.net

There are multiple new therapies with potent action coming available in CLL that we hope to bring to the Northeast in clinical trials eg Ibrutinib, GS1101 (CAL-101). For any trials not available locally, many more are available in Leeds and can be accessed via Prof Peter Hillmen. peter.hillmen@nhs.net
Current trials open in the Northeast

1) FLAIR trial – front line treatment of CLL in patients fit for Fludarabine therapy
   - Open at Gateshead – only centre in Northeast
   - Ibrutinib/ Rituximab vs FCR – uses MRD to assess disease response
   - Currently does not accept 17p deleted/TP53 mutated disease but amendments in progress to develop additional investigational arms including venetoclax. Planned that such patients will be included following the amendment

2) RIALTO trial – front line treatment of CLL in patients not fit for fludarabine therapy
   - Chlorambucil/ Ofatumumab vs Bendamustine/ Ofatumumab
   - Idelalisib arms now closed to new patients recruited
   - 17p deleted/ TP53 mutated not currently excluded

3) Galactic trial – assessment of consolidation treatment with Obinutuzumab offered to patients who have achieved at least a partial response to treatment and who remain MRD positive after treatment
   - Opened to patients after first, second or third line of therapy
   - Previous consolidation phase II trials with alemtuzumab showed significant improvement in disease control for many months
   - Obinutuzumab given IV 1000mg weekly for 4 weeks then 2 weekly for further 4 doses
   - Phase III trial - Patients who are MRD positive are randomized to receive consolidation or no consolidation
   - Planned to open in Sunderland by June 2016 – only centre in the Northeast

Summary of CLL Trials Portfolio (February 2016):

<table>
<thead>
<tr>
<th>Patients considered fit for FCR (previously untreated)</th>
<th>Recently Closed Trials in follow-up</th>
<th>Currently Open or soon to Open Trials</th>
<th>Future Planned Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloodwise IclICLLe (Ibrutinib)</td>
<td>CLL10 (FLAIR) – Phase III Ibrutinib-R vs FCR</td>
<td>FLAIR amendment</td>
<td></td>
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<tr>
<td>Bloodwise TAP (CALiBRe [Idelalisib monotherapy])</td>
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<td>Bloodwise TAP (CALiBRe [Idelalisib])</td>
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<td>Bloodwise IclICLLe (Ibrutinib)</td>
<td>RiAItO (Chl-Of vs Benda-Of – +/- idelalisib or placebo)</td>
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<td>PCYC-1130 (Chl+obinutuzumab vs ibrutinib+obinutuzumab)</td>
<td>Acerta ACE-007 (Chl+obinutuzumab vs ACP-196+obinutuzumab vs ACP-196)</td>
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<td>Bloodwise TAP (CALiBRe [Idelalisib])</td>
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<td>Gilead CLL 312-0133 Study – idelalisib + rituximab in 17p del front-line</td>
<td>Acerta ACE-007 (Chl+obinutuzumab vs ACP-196+obinutuzumab vs ACP-196)</td>
<td>FLAIR amendment</td>
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<td>CLL210 (OfaDexRev)</td>
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<tr>
<td>17p deleted CLL (previously untreated)</td>
<td>GALACTIC (CLL8; Obinutuzumab consolidation)</td>
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<td>Consolidation</td>
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<td>Bloodwise TAP CyCLLe (CyA/heavy glucose)</td>
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<td>Richter’s Transformation</td>
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<td>CHOP-OR (CLL211)</td>
<td>NCRN 3130: Acerta ACE-CL-001: Phase 1, of ACP-</td>
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<td>?ACP-196 Bloodwise TAP Trial</td>
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<td>Study Details</td>
<td>Clinical Trials</td>
<td>Eligibility</td>
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<tr>
<td>Relapsed CLL</td>
<td>Bloodwise IcICLLe (Ibrutinib) NCRN 3130: Acerta ACE-CL-001: Phase 1, of ACP-196 in CLL</td>
<td>COSMIC (CLL212)</td>
<td>Bloodwise CLARITY (formerly IcICLLe3) (Ibrutinib + venetoclax)</td>
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<td>ACERTA ACE-006 (ACP-196 vs ibrutinib)</td>
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<td>Bloodwise TAP (CALiBRe [Idelalisib])</td>
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<td>Bloodwise IcICLLe amendment (Ibrutinib + obinutuzumab)</td>
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<tr>
<td>Refractory CLL</td>
<td>Bloodwise IcICLLe (Ibrutinib) CLL210 (OfaDexRev) NCRN460: GP28331 (GDC-199 + obinutuzumab in rel/refr CLL)</td>
<td>ACERTA ACE-006 (ACP-196 vs ibrutinib)</td>
<td>Bloodwise CLARITY (formerly IcICLLe3) (Ibrutinib + ABT-199)</td>
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<td>Bloodwise TAP (CALiBRe [Idelalisib]; ?open March 2015)</td>
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<td>Bloodwise IcICLLe amendment (Ibrutinib + obinutuzumab)</td>
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<td>Bloodwise IcICLLe amendment (Ibrutinib + obinutuzumab)</td>
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<tr>
<td>Relapsed 11q del CLL (T-PLL)</td>
<td>PiCLe (PARP inhibitor)</td>
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CLL TREATMENT ALGORITHM

CLL

- Therapy required
  - Yes
  - CONSIDER CLINICAL TRIAL
  - First line treatment according to Performance status/ Cytogenetics

- No
  - Poor risk prognostic factors
    - 3 month review
    - CONSIDER CLINICAL TRIAL

- No progression
  - 6 month annual follow up by GP
  - If early signs of progression consider treatment

- 3 monthly review
  - Clinical trial

Assessment of Response – length of disease control correlates with depth of response

RELAPSE/PROGRESSION REQUIRING TREATMENT

- CONSIDER CLINICAL TRIAL

- Consider length of response to previous treatment

  - Good response – consider repeat treatment
  - Poor response – consider alternative treatment
  - Fludarabine resistance

- CONSIDER CLINICAL TRIAL

Consider appropriate treatments
Consider suitability of allogeneic transplant and refer to Newcastle on proving that patient has therapy responsive disease

Proceed to transplant if CR achieved, donor available and patient fit!
HAIRY CELL LEUKAEMIA

Diagnosis

1. Cytopenias
2. Splenomegaly
   - Hairy cells in blood or bone marrow. Peripheral blood to be assessed for diagnostic morphology + monocytopenia
   - Bone marrow biopsy with special stains on sections: CD20, DBA44, TRAP
     - Flow cytometry on PB or BM cell suspensions with a panel of McAbs:
       - B-cell panel: CD19, CD20, CD22, Smlg
       - HCL panel: CD11c, CD25, CD103, HC2
   - Molecular Studies: assess for presence of BRAF mutation

Indications for treatment

1. Systemic symptoms
2. Significant cytopenias (Hb <12 g/dL, Neutrophils <1.5x10^9/L, Platelets <100x10^9/L)

Treatment

At presentation:
- Cladribine (Litak®) 0.14mg/kg SC daily for 5 days.
- Pentostatin 4 mg/m^2 IV every 2 weeks until maximum response plus 1 or 2 extra injections may be used as an alternative.
- If pancytopenic, consider treatment with interferon alfa to improve blood counts before purine analogues, but this is usually not necessary.

All blood products administered are to be irradiated, and *Pneumocystis jiroveci* prophylaxis is indicated for at least 6 months after therapy completed or until CD4 count exceeds 200/mm^3^.

At relapse:
- Repeat administration of initial therapy.
- If resistance develops, the alternative therapy can be used eg Pentostatin if cladribine used previously.
- Rituximab 375mg/m^2 weekly for 8 weeks is recommended in the current BCSH guidelines (2012), funding for this has been confirmed by NHS-England..

Other treatment options:
- Splenectomy may be considered for
- Symptomatic splenomegaly (massive enlargement, pain, infarction, rupture)
- Pancytopenia which is still present after other treatments.
- As a temporising measure in symptomatic pregnant women.

The response to splenectomy is maintained for a median of 20 months, approximately one-half have disease progression within five years, and the overall survival at five years is 60 to 70 percent.
T-PROLYMPHOCYTIC LEUKAEMIA

Diagnostic Criteria

- Immunophenotype: CD2+, CD3+, CD4+, CD5+, CD7+, TCRαβ+, HLA-DR-.
- Expression of CD52 antigen should be demonstrated in all cases for therapeutic purposes.
- All cases must have TCR gene rearrangement studies.
- High proportion of cases show inv(14) by cytogenetics.

Primary Treatment

- Alemtuzumab to maximum response for patients without CNS disease or possibly significant effusions.
- Conventional or reduced intensity allogeneic transplant for eligible patients
- Drainage of pleural effusion and/or ascites due to T-PLL is recommended at the beginning of treatment to reduce tumour mass.

Refractory Disease

- Consider higher doses of alemtuzumab or combination therapy of alemtuzumab with cytotoxic chemotherapy.

Relapse Treatment

- Repeat treatment with alemtuzumab may be appropriate (confirm that leukaemia cells express CD52)
- Low response rates to purine analogues reported but may be considered in refractory patients.
WALDENSTRÖM MACROGLOBULINAEMIA

Waldenström macroglobulinaemia is a low grade lymphoplasmacytic non-Hodgkin lymphoma seen in association with an IgM monoclonal protein of any concentration. The MYD88L265P mutation is seen in approximately 90% of patients with Waldenstroms or non-IgM-secreting lymphoplasmacytic lymphoma, however this mutation is also found in smaller numbers (~5-10%) of splenic marginal zone lymphoma and IgM MGUS.

Diagnostic criteria for Waldenström macroglobulinaemia (WM)
- IgM monoclonal gammopathy of any concentration
- Bone marrow infiltration by small lymphocytes showing plasmacytoid / plasma cell differentiation. Intertrabecular pattern of bone marrow infiltration
- Surface IgM+, CD5-, CD10-, CD19+, CD20+, CD22weak, CD23-, CD25+, CD27+, FMC7+, CD103-, CD138- immunophenotype

If end-organ damage is present then patients are classified as having Waldenström macroglobulinaemia. Otherwise smouldering WM (IgM >30g/dl and / or marrow infiltration >10%) or IgM MGUS (IgM <30g/dl and <10% marrow infiltration).

Patients are said to have an IgM-related disorder if IgM MGUS and symptoms due to the paraprotein. Such symptoms can include hyperviscosity, cold agglutinins, cryoglobulinaemia, autoimmune disease, neuropathy or amyloidosis.

Prognosis is by the ISSWM. Risk factors (1 point for each) are: age >65yr; β2 microglobulin >3mg/L; paraprotein >70g/L; Hb <115g/L and platelets <100 x10^9/L. Risk is low 0-1 (unless age), intermediate (2) or high (3-5). Five year survival is 87% if low-risk, 68% intermediate or 36% high-risk.

Treatment
- BCSH guidance recommends baseline haemophilus influenza type B and pneumococcus vaccination, as well as annual influenza vaccination. Vaccination should be avoided, if possible, 2 weeks prior to, during and for 6 months after chemo-immunotherapy.
- Therapy should currently be reserved for patients who are symptomatic or in whom there is haematological suppression or clear evidence of disease progression.
- The aim of treatment should be to improve the quality and duration of life with minimal side-effects in the most cost-effective manner. It is not yet clear that achievement of a complete remission confers clinical benefit, and it is possible that prolonging therapy to maximal response may increase toxicity without extra benefit.

The BCSH (2014) and IWWM-7 (2014) guidelines both suggest that:
- Rituximab combinations (e.g. DRC, R-bendamustine) are recommended first therapies in patients who can tolerate this treatment. BCSH guidance also suggests fludarabine combinations as possible first-line therapy, although there is concern about toxicity.
- At relapse can treat with similar agents or fludarabine combinations (e.g. R-fludarabine, R-FC, R-cladribine). Consider R-CHOP if evidence of high grade transformation (younger patients should be discussed with a transplant centre).

- Chlorambucil, with or without prednisolone, is often used as the initial therapy for frail or elderly patients. Responses are usually slow but toxicity is minimal providing that the dose is adjusted if cytopenias ensue.

- Rituximab is active in the treatment of WM but associated with the risk of transient IgM flare so should be used with caution in patients with symptoms of hyperviscosity and / or IgM levels >40 g/L.

- Bendamustine is available via the Cancer Drug Fund as first line therapy, or for relapsed / refractory patients who are unable to receive R-CHOP, R-FC or high dose therapy. Since the previous guideline update, bortezomib is no longer available via the CDF.

- Plasma exchange (1-2 treatments of 1.5-2.0 plasma volumes) is indicated for the acute management of patients with symptomatic hyperviscosity symptoms.
GUIDELINES FOR THE MANAGEMENT OF LOW-GRADE NON-HODGKIN LYMPHOMA
FOLLICULAR LYMPHOMA

Histological features

Follicular lymphoma is a tumour of the germinal centre cell that in lymph nodes shows a follicular growth pattern.

In lymph node biopsy specimens the following features must be present:

- The tumour must contain a mixture of cells with the morphology of centrocytes and centroblasts. Centrocytes predominate generally.
  
  Grade 1/2    0-5 centroblasts/hpf  
  Grade 2    6-15 centroblasts/hpf  
  Grade 3A    >15 centroblasts/hpf with centrocytes present  
  Grade 3B    >15 centroblasts/hpf with solid sheets of centroblasts

- The tumour must have a germinal centre phenotype:
  - Immunocytochemistry: CD20+, CD79+, CD10+, BCL-6+, CD23variable
  - BCL-2 expression and/or t(14;18) by FISH or PCR.
  - Partially or wholly follicular growth pattern.

**Histological grade 3B**

Treat as for diffuse large B cell lymphoma (DLBCL).

Follicular lymphoma International Prognostic Index

Score 1 for each of the following:

- Age > 60 years
- Hb <12g/dL
- Elevated LDH
- Stage III/IV disease
- Nodal sites >4

<table>
<thead>
<tr>
<th>FLIPI Risk Group</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>0-1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
</tr>
<tr>
<td>Poor</td>
<td>≥3</td>
</tr>
</tbody>
</table>

Essential Investigations

- FLIPI calculated for all patients (BCSH guidelines 2011 suggest recording of FLIPI2)
- CT scan of thorax, abdomen, pelvis (and neck if clinically involved)
- PET-CT scan for stage I
- Bone marrow biopsy
- HIV, hepatitis B and hepatitis C serology

Primary Treatment

*Early stage (Stage 1 and Stage II where involved nodes are contiguous and can be encompassed in a single radiation field)*

There is some evidence that patients with early stage disease may be cured of their disease. Patients with early stage follicular NHL, confirmed by PET-CT scan, should be referred for consideration of radiotherapy.

*Advanced stage (Stages II (where radiotherapy is not appropriate)-IV)*
‘Active monitoring’ in asymptomatic patients with stage II disease where disease can not be encompassed in a single radiotherapy field.

Rituximab-containing regimen e.g. for the majority of patients. R-CHOP is preferred by some groups following publication of the PRIMA trial data but R-CVP is still the standard in many MDT’s. Suggest that physician/patient choice is taken into account when choosing the front line regimen for new patients starting treatment

Bendamustine plus rituximab has also been approved by the cancer drug fund (Bendamustine funded from CDF, Rituximab from NHS–England) as first line treatment though given that bendamustine does not have a licence for this indication, clinical governance decisions would need to be taken in conjunction with the patient and the local Trust in regard to its use in this setting.

Chlorambucil (with or without rituximab) should be considered if other therapies are not tolerated.

Patients who achieve complete remission after first-line chemotherapy containing rituximab should be treated with subcutaneous rituximab maintenance therapy 1400mg every 2 months for 2 years.

High Grade transformed follicular lymphoma

This includes patients presenting in transformation and those relapsing with transformed disease.

Investigate and treat as for DLBCL.

CHOP-R should be given as primary therapy.

CNS prophylaxis should be considered using the same criteria as for DLBCL.

Those previously treated with CHOP should receive salvage regimen e.g. IVE, DHAP, ESHAP.

Consider autologous haemopoietic stem cell transplant in suitable patients achieving CR.

Relapsed Follicular Lymphoma

Patients not considered suitable for high dose therapy

If rituximab-naïve, treat with rituximab-containing regimen.

If remission > 1 year with original regimen consider re-treating with same (care needed with total anthracycline dose if R-CHOP was used)

If intolerant or poor duration of response with initial regimen, then suitable regimens include fludarabine/cyclophosphamide, chlorambucil +/- steroids or R-CHOP.

Clinical Trials.

Currently there are several clinical trials for patients with recurrent follicular (and other histological subtypes of low grade lymphoma), open across the region: in Newcastle, Sunderland and Carlisle. Investigational agents will vary as will inclusion and exclusion criteria so MDT discussion, and dialogue with the research representative of the MDT is recommended.

See list below

Maintenance Rituximab

Rituximab maintenance therapy is indicated for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without rituximab. It is given every 3 months until disease progression or for a maximum period of 2 years.
Patients considered suitable for high dose therapy

- High dose therapy should be considered in all patients <65 years who achieve CR after treatment of relapse.
- Allogeneic transplant may be an option in highly selected patients. Consider transplant referral in patients of suitable age with a view to transplant in second or subsequent CR.

Second and subsequent relapse

There are a number of treatment options which will depend on previous treatment, response duration and performance status.

Options include:

- Repeating previous treatments if response >1 year
- Using regimens listed above not so far used
- Radiotherapy
- Idelalisib (available via an early access program) can be considered for relapsed and refractory disease that is refractory to at least 2 prior lines of rituximab or alkylating agent chemotherapy.
- Palliative/best supportive care
- Clinical trial

NRCl-badge Clinical Trials for Follicular Lymphoma available in the network

- Dose Optimization Study of Idelalisib in Follicular and Small Lymphocytic Lymphoma.
- A Study of PF-05280586 (Rituximab-Pfizer) or MabThera (Rituximab-EU) for the first-line treatment of patients with CD20-positive, low tumor burden, follicular lymphoma (REFLECTIONS B328-06).open in Sunderland
- A Phase 3, Randomized, Parallel-Group, Active-Controlled,Double-Blind Study to Compare Efficacy and Safety between CTP10and Rituxan in Patients with Low Tumour Burden Follicular Lymphoma
MARGINAL ZONE B CELL LYMPHOMA

Marginal zone B cell lymphoma has 3 distinct clinical presentations:

- Localised extranodal disease – stomach, intestine, thyroid, skin and salivary glands (MALTomas)
- Splenic marginal zone lymphoma (SMZL) with or without circulating villous lymphocytes and marrow disease
- Solitary nodal disease; this is sometimes associated with occult extranodal involvement

Diagnostic Criteria

Immunophenotype: CD5-, CD10-, CD19+, CD20+, CD23-, slgM+, slgD+ or -, BCL6 -

Investigations

- Immunophenotyping of circulating lymphoma cells
- Biopsy of involved tissue
- Bone marrow aspirate and trephine
- CT scan of thorax, abdomen and pelvis (and neck if clinically involved)
- LDH
- HIV, hepatitis B and hepatitis C serology

Primary Treatment

- Patients with stage I disease should be referred for consideration of local radiotherapy.
- All other patients, if asymptomatic, require active monitoring (watch and wait) only.
- Splenectomy may be considered in patients with bulky symptomatic splenomegaly (see algorithm: treatment of splenic marginal zone lymphoma).
- For symptomatic systemic disease, or if the patient is not fit for splenectomy, treatment with a Rituximab containing regimen is recommended, eg R-CVP
- Maintenance rituximab 2 monthly for 2 years is routinely commissioned

Relapse Treatment

- If more than 1 year from completion of primary treatment, retreat with the same agent again.
- If within a year, alternative rituximab-containing chemotherapy is recommended.
- Consider clinical trial
- High dose therapy may be considered in younger patients with relapsed disease.
Algorithm: Treatment of Splenic Marginal Zone Lymphoma (SMZL)

1. SMZL Diagnosis
2. HCV+
   - Symptomatic/progressive disease
3. Inf/Ribavirin
   - Observe: NO, YES
     - Splenomegaly fit for surgery: NO, YES
       - Bulky adenopathy heavy marrow infiltration: NO, YES
         - Splenectomy
         - Relapse
     - Rituximab +/- chemotherapy
4. Observe: NO
GASTRIC MALTONAS

Investigations

- FBC, U&E, LFT, LDH, β2M, immunoglobulins, serum immunoelectrophoresis
- CT chest, abdomen and pelvis
- Bone marrow aspirate and trephine (optional)
- Gastric biopsy for histological diagnosis and to confirm H.pylori infection
- Endoscopic ultrasound scan of stomach to pick up non-specific mucosal alterations or a mass with no associated ulceration or disease affecting submucosa but not the mucosa
- FISH for t(11;18) or AP12-MALT1 fusion protein (Many cases have t(11;18) resulting in activation of NFκβ and H.pylori-independent MALT lymphoma. The t(11;18) is often associated with a lack of response to antibiotics.).

Lugano Staging

- I confined to GI tract
- II1 local node involvement (perigastric)
- II2 distal node involvement (more distant regional nodes)
- IIE penetration of serosa to adjacent organs/tissues
- IV disseminated extranodal involvement or supradiaphragmatic involvement

Treatment

1. Stage I and II – see algorithm
2. Stage IIE – IV or recurrence post radiotherapy

Chemotherapy options include:

- chlorambucil ± dexamethasone, +/- Rituximab
- Other Rituximab containing regimens eg R-CVP
- fludarabine-containing regimes, and
- rituximab monotherapy.

Long-term Follow up

- H.pylori negative patients who have achieved a histological response should be followed up with repeat endoscopy and biopsy from multiple sites every 6 months for at least 2 years.
- In the absence of evidence of histological progression consideration should be given to ongoing annual endoscopic surveillance as a six times increase in risk of gastric carcinoma is recognised in patients with gastric MALT lymphoma.

NRCl-badged Clinical Trials for Marginal Zone Lymphoma available in the network

**Algorithm: Treatment of Stage I and II Gastric Maltoma**

- **H. pylori eradication antibiotic therapy**
  - Restage at 3 months with endoscopy and biopsy of abnormal areas

  - **H. pylori negative**
    - **lymphoma negative**
      - Lymphoma load less or stable
        - Observe
    - **lymphoma positive**
      - Lymphoma load increased or presence of t(11,18)
        - Radiotherapy
  - **H. pylori positive**
    - **lymphoma negative**
      - Lymphoma load less or stable
        - 2nd line antibiotics
    - **lymphoma positive**
      - Lymphoma load increased or presence of t(11,18)
        - Radiotherapy

  - Restage at 6 months with endoscopy and biopsy of abnormal areas
MANTLE CELL LYMPHOMA

There is no current international consensus for treatment of this disorder, although BCSH guidelines have been published (McKay P et al, 2012).

Diagnostic criteria

Typical cases

- Monomorphic population of small- to intermediate-sized B cells
- Phenotype: sIg ++/+++ (IgM & IgD), CD5+, CD23-, CD20+
- Cyclin-D1 expression / t(11;14)

Variants

- Blastic or large cell variant associated with an aggressive clinical course

Essential investigations

- Bone marrow aspirate and trephine biopsy
- CT scan of thorax, abdomen and pelvis (and neck if clinically involved)
- Calculation of International Prognostic Index
- HIV, hepatitis B and hepatitis C serology
- Gastrointestinal investigations e.g. upper GI endoscopy / sigmoidoscopy and biopsy if the patient has GI symptoms
- Low threshold of investigation of the CNS if there are any symptoms
- PET is NOT recommended

Prognosis

The MIPI score (Hoster et al, 2008) has been validated in large patient cohorts but is cumbersome to calculate. An online calculator can be found at: http://www.european-mcl.net/en/clinical_mipi.php

A simplified MIPI score (sMIPI) is also validated in large patient cohorts (stage III or IV disease) and is easier to use. It considers age, performance status, LDH and white cell count.

<table>
<thead>
<tr>
<th>Category</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>&lt;50</td>
<td>50-59</td>
<td>60-69</td>
<td>70 or greater</td>
</tr>
<tr>
<td>Performance status</td>
<td>0-1</td>
<td></td>
<td>2-4</td>
<td></td>
</tr>
<tr>
<td>LDH (relative to ULN)</td>
<td>&lt;0.67</td>
<td>0.67-0.99</td>
<td>1.0-1.49</td>
<td>1.5 or greater</td>
</tr>
<tr>
<td>WCC (x10^9/L)</td>
<td>&lt;6.7</td>
<td>6.7-9.9</td>
<td>10-14.9</td>
<td>15 or greater</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Category</th>
<th>Median OS (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>Low risk</td>
<td>&gt;90</td>
</tr>
<tr>
<td>4-5</td>
<td>Intermediate risk</td>
<td>58</td>
</tr>
<tr>
<td>6-11</td>
<td>High risk</td>
<td>37</td>
</tr>
</tbody>
</table>
Asymptomatic disease
Watchful waiting only, no benefit to starting chemo in this group

Stage 1 disease
Radiotherapy

Primary treatment for symptomatic patients stage 2-4
Young fit patients up to the age of 65, may be considered for more aggressive therapy based on the Nordic Lymphoma Group protocol (maxi-CHOP/high dose ara-C) followed by autologous HSCT. Allogeneic HSCT may be considered in CR1.

Nordic protocol:

**Cycle 1: maxiCHOP**
Mesna 240mg/m2 IV
Cyclophosphamide 1200mg/m2
Doxorubicin 75mg/m2
Vincristine 1.4mg/m2, max 2mg
Mesna 480mg/m2 oral 2 hrs and 6 hrs post cyclo
Prednisolone 100mg oral for 5 days

**Cycles 2-4**
Rituximab 375mg/m2 D1 only
Cytarabine 3g/m2 every 12 hours for 4 doses

**Cycles 3-5**
Rituximab 375mg/m2
Mesna 240mg/m2 IV
Cyclophosphamide 1200mg/m2
Doxorubicin 75mg/m2
Vincristine 1.4mg/m2, max 2mg
Mesna 480mg/m2 oral 2 hrs and 6 hrs post cyclo
Prednisolone 100mg oral for 5 days

**Cycle 6**
Rituximab 375mg/m2 D1 and 9
Cytarabine 3g/m2 every 12 hours for 4 doses
Mobilise with gcsf starting day 5 with harvest day 14

Autologous stem cell transplant

Older patients not fit for Nordic protocol, options include:

- **VR-CAP (NICE approved TA370 based on LYM-3002 trial) for 6-8 cycles**
  1. Bortezomib 1.3mg/m2 days 1, 4, 8 and 11 (note the trial used IV bortezomib, but the network recommends subcut due to lower rates of neuropathy
  2. Rituximab 375mg/m2
  3. Cyclophosphamide 750mg/m2
  4. Doxorubicin 50mg/m2
  5. Prednisolone 100mg/m2 days 1-5

Median PFS 24 months and median survival not reached by 4.5 years,
85% grade 3 or above neutropenia,
60% any infection and 21% rate of grade 3 infection,
Bendamustine and rituximab x6-8 (StiL and Bright studies)
Bendamustine in this indication is on the cancer drugs fund for the following situations: first line treatment for mantle cell lymphoma lymphoma. Can use with rituximab which is financed through NHS England.
- Bendamustine 90mg/m² days 1 and 2 of 4 week cycle
- Rituximab 375mg/m² on day 1

Median PFS 35months.
29%-49% grade 3 or above neutropenia,
37%-53% any grade of infection

- Standard dose CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) x6 with rituximab delivered at standard dose of 375mg/m² with each course (6 doses). This however has been shown to be inferior to bendamustine and rituximab (PFS 22m vs 35 with BR)
- FC is less favoured as it is associated with higher incidence of infections and is difficult to give more treatment later.
- Patients unfit for the above will be treated at the physician’s discretion, e.g. R-chlorambucil

Maintenance rituximab is not routinely commissioned following these therapies

All Patients who respond to chemotherapy induction are eligible for rituximab maintenance every 2 months for 2 years, funded by NHS England

Relapse treatment

- Patients in second or subsequent response may be eligible for clinical trials.
- Ibrutinib is available via CDF and will be the preferred second line option for many patients.
The indications on the CDF are as below:
  1. Relapsed/refractory mantle cell
  2. Failure to achieve at least a partial response or progression after last chemo
  3. ECOG 0-2
  4. Has received at least 1 but no more than 5 previous lines of chemotherapy
- Consider allograft once in second remission
GUIDELINES FOR THE MANAGEMENT OF HIGH GRADE B CELL NON-HODGKIN LYMPHOMA (NHL)

These guidelines will cover the management of:

- Diffuse large B cell lymphoma (DLBCL), including primary cerebral lymphomas
- Burkitt lymphoma
- Primary mediastinal large B cell lymphoma

DIFFUSE LARGE B CELL LYMPHOMA (DLBCL)

1. **Investigations**
   - Full blood count
   - Renal and liver function tests, bone profile, urate
   - Lactate dehydrogenase
   - HIV, hepatitis B and hepatitis C serology
   - Bone marrow aspirate and trephine biopsy for staging, if widespread disease, abnormal blood count or clinical suspicion of bone marrow infiltration by low grade lymphoma
   - CT scan of the chest, abdomen and pelvis (neck, nasopharyngeal areas and sinuses as clinically indicated)
   - Baseline FDG-PET/CT scan – when treatment is given with a curative intent
   - Measured or estimated creatinine clearance if serum creatinine abnormal
   - Assessment of left ventricular function by MUGA or Echocardiogram for patients with previous cardiac history or age > 60 years

2. **International Prognostic Index (IPI)**
   
The IPI should be calculated to allow risk group assignment, and will aid in the counselling of patients and their families. Either the index for all patients or the age-adjusted index (for patients < or > 60 years) may be used. The age adjusted IPI only uses three factors: LDH, stage and performance status.

Criteria:

- age > 60 years
- LDH above normal range
- > 1 extranodal site
- Clinical stage III or IV disease
- ECOG performance status 2-4

**Risk groups are assigned as follows:**

<table>
<thead>
<tr>
<th>Number of risk factors:</th>
<th>All patients</th>
<th>Age adjusted IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0,1</td>
<td>0</td>
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<tr>
<td>Low/intermediate</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>High/intermediate</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>High</td>
<td>4,5</td>
<td>3</td>
</tr>
</tbody>
</table>
Prognosis can be estimated according to risk group:

For all patients:

<table>
<thead>
<tr>
<th>IPI risk group</th>
<th>CR(%)</th>
<th>RFS(%,5yrs)</th>
<th>OS(%,5yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>87</td>
<td>70</td>
<td>73</td>
</tr>
<tr>
<td>Low/intermediate</td>
<td>67</td>
<td>50</td>
<td>51</td>
</tr>
<tr>
<td>High/intermediate</td>
<td>55</td>
<td>49</td>
<td>43</td>
</tr>
<tr>
<td>High</td>
<td>44</td>
<td>40</td>
<td>26</td>
</tr>
</tbody>
</table>

For aged 60 years or under:

<table>
<thead>
<tr>
<th>IPI risk group</th>
<th>CR(%)</th>
<th>RFS(%,5yrs)</th>
<th>OS(%,5yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>92</td>
<td>86</td>
<td>83</td>
</tr>
<tr>
<td>Low/intermediate</td>
<td>78</td>
<td>69</td>
<td>66</td>
</tr>
<tr>
<td>High/intermediate</td>
<td>57</td>
<td>53</td>
<td>46</td>
</tr>
<tr>
<td>High</td>
<td>46</td>
<td>58</td>
<td>32</td>
</tr>
</tbody>
</table>

For aged > 60 years:

<table>
<thead>
<tr>
<th>IPI risk group</th>
<th>CR(%)</th>
<th>RFS(%,5yrs)</th>
<th>OS(%,5yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>91</td>
<td>46</td>
<td>56</td>
</tr>
<tr>
<td>Low/intermediate</td>
<td>71</td>
<td>45</td>
<td>44</td>
</tr>
<tr>
<td>High/intermediate</td>
<td>56</td>
<td>41</td>
<td>37</td>
</tr>
<tr>
<td>High</td>
<td>36</td>
<td>37</td>
<td>21</td>
</tr>
</tbody>
</table>

3. Treatment of non-bulky stage IA disease

Non-bulky stage IA disease is treated by a combined modality approach, with 3 cycles of CHOP or CHOP-R followed by involved field radiotherapy.

4. Treatment of all other patients

4.1 Patients Eligible for Clinical Trials

There are currently no first line NCRI treatment studies open for recruitment.

Patients whose diagnostic material is deemed adequate may be approached re entry into the observational study MaPLE: Molecular profiling for lymphoma study. This study aims to aid identification of patients who may be suitable for specific targeted therapies

Patients aged between 15 and 29 are also eligible for the Non Hodkgins Lymphoma in Young Adults study: A prospective UK population-based study of incidence, treatment and outcomes of patients in the above age group with all subtypes of Non Hodgkins lymphoma diagnosed between January 2015 and December 2017.
4.2 Management of Non-trial Patients

All new patients should be discussed at MDT for review of histology and imaging to inform the treatment plan. Staging CT and PET are required unless there are clinical reasons why PET cannot be performed as planned. The MDT proforma should document any sites of bulk disease and bony involvement. The current recommendation is treatment with the CHOP-R-21 regime. The usual total number of cycles intended should be 6, with a repeat CT scan after 3 cycles to confirm disease response. This should be modified depending on stage as outlined below. Earlier scanning may be required if there is a suspicion of clinical non-response or disease progression. Patients with bone marrow involvement pre-treatment may need a repeat bone marrow examination at the end of treatment to confirm a complete response. PET-CT scan 4-6 weeks post R-CHOP cycle 6 is the preferred method of assessing disease response for those patients with no features of bulk and no bone involvement.

5. Indications for Radiotherapy

Stages IA-IIA

- Usually 3 cycles of CHOP or CHOP-R plus involved field radiotherapy are recommended.

Stages IIB-IV

- Radiotherapy may be given to sites of residual tumour activity (as assessed by PET-CT scan) following chemotherapy to convert PR to CR or good PR, sometimes followed by high dose chemotherapy with stem cell rescue as consolidation.
- Radiotherapy may also be useful to salvage localised sites of relapse.
- The role of radiotherapy to initial bulk disease following a chemotherapy-induced metabolic CR is evolving. Such patients should be discussed at MDT. In general for patients with initial bulk disease (>7.5cm) radiotherapy to the site of original bulk should be considered at the end of 6 cycles of CHOP-R with a PET CT on approximately day 21 of cycle 6 and a further PET CT 12/52 after radiotherapy is completed (this final PET-CT can be omitted if the PETCT prior to radiotherapy commencement was negative).
- Radiotherapy should also be considered to areas of initial bone involvement with bone destruction – typically where <3 areas are involved.
- Patients with other extranodal sites of disease at presentation should have this highlighted at the initial MDT and need for radiotherapy documented on an individual basis.

Patients unfit for R-CHOP

Patients with a history of myocardial problems or with multiple co-morbidities can present a challenge for treatment. There is some evidence to suggest that in some patients a steroid pre-phase can improve performance status sufficiently to allow conventional chemotherapy to start. Other options include R-DECC, reduced dose CHOP or referral for clinical trial with novel combinations eg Inotuzumab Ozogamicin (INCA) - A multicentre randomised phase II clinical trial of Inotuzumab Ozogamicin plus Rituximab and CVP (IORCVP) versus Gemcitabine plus Rituximab and CVP (GemRCVP) for the first line treatment of patients with diffuse large B cell lymphoma who are not suitable for anthracycline containing chemotherapy)
Double Hit Lymphoma

The best treatment for this group of patients is not yet understood and there are a number of available modalities including CHOP-R plus autograft. It is very reasonable to consider DA-EPOCH-R given the data available to date, albeit mainly from a single centre. This is our preferred treatment option. Intrathecal chemotherapy prophylaxis against secondary CNS disease should be offered.

We would not routinely offer allograft in CR1 but cases can be discussed with the transplant team to provide an individualized approach in this uncertain area.

6. Treatment of relapsed disease

6.1 Intensive salvage treatment

Salvage chemotherapy regimens are available for the treatment of relapsed DLBCL but the comparative efficacy of individual regimes is very hard to ascertain. High dose chemotherapy and autologous stem cell transplant (ASCT) is generally incorporated as part of salvage treatment. The addition of rituximab is approved for relapse >12 months from initial R-CHOP chemotherapy.

Commonly used salvage regimes include:

- GDP – Gemcitabine (days 1 and 8), Cisplatin (day 1) and dexamethasone (days 1-4) (±rituximab)
- IVE – Ifosfamide (days 1-3), etoposide (days 1-3) and epirubicin (day 1) (±rituximab)
- DHAP – dexamethasone (days 1-4), high dose cytarabine (day 2), cisplatin (day 1) (± rituximab)
- ESHAP – etoposide (days 1-4), methylprednisolone (days 1-5), high dose cytarabine (day 1), cisplastin (days 1-4) (± rituximab)
- FluDAP – Fludarabine (days 2,3), dexamethasone (days 1,3), high dose cytarabine (days 2,3), cisplatin (days 2,3)

The choice of regime must be discussed and agreed at the lymphoma MDT meeting, and in this uncertain area consideration of available clinical trials is recommended.

6.2 Autologous stem cell transplantation (ASCT)

- ASCT has become part of routine intensive salvage treatment for relapsed DLBCL.
- Because under half of patients treated with ASCT will be cured, prognostic factors are important to predict outcome. An age-adjusted IPI at the time of initiation of second-line treatment is available as a predictor of event-free survival (EFS) and OS in such patients.

For patients aged 60 or under:
Risk factors:  LDH above upper limit of normal
Stage III/IV disease
ECOG performance status 2-4 or Karnofsky score =< 70

Low risk:  0 factor
Intermediate risk:  1 factor
High risk:  2 or 3 factors
6.3 Non-intensive palliative treatments

Various outpatient-based oral palliative regimes are available. Caution should be exercised as such combination regimes may be significantly myelotoxic, especially in the elderly, and lead to the risk of neutropenic sepsis.

- CEPP – cyclophosphamide (day 1), etoposide (days 1-3), procarbazine (days 1-10), prednisolone (days 1-10)
- DECC – lomustine (day 1), etoposide (days 1-3), chlorambucil (days 1-4), dexamethasone (days 1-5) (This is the new version of PECC – see page 92.)
- PIXANTRONE: NICE approval granted for use in patient who have previously received rituximab and who are requiring either 3rd or 4th line therapy.

In this area of unmet need new treatments are required and enquiry re currently available clinical trials is recommended for patients who are fit enough for further active treatment.

7. Central nervous system (CNS) prophylaxis

The BCSH has published guidelines in this area, which the MDT endorses. It should be noted that historically about 5% of patients with DLBCL develop CNS disease at relapse but this figure may be less in the Rituximab era. Optimal approach to CNS prophylaxis is uncertain.

In patients with DLBCL, CNS prophylaxis should be considered if the following features are present:

1. A raised LDH in the presence of ≥1 extranodal site of disease
   or
2. Involvement of breast, testicular or epidural tissue

CNS prophylaxis should be intrathecal methotrexate 12.5mg with each cycle of CHOP-R for 4 cycles.
The use of high-dose intravenous methotrexate is the subject of a prospective audit to evaluate likely effect on in-patient resource if adopted. Currently the decision is left to the discretion of individual clinicians and MDTs.

8. **Treatment of Primary CNS lymphoma**

Key recommendations in the investigation and management include:

- Full CT scan staging, testicular ultrasonography in elderly males, lumbar puncture for CSF analysis (including cytology, protein, glucose, flow cytometry and Ig gene rearrangement studies), examination of the anterior chamber, vitreous and fundus of the eye, and HIV serology, MRI head and MRI spine.
- Stereotactic biopsy should be carried out prior to the use of corticosteroids if at all possible.
- Prognostic score should be calculated according to age (>60 years), ECOG performance status (>1), raised LDH, raised CSF protein, and involvement of deep brain matter (Ferreri et al, 2003).

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Factors</th>
<th>2-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>4-5</td>
<td>15%</td>
</tr>
<tr>
<td>Medium</td>
<td>2-3</td>
<td>48%</td>
</tr>
<tr>
<td>Low</td>
<td>0-1</td>
<td>80%</td>
</tr>
</tbody>
</table>

- Dexamethasone may be used as short-term palliation.

- All patients sufficiently fit should be offered chemotherapy.
- Following presentation of preliminary results of the IELSG study at Lugano 2015 the recommended regime is:
  - Rituximab 375 mg/m² Day -5 and Day 0
  - Methotrexate 3,5gm/m² Day 1
  - Ara C 2 gm/m² x 2 Days 2 and 3
  - Thiotepa 30 gm/m² Day 4
  - Treatment is given every 3 weeks with repeat MRI after course 2 to ascertain response.
  - The aim is to deliver 4 cycles.
  - Consolidation with ABMT for patients achieving CR PR and SD is currently under discussion with commissioning groups and a decision is expected Q3 2016 after results from this part of the IELSG 32 study are revealed.

- Consolidative whole brain radiotherapy (WBRT) for non responders should be discussed with patients on an individual basis as the risks of neurocognitive deficit may out weigh benefits especially in those over 60 years.
- Intrathecal chemotherapy as an adjunct to high-dose MTX is not indicated.
- Treatment of relapsed or refractory disease will depend on patients performance status.
- Options include:
  - Salvage chemotherapy
  - Whole brain radiotherapy
  - Palliative steroids
Treatment of Secondary CNS Lymphoma

No consensus treatment guidelines available. Staging and investigation broadly in line with those listed under Primary CNS lymphoma.

Treatment options will depend on nature of CNS involvement e.g. meningeal or space occupying lesion and on treatment intent. In most patients this is likely to be a palliative situation and symptom control is paramount. Options could include intra-thecal chemotherapy for meningeal disease, chemotherapy or radiotherapy. Suggest MDT discussion to guide treatment decisions.

Clinical trial currently in set up for patients in this situation

IELSG 42: An international Phase 11 trial assessing tolerability and efficacy of sequential Methorexate-Aracytin-based combination and R-ICE combination, followed by high-dose chemotherapy supported by autologous stem cell transplant, in patients with systemic B-cell lymphoma with central nervous system involvement at diagnosis or relapse (MARIETTA regimen)

BURKITT LYMPHOMA

This malignancy is defined as a germinal centre cell lymphoma with deregulation of the c-myc oncogene, and absence of other balanced translocations. There is an association with HIV infection and this should be tested for prior to chemotherapy.

It is characterised by:

- morphologically, large B cells with round nuclei, central nucleoli and vacuolated cytoplasm
- immunohistochemically, SmIg+, CD10+, bcl-6+, bcl-2-, high proliferation index Ki67 (≈100%) and evidence of apoptosis, and
- cytogenetically, t(8;14) or variants by FISH.

Primary treatment:

- Patients must be treated at a BCSH level 2b centre or above.
- R-CODOX-M/R-IVAC regimen is recommended. Patients should be entered into clinical trial where possible.
- Rasburicase should be used before and during the first cycle of treatment. Frequent biochemical measurements paying special attention to renal function, potassium, calcium and phosphate levels should be carried out. Twice daily measurements may be required over the first few days. Urate level is rarely helpful in patients who have received rasburicase as it will almost always be unrecordable.
- There is increasing evidence that DA-EPOCH-R can be used to treat Burkitt Lymphoma effectively. Whilst we have not moved wholesale to this approach, DA-EPOCH-R is easier to tolerate than R-CODOX-M or R-IVAC and thus could be considered in some patients thought unfit for the latter regimens

Relapsed disease:

- There is no consensus or trial. The outcome is very poor.
PRIMARY MEDIASTINAL LARGE B CELL LYMPHOMA (PMLBCL)

PMLBCL is a distinct clinico-pathological entity recognised by the WHO. Pathologically it is derived from B cells, but has clinico-pathological features and molecular characteristics reminiscent of nodular sclerosis classical Hodgkin lymphoma.

Primary treatment:

- Using historical comparisons, dose-dense and dose-intense regimens may be more effective than CHOP chemotherapy (before the advent of rituximab), but there is no phase III trial data to support this.
- Currently DA EPOCH-R, CHOP-R or R-MACOP-B as primary treatments for PMLBCL are all used.
- It is recommended where possible that patients are entered into the IELSG 37 clinical trial: A randomised, open-label, multicentre, two-arm Phase 111 comparative study assessing the role of mediastinal radiotherapy after Rituximab containing chemotherapy regimens to patients with newly diagnosed Primary Mediastinal Large B-Cell Lymphoma (PMLBCL). This study is using a PET directed approach to answer the question of whether radiotherapy is required in those patients who become PET negative after primary chemotherapy.
- Outside a clinical trial our current chemotherapy preference is for DA EPOCH-R but it is reasonable for clinicians to discuss choice of regimen on a case by case basis with patients.
- Upfront ASCT has been used with success, with one study reporting 15 patients with DFS of 93% after a median follow-up of 35 months. However its use has been declining with documented improved outcomes using more up to date chemotherapy regimens and it is recommended that individual requests are discussed with the transplant centre. ASCT is not part of the IELSG treatment protocol. Consolidation radiotherapy may be considered for patients who presented with bulky disease. PET scan may inform decision making for consolidation radiotherapy: see IELSG 37 information above

Salvage treatment:

- Treatment failures tend to occur within the first 6-12 months. Relapses beyond 2 years are rare. Salvage treatments should be as for DLBCL.

References:

- NICE website: www.nice.org.uk
GUIDELINES FOR MANAGEMENT OF HODGKIN LYMPHOMA

PROGNOSTIC INDICES - HODGKIN LYMPHOMA

Early Stage Hodgkin lymphoma

Patients with stage I and II disease have an excellent prognosis and the treatment is aiming to optimise disease control whilst minimising long term toxicities associated with treatment.

Optimal disease control is with combined modality therapy and for most patients this approach should be used.

The German Hodgkin Study Group GHD10 and HD11 stratified patients into early favourable, early unfavourable and advanced groups as below.

**GHSG Criteria for Hodgkin Disease**

<table>
<thead>
<tr>
<th>Early Favourable</th>
<th>Stage I or II without risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Unfavourable</td>
<td>Stage I or II A with ≥ 1 risk factors or Stage II B with risk factors C/D but not A/B</td>
</tr>
<tr>
<td>Advanced</td>
<td>Stage II B with risk factors A/B or Stage III or IV</td>
</tr>
</tbody>
</table>

**Risk Factors**

- **A**: Large Mediastinal Mass
- **B**: Extranodal Disease
- **C**: Elevated ESR
- **D**: ≥ 3 nodal areas

Large Mediastinal Mass: >1/3 horizontal chest diameter
Elevated ESR: ≥50 without B symptoms or >30 in presence of B symptoms

**Lymph node areas as defined by GHSG**

- Area A: right cervical + right infra-/supra-clavicular/nuchal lymph nodes
- Area B: right cervical + right infra-/supra-clavicular/nuchal lymph nodes
- Area C: right/ left hilar + mediastinal lymph nodes
- Area D: right axillary lymph nodes
- Area E: left axillary lymph nodes
- Area F: lymph nodes of the upper abdomen (spleen hilum, liver hilum, coeliacal)
- Area G: lymph nodes of the lower abdomen (spleen hilum, liver hilum, coeliacal)
- Area H: right iliac lymph nodes
- Area I: left iliac lymph nodes
- Area K: right inguinal + femoral lymph nodes
- Area L: left inguinal + femoral lymph nodes
Early favourable disease

The majority of patients with early stage disease should have combined modality therapy as it is associated with better disease control than chemotherapy or radiotherapy alone.

In the HD 10 trial (Engert et al NEJM 2010; 363:640-653) patients who received 2 courses of ABVD with 20Gy involved field radiotherapy (IFRT) had a 5 year freedom from treatment failure of 97% and 5 year overall survival (OS) 92%. There was no benefit demonstrated in the more intensive treatment arms.

There are some situations associated with a higher risk of the late effects of radiotherapy, for example a women in her early twenties with a radiation field involving breast tissue. In this situation a “RAPID” approach could be considered.

A “RAPID” approach algorithm to consider if concerns regarding long term effects of radiotherapy:

This approach following the RAPID protocol (Radford et al NEJM 2015; 372:1598-1607) will be associated with a reduction of PFS of 6% (RAPID data per protocol analysis) but in a patient who is able to tolerate salvage therapy and in whom you wish to avoid radiotherapy it could be considered. Patients who may be eligible for a “RAPID” approach should discuss the risks of radiotherapy with a clinical oncologist at diagnosis.

The patient following a “RAPID” approach should be made aware that 25% of patients will be PET positive after the 3rd cycle of ABVD and will require a further cycle of ABVD and radiotherapy as opposed to a German approach of 2 X ABVD plus 20Gy IFRT.
Early unfavourable disease

Patients should receive 4 X ABVD with IFRT as per the HD11 trial (Eich et al JCO 2010;28(27):4199-4206) which demonstrated 95% OS at 8 years.

In some patients with stage II unfavourable disease there are geographically distant nodes which would require a large radiotherapy field. In this situation 6 X ABVD following the RATHL protocol should be considered following a discussion with a Clinical Oncologist.

PET scanning in early Hodgkin lymphoma

- All patients should have a baseline PET scan.
- The treatment pathway decision should be made as diagnosis.
- For patients following a German Approach (ie 2X ABVD with 20Gy IFRT for early favourable or 4 X ABVD for early unfavourable) there is no requirement for an interim PET scan. An end of treatment PET scan should be done 3 months after completion of radiotherapy.
- For patients in whom you are hoping to avoid radiotherapy and are following a “RAPID” approach, a PET scan is required 10-12 days following the 3rd course of ABVD. If this is negative (in this situation Deaville score 1 or 2) then no further imaging is required. If the PET scan is positive the patient will have a further course of ABVD and IFRT and a further end of treatment PET scan is required 3 months following completion of the radiotherapy.
Advanced Hodgkin Lymphoma

For patients with stage III and IV disease, the majority will be treated as per the RATHL protocol as in the following algorithm:

**Baseline PET scan**

- **ABVD X 2**

**PET scan day 9-13 after second cycle ABVD**

- **PET negative** (Deauville 1, 2 and 3)
  - **4 X AVD (remove bleomycin)**
  - **Bulk disease (>10cm, or thoracic ratio at T5/6 >0.33) at diagnosis and radiotherapy to bulk planned**
    - **No**
      - **End of treatment PET scan 6 weeks post chemotherapy**
    - **Yes**
      - **PET scan 3 weeks post chemotherapy then radiotherapy* to site of initial bulk disease** (This decision should be made upfront at initial MDT, patient should discuss with Clinical Oncologist during chemotherapy if individual risk /benefit not clear as evidence is limited)
      - **End of treatment PET scan 3 months post radiotherapy**

- **PET positive** (Deauville 4 and 5)
  - **4 X escalated BEACOPP**

*See appendix

Note: If the PET scan after 2 courses of ABVD is negative then the RATHL data suggests there is non-inferiority in the group of patients who had bleomycin removed. This group of patients should therefore receive 4 more courses of AVD.

With 34 months median follow-up, this RATHL protocol demonstrated an 82% progression-free survival and 95% overall survival.
Intensification of treatment up front with escalated BEACOPP

There are some patients with high IPI (see appendix) stage IV disease in whom a discussion about using 6 courses of escalated BEACOPP as per the German Hodgkin Study Group HD15 trial should be undertaken. This approach is associated with increased PFS and a meta-analysis has suggested that there is a 10% overall survival benefit.

It should be noted that there have only been 4 small trials directly comparing escalated BEACOPP with ABVD. Escalated BEACOPP is associated with significant toxicity in comparison to ABVD and should be given with caution to patients over 45 years of age. It is also associated with higher infertility when compared with ABVD and a risk/benefit discussion should be undertaken with the patient.

* See appendix
Hodgkin lymphoma in older patients

Fit patients should be treated with AVD (caution with bleomycin over 60 years of age, see appendix) or VEPMB (protocol used in SHIELD study, Proctor et al Blood 2012;119:6005-6015)

Other options include CHLVPP (chlorambucil, vinblastine, procarbazine, prednisolone) although this is associated with an inferior response rate but it is less toxic for patients.
Management of relapsed classical Hodgkin lymphoma

- A biopsy should be performed to confirm relapse and the patient staged with CT and PET
- Relapse greater than 5 years from initial disease could be treated as new disease
- Consider radiotherapy or combined modality if limited disease
- If patient unfit consider radiotherapy, palliative chemo eg DECC/CHLVPP/, brentuximab if eligible or steroids for symptom control
- Patients who are fit should have salvage regimen such as DHAP (dexamethasone, cisplatin and cytarabine) or IVE (Ifosfamide, etoposide and epirubicin) there is no evidence that there is one salvage regimen that is better than others.
- A CT scan should be done after 2 courses of first line salvage to ensure response (or earlier if concerns about response). A total of 3 courses should be given and then a PET scan 3 weeks after 3rd salvage. If PET negativity achieved then a BEAM auto performed.
- If a patient achieves a complete metabolic remission (CMR) on PET prior to autograft then they will have an event free survival of >80% (Moskowitz et al Blood 2010;116,4934-4937) even if they require 2 lines of salvage chemotherapy to achieve PET negativity. If first line salvage does not achieve PET negativity then second line salvage should be given.
- Brentuximab vedotin can be given if the patient has had 2 prior lines of therapy. There is no evidence available as to whether second line salvage chemotherapy or brentuximab vedotin should be used although most UK centres use a second salvage chemotherapy. If brentuximab vedotin is used, a PET scan should be done after 6 cycles and proceed to autograft if CMR achieved.
- Allogeneic transplant should be considered if the patient has relapsed post autograft or has disease which is chemotherapy responsive to salvage treatment but has not achieved a negative PET scan.
Algorithm for relapsed disease

1. Repeat biopsy
2. Stage with PET CT scan
3. Patient fit for salvage chemotherapy?
   - Yes
     - Salvage chemo (rarely radiotherapy alone if limited disease)
     - Responding? (CT after 2 courses or earlier if clinical concern)
       - Yes
         - Complete 3 courses of first-line salvage
         - PET scan
           - PET negative
           - PET positive
         - Second-line salvage chemotherapy
         - PET scan
           - PET negative
           - PET positive
         - Third-line salvage chemotherapy, brentuximab vedotin or salvage radiotherapy
         - Disease response
           - Yes
             - Autograft
           - No
             - Allograft
       - No
         - Consider radiotherapy, depending on site of relapse
         - Radiotherapy appropriate
           - Yes
             - Options include brentuximab vedotin if eligible, DECC/CHLVPP or palliative steroids
           - No
             - Clinical trial using checkpoint inhibition or palliation
             - Radiotherapy
Reduction of the late effects of treatment

Breast screening

Indications for Referral
- Women treated with mantle irradiation aged under 35 years, or other irradiation which included breast tissue, are at increased risk of breast cancer from 8 years after treatment.
- Women should be referred for screening from 8 years after radiotherapy if aged under 35 years at the time of treatment.

Screening Policy
- Under 30 years at referral – MRI scan and education in breast self-examination and importance of early investigation of any breast problems.
- 30-35 years baseline mammogram to assess breast density then annual mammography if suitable.
- 35-50 years annual mammography.
- >50 years National Breast Screening Programme.

Thyroid dysfunction

Patients have a 30% chance of hypothyroidism after radiotherapy to the neck (greater if >30 Gy given). Annual thyroid function tests required.

Smoking cessation advice

Patients have 4-11 x the age-matched population risk of developing lung cancer. This “normalises” if they are non-smokers.

Malignant Melanoma

Risk increases to 5-8 x normal if the patient is exposed to sun burn.

Osteoporosis

Women and men both have decreased bone density. 10% of patients who have had combined modality treatment may develop osteoporosis.

References
Appendix

Deauville 5 point score
An internationally recommended scale for reporting of PET scans. The score is based on 2 visual reference points of the individual patient relating to FDG uptake.

- Deauville 1: No uptake
- Deauville 2: Slight uptake but below blood pool (mediastinum)
- Deauville 3: Uptake above mediastinal but below or equal to uptake in the liver
- Deauville 4: Uptake slightly to moderately higher than the liver
- Deauville 5: Markedly increased uptake in comparison to liver.

Deauville 1 and 2 relate to a complete metabolic remission and 4 and 5 probable disease or relapse. Deauville 3 is usually a negative score unless it is used in a “de-escalation” study such as the RAPID study when it is positive. A Deauville score of 3 in the RATHL study was negative due to the escalation nature of the protocol.

Bleomycin
The risk factors for bleomycin induced pneumonitis include:
- age over 40 years
- smoking and pre-existing lung disease
- Impaired renal function.

Patients receiving bleomycin should have baseline pulmonary function tests (PFTs) including TCLO. If respiratory symptoms or basal crepitations develop then the PFTs should be repeated and the bleomycin stopped if there is a greater than 10% reduction in TLCO. It should be used with caution in patients over the age of 60 years.

International prognostic index (Hasenclever Score)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin &lt;40 g/L</td>
<td>1</td>
</tr>
<tr>
<td>haemoglobin &lt; 10.5 g/dL</td>
<td>1</td>
</tr>
<tr>
<td>Male sex</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 45 years</td>
<td>1</td>
</tr>
<tr>
<td>Stage IV disease</td>
<td>1</td>
</tr>
<tr>
<td>WCC&gt; 15 x 10⁹/L</td>
<td>1</td>
</tr>
<tr>
<td>Lymphocytes &lt; 0.6 x 10⁹/L</td>
<td>1</td>
</tr>
</tbody>
</table>

Score 1 point for each factor

PFS (by points)

<table>
<thead>
<tr>
<th>Score</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>84%</td>
</tr>
<tr>
<td>1</td>
<td>77%</td>
</tr>
<tr>
<td>2</td>
<td>67%</td>
</tr>
<tr>
<td>3</td>
<td>60%</td>
</tr>
<tr>
<td>4</td>
<td>51%</td>
</tr>
<tr>
<td>≥5</td>
<td>42%</td>
</tr>
</tbody>
</table>


Radiotherapy dose/volume
Involved field radiotherapy. 30Gy in 15 fractions to sites of residual masses after chemotherapy 30Gy in 15 fractions to sites of initial bulk disease.
Use of PET in Hodgkins – additional notes

1. This flow chart is only a guide.

2. Risk scoring – If PVACEBOP is your preferred high dose treatment then SNLG index should be performed as a minimum. If RATHL style treatment is your preferred high dose treatment then use Hasencleaver. Many people now calculate both, which seems sensible.

3. Risk factors:
   a. B symptoms,
   b. high ESR
   c. bulky disease >10cm, mediastinal mass >1/3 of thorax,
   d. E stage,
   e. >50 years old

4. Stage 2 disease – it is a clinical decision for each patient as to whether you follow the localised disease pathway or not. If the disease is limited to one radiotherapy field and there are no risk factors and the patient is likely to tolerate radiotherapy then sensible to treat as early stage disease. If the stage 2 disease has geographically distant nodes (not in one radiotherapy field), has risk factors or you would rather avoid radiotherapy (eg female <35yrs with mediastinal disease), then sensible to treat with chemo eg6 ABVD.

5. Guidance on how to interpret intermediate PET score of 3
   a. PET-CT score 3 after 3 cycles of ABVD (RAPID Study – give 4th ABVD and IFRT – in other words taken as a positive result and not enough evidence to affect standard of care).
   b. PET score 3 after 2 cycles of ABVD – proceed with another 4 cycles ABVD (RATHL protocol = continue to 6 ABVD if the PET after 2 cycles = score 3 ie not enough evidence to escalate treatment).
   c. Any further PET questions should be discussed at the MDT when discussing the patient. All scenarios of PET results cannot be summarised here
NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA (NLPHL)

NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA (NLPHL) – BCSH guidelines 2015

Key Issues
- Recognised as a separate disease entity from classical Hodgkin lymphoma
- Indolent disease, 75% present with early stage disease.
- Data on treatment and outcomes confused by inclusion of most cases in trials with classical Hodgkin lymphoma
- Possible role of Rituximab as single agent therapy (Ekstrand et al, 2003)

Diagnostic Criteria
LPNHL is clinically, pathologically and prognostically distinct from classical Hodgkin lymphoma.
- Immunophenotype: CD20+, CD30-, BCL-6+, CD79+, CD15-, Bob1+/ Oct2+++ 
- 5-14% of cases transform to diffuse large B cell lymphoma (DLBCL).

Essential investigations
- Bone marrow biopsy only indicated if there is abnormal bone signal on the PET scan
- Staging CT and PET scanning of neck, thorax, abdomen and pelvis
- Note a PET is not recommended at the end of treatment, even if the CT indicates partial remission as the disease process is so indolent
- All patients should be listed for irradiated blood products

Primary Treatment
Stage I A and limited IIA(with 1-2 sites of disease)
- Following complete resection, no treatment is an option, after discussion with radiation oncologists
- Involved field radiotherapy for other patients

All other patients
- Advanced stage LPNHL is unusual at presentation.
- B symptoms and splenic involvement are rare and if present the possibility of transformed disease should be considered.
- Bone marrow involvement extremely rare
- There is no RCT to support the use of rituximab in all the below regimes, however BCSH guidelines recommend its use given the efficacy in other CD-20 positive lymphomas
- The distinction between disseminated LPNHL and the T-cell rich variant of DLBCL may be difficult and is to some extent arbitrary.

1. Asymptomatic – watch and wait
2. Symptomatic – there are several options:
   - R-ABVD
   - R-CVP
   - R-CHOP especially if there are concerns about transformation to high grade NHL
   - R monotherapy if serious co-morbidities, however remissions are short lived
- Rituximab maintenance is not recommended for patients responding to chemo

Relapse treatment
- Re-biopsy is essential, as reactive lymph nodes are common.
Asymptomatic – watch and wait

Symptomatic
1. If long remission from previous chemo then treat with the same again, adding in rituximab if not previously received.
2. If shorter remission then consider another chemo option from those outlined above
3. If there are concerns about aggressive or high grade disease RCHOP is recommended
4. Multiply relapsed disease with previous exposure to combination chemo, consider a more intensive regime and autologous stem cell transplant
5. Consider rituximab monotherapy if not suitable for chemotherapy, however remissions are short lived

Patients <19yrs old
- Full resection – watch and wait
- Unresectable early stage disease – Radiotherapy for fully grown adolescents only, otherwise chemotherapy is preferred eg CVinP x 3. It is recommended to liaise with the TYA team and radiation oncologists.
- Advanced disease – as per adult

Chemo regimes:
- Rituximab monotherapy – weekly x 4 375mg/m2, with possibility of repeating every 6 months for 2 years
- R-CVP and RCHOP regimes are the same as for follicular NHL
- R-ABVD – rituximab is given day 1 375mg/m2, then ABVD as per classical hodgkins
- CVinP
  o prednisolone 40mg/m2 days 1-6
  o vinblastine 6mg/m2 max of 9mg, days 1 and 8
  o cyclophosphamide 500mg/m2 day 1
GUIDELINES FOR THE MANAGEMENT OF MATURE T-CELL AND NK-CELL NEOPLASMS

Please see recently written BCSH guidelines:
 SECTION 14

GUIDELINES FOR MANAGEMENT OF PLASMA CELL MYELOMA

Diagnostic criteria

<table>
<thead>
<tr>
<th>MGUS</th>
<th>Asymptomatic myeloma</th>
<th>Symptomatic myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-protein in serum &lt;30 g/L</td>
<td>M-protein in serum &gt;30 g/L and/or</td>
<td>M-protein in serum and/or urine**</td>
</tr>
<tr>
<td>Bone marrow clonal plasma cells &lt;10 % and low level of plasma cell infiltration on trephine biopsy</td>
<td>Bone marrow clonal plasma cells &gt;10 %</td>
<td>Bone marrow (clonal) plasma cells or biopsy proven plasmacytoma</td>
</tr>
<tr>
<td>No myeloma-related organ or tissue impairment (including bone lesions) or symptoms</td>
<td>No myeloma-related organ or tissue impairment (including bone lesions) or symptoms</td>
<td>Myeloma-related organ or tissue impairment (including bone lesions)</td>
</tr>
<tr>
<td>No evidence of other B-cell proliferative disorders or light-chain associated amyloidosis or other light-chain, heavy-chain or immunoglobulin-associated tissue damage*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Myeloma Related Organ or Tissue Impairment ROTI

<table>
<thead>
<tr>
<th>Clinical effects due to myeloma</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased calcium levels</td>
<td>Corrected serum calcium &gt;0.25mmol/L above the upper limit of normal or &gt;2.75mmol/L</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Attributable to myeloma</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Haemoglobin 2 g/dL below the lower limit of normal or haemoglobin &lt;10 g/dL</td>
</tr>
<tr>
<td>Bone lesions</td>
<td>Lytic lesions or osteoporosis with compression fractures (MRI or CT may clarify)</td>
</tr>
<tr>
<td>Other</td>
<td>Symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (&gt; 2 episodes in 12 months)</td>
</tr>
</tbody>
</table>

Prognostic Factors

Poor indicators are:

- Peripheral blood plasma cells > 1x 10^6/L
- 13q- by cytogenetics, 4:14 translocation 4:16 translocation by FISH, 17P Abnormalities.
- β2 microglobulin > 5.5mg/L
- LDH greater than upper limit of normal
### International Staging System (ISS)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Median survival in months</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Serum ß2 microglobulin &lt; 3.5 mg/L (296 nmol/L) and Serum albumin &gt; 3.5 g/dL (35g/L or 532 µmol/L)</td>
<td>62 months</td>
</tr>
<tr>
<td>II</td>
<td>Neither I or III*</td>
<td>45 months</td>
</tr>
<tr>
<td>III</td>
<td>Serum ß2 microglobulin &gt; 5.5 mg/L (465 nmol/L)</td>
<td>29 months</td>
</tr>
</tbody>
</table>

### Investigations

<table>
<thead>
<tr>
<th>Screening tests</th>
<th>Tests to establish diagnosis</th>
<th>Tests to estimate tumour burden and prognosis</th>
<th>Tests to assess myeloma-related organ impairment (ROTI)</th>
<th>Special tests indicated in some patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full blood count (FBC)</td>
<td>Bone marrow aspirate + trephine biopsy with plasma cell phenotyping</td>
<td>Bone marrow cytogenetics and/or fluorescence in situ hybridisation (FISH) analysis in selected patients</td>
<td>FBC</td>
<td></td>
</tr>
<tr>
<td>ESR or plasma viscosity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum urea and creatinine, calcium, albumin</td>
<td>Immunofixation of serum and urine</td>
<td>Quantification of monoclonal protein in serum and urine</td>
<td>Serum urea and creatinine</td>
<td>Serum free light chains assay in oligosecretory, light chain only and non-secretory disease</td>
</tr>
<tr>
<td>Electrophoresis of serum and concentrated urine</td>
<td></td>
<td>Albumin</td>
<td>Creatinine clearance (measured or calculated)</td>
<td></td>
</tr>
<tr>
<td>Quantification of non-isotypic immunoglobulins</td>
<td></td>
<td>ß2 microglobulin</td>
<td>Calcium</td>
<td></td>
</tr>
<tr>
<td>X-ray of symptomatic areas</td>
<td>Skeletal survey</td>
<td>Skeletal survey</td>
<td>Albumin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Plasma viscosity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tissue biopsy (or fat pad aspirate) for amyloid (if suspected)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Quantification of non-isotypic immunoglobulins</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Magnetic resonance imaging (MRI)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Computerised tomography (CT) scan</td>
</tr>
</tbody>
</table>
**International Myeloma Working Group: Response Criteria**

<table>
<thead>
<tr>
<th>Subcategory</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>No M-protein detected in serum or urine by immunofixation for a minimum of 6 weeks AND Fewer than 5% plasma cells in bone marrow</td>
</tr>
<tr>
<td>Partial response</td>
<td>&gt;50% reduction in serum M-protein level AND/OR 90% reduction in urine free light chain excretion or reduction to &lt;200 mg/24 h for 6 weeks</td>
</tr>
<tr>
<td>Minimal response</td>
<td>25–49% reduction in serum M-protein level AND/OR 50–89% reduction in urine free light chain excretion which still exceeds 200 mg/24 h for 6 weeks</td>
</tr>
<tr>
<td>No change</td>
<td>Not meeting the criteria of either minimal response or progressive disease</td>
</tr>
<tr>
<td>Plateau</td>
<td>No evidence of continuing myeloma-related organ or tissue damage &lt;25% change M-protein levels and light chain excretion for 3 months</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>Requires at least one of the following – &gt;25% increase in serum M-protein in 3 months (absolute increase must be &gt;5g/L) &gt;25% increase in urine M-protein in 3 months (absolute increase must be &gt;200mg/24hr) &gt;25% increase in the difference between involved and uninvolved SFLC levels (applicable only to patients without measurable serum and urine M-protein. Absolute increase must be &gt;10mg/dL) &gt;25% increase in bone marrow plasma cell percentage (absolute percentage must be &gt;10%) Development of new bone lesions or soft tissue plasmacytoma Development of hypercalcaemia</td>
</tr>
<tr>
<td>Clinical relapse</td>
<td>Requires at least one of the following – Development of new bone lesions or soft tissue plasmacytoma Increase in size of existing plasmacytomas or bone lesions Any of the following attributable to myeloma – Development of hypercalcaemia Development of anaemia (drop in Hb of &gt;2g/dL) Rise in serum creatinine</td>
</tr>
<tr>
<td>Relapse from CR</td>
<td>Requires at least one of the following – Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of &gt;5% plasma cells in the bone marrow Appearance of any other sign of progression</td>
</tr>
</tbody>
</table>

**Indications for Treatment**

- Chemotherapy is indicated for the management of symptomatic myeloma defined by the presence of ROTI.
- Chemotherapy should also be considered for patients with rising M-protein in the absence of ROTI.

**Bisphosphonate Therapy**

- Bisphosphonate therapy is recommended for all patients with myeloma requiring chemotherapy, whether or not bone lesions are evident.
- There is at present insufficient data to make a recommendation for the use of bisphosphonates in patients with asymptomatic myeloma.
- Zoledronic acid has been shown to be superior to other bisphosphonates with improved survival, and should be considered to be the bisphosphonate of first choice.
All patients to be stated on long term bisphosphonate should be warned of the risk of bisphosphonate induced osteonecrosis of jaw (BONJ) and its predisposing factors. Readily available and easy to read information should be offered at time of diagnosis and discussion of therapeutic options should take place.

- All patients to be started on intravenous (IV) bisphosphonate should be referred for a dental opinion (except in the emergency treatment of severe hypercalcaemia) and any teeth of poor prognosis extracted before initiation of chemotherapy.
- Patients on long-term oral bisphosphonates should beware of the potential risk of BONJ and have regular dental care and maintain excellent oral hygiene.
- Invasive dental procedures in patients on IV or long-term oral bisphosphonates should be avoided as much as possible. For patients on IV bisphosphonates specialist opinion should be sought prior to any extractions.
- Patients with suspected BONJ should be referred to a clinician with special interest and expertise in the management of this condition.

Special caution is required with all bisphosphonates in patients with moderate to severe renal failure; zoledronic acid and pamidronate are contraindicated if creatinine clearance is <30 ml/min. Zoledronic acid dose must be adjusted according to creatinine clearance.

<table>
<thead>
<tr>
<th>Baseline creatinine clearance (ml/min)</th>
<th>Recommended dose of zoledronic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>4.0 mg</td>
</tr>
<tr>
<td>50-60</td>
<td>3.5 mg</td>
</tr>
<tr>
<td>40-49</td>
<td>3.3 mg</td>
</tr>
<tr>
<td>30-39</td>
<td>3.0 mg</td>
</tr>
<tr>
<td>&lt;30</td>
<td>contraindicated</td>
</tr>
</tbody>
</table>

High Dose Therapy (HDT) and Autologous Stem Cell Transplant (ASCT)

- HDT with ASCT should be part of the primary treatment strategy in newly diagnosed patients up to the age of 70 years with adequate performance status and organ function, following initial chemotherapy (see below).
- Conditioning with melphalan alone, without TBI, is recommended. The usual dose is 200 mg/m² but the dose should be reduced in older patients (over 65-70 years) and in renal failure.

Initial Chemotherapy prior to High Dose Therapy

Recommendations

- All patients should be considered for entry into a clinical trial (Myeloma XI).
- Induction regimens should contain at least one novel agent.
- CTD is the recommended first line induction regimen.

* Cyclophosphamide 500 mg oral days 1,8,15
* Thalidomide 100 mg oral daily (increasing to 200 mg daily after 3 weeks, if tolerant)
* Dexamethasone 20 mg oral days 1-4 and 12-15

(21-day cycle, minimum 4 cycles, maximum 6 cycles)
For patients intolerant of thalidomide or for whom thalidomide is contraindicated another combination therapy containing a novel agent (e.g. bortezomib) is recommended. This is not currently routinely funded and an individual funding request to the Cancer Drug Fund would be needed outlining the exceptional circumstances of the patient.

For patients refractory to first-line therapy, a bortezomib (funded under NICE TA 129) or lenalidomide-based (funded from the CDF) induction therapy is recommended.

**Prophylaxis against venous thromboembolism (VTE) when using thalidomide and lenalidomide**

- Patients with one or more major risk factor for VTE or a previous history of VTE should be given prophylaxis with a low molecular weight heparin. The duration of thromboprophylaxis is guided by risk factors such as active disease (e.g. for the first 4 to 6 months of treatment until disease control achieved) and de-escalated or discontinued unless there are ongoing significant risk factors.
- If no other VTE risk factors, aspirin 75-150 mg o.d. may be considered as VTE prophylaxis unless contraindicated.

**Initial Chemotherapy where HDT is not planned**

All patients should be recruited into Myeloma XI trial.

For non-trial patients, the following treatments are recommended.

1. Thalidomide in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of plasma cell myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate.

   **Suggested regimes**

   **CTDa**

   - Cyclophosphamide 500 mg oral days 1,8,15,22
   - Thalidomide 50 mg oral daily (increasing by 50 mg increments every 3 weeks up to 200 mg daily, if tolerant)
   - Dexamethasone 20 mg oral days 1-4 and 15-18

   (28-day cycle, minimum 6 cycles, maximum 9 cycles)

   **Or**

   **MPT**

   - Melphalan 4mg/m² oral daily for 7 days
   - Prednisolone 40 mg/m² oral daily for 7 days
   - Thalidomide 50 mg oral daily (increasing by 50 mg increments every 28 days up to 200 mg daily, if tolerant)

2. Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma if: high-dose chemotherapy with stem cell transplantation is considered inappropriate and the person is unable to tolerate or
has contraindications to thalidomide.

**Suggested regime**

**VMP**

Bortezomib (Velcade®) 1.3 mg/m^2 subcutaneous on days 1, 4, 8, 11, 22, 25, 29, 32  
Melphalan 9mg/m^2 days 1-4  
Prednisolone 60 mg/m^2 days 1-4  
Repeat every 42 days for 4 cycles and then reduce to:

Bortezomib (Velcade®) 1.3 mg/m^2 subcutaneous on days 1, 8, 15, 22  
Melphalan 9mg/m^2 days 1-4  
Prednisolone 60 mg/m^2 days 1-4  
Repeat every 42 days, continue until signs of disease progression or unacceptable toxicity or to a maximum of 9 treatment cycles (including the previous 4). It is recommended that patients with a confirmed complete response receive 2 additional cycles of treatment beyond confirmation of this status.

All patients should receive acyclovir prophylaxis to prevent shingles.

Where bortezomib is used as second line treatment, NICE (TA129) authorisation states that if patients have failed to reach at least a 50% reduction in paraprotein after 4 cycles, there will be no funding for any further courses and the drug must be stopped. In those circumstances the manufacturers will refund the cost of the 4 cycles via the established rebate scheme (VRS).

3. For patients with significant renal impairment see below.

**Allogeneic Transplantation**

See Guidelines for Indications for Haemopoietic Stem Cell Transplantation.

**Maintenance Chemotherapy**

- Interferon alfa or single-agent corticosteroids cannot be routinely recommended.
- Maintenance with single agent thalidomide therapy may improve EFS and OS in patients who did not achieve VGPR post high-dose. The dose of thalidomide should not be higher than 150 mg and no recommendation can be made with regards to the duration of thalidomide maintenance.
- In the maintenance setting, routine anticoagulant prophylaxis is not required.
- At present, there is no evidence of benefit for the use of thalidomide maintenance in elderly patients who did not undergo autologous transplantation.

**Treatment of Relapsed Disease**

- Decision to treat should be based on the rapidity of increase of serum and/or urinary M-protein and the development of clinical symptoms or evidence of new or progressive end-organ damage.
- The most appropriate management must be determined on an individual basis depending on the timing of relapse, age, prior therapy, bone marrow function and co-morbidities and patient-centred considerations.
- Extensive clinical trials support the use of thalidomide, bortezomib, lenalidomide, or conventional chemotherapy as treatment modalities at first and subsequent relapse.
- Where clinically appropriate patients should have the opportunity to receive all of these treatment modalities.
- Clinical effectiveness of thalidomide, bortezomib and lenalidomide is not dependent on the
number of previous lines of therapy, or type of therapy previously received.

- Unless contraindicated treatment with thalidomide, bortezomib or lenalidomide treatment should be delivered with dexamethasone to increase the response rate. In some instances the addition of a further conventional chemotherapy agent (eg alkylating agent, anthracycline) may also be appropriate.
- Bendamustine can be considered if relapse occurs after lenalidomide treatment (CDF funded)
- A second autologous transplant may be considered in patients who had a good response to the initial transplant procedure (≥ 18 months to disease progression).
- Where possible, patients should be treated in the context of a clinical trial. In particular, patients with early relapse and good performance status should be considered for phase I and II trials.

Suggested regimes

For patients intolerant of thalidomide, or refractory to first-line therapy, a bortezomib-based salvage regimen is recommended.

- Bortezomib 1.3 mg /m² subcutaneous days 1, 4, 8 and 11 with dexamethasone 20-40 mg oral days 1-4 and 9-12 for 1st 4 cycle and days 1-4 only in subsequent cycles, 21 day cycle. Patients with a confirmed response receive 2 additional cycles. Responding patients who do not achieve a complete remission receive a total of 8 cycles. All patients should receive acyclovir prophylaxis.

The NICE (TA129) authorisation states that if patients have failed to reach at least a 50% reduction in paraprotein after 4 cycles, there will be no funding for any further courses and the drug must be stopped. In those circumstances the manufacturers will refund the cost of the 4 cycles via the established rebate scheme (VRS).

Where Bortezomib is used after first relapse, funding will be through the Cancer Drug Fund, otherwise the treatment will be funded directly from NHS England. The VRS only applies at first relapse.

Patients with ≥grade 2 peripheral neuropathy or intolerant of or refractory to bortezomib should receive a lenalidomide-based regimen.

- Lenalidomide 25 mg oral daily with dexamethasone 20–40 mg oral daily days 1-4, 9-12,17-20 for 4 cycles then days 1-4 thereafter until relapse.

For patients who receive lenalidomide at first relapse, the patient will be funded from the Cancer Drugs Fund. For patients treated at second or subsequent relapse the treatment will be funded by NHS England.

Treatment in patients with Renal Failure

- Dexamethasone alone can be given as initial treatment pending decisions on subsequent chemotherapy and the outcome of full supportive measures.
- If creatinine clearance remains below 10 ml/min after all appropriate renal rescue treatments (e.g. correction of hypercalcaemia, hydration), irrespective of requirement for dialysis, treatment with bortezomib and dexamethasone is recommended.

<table>
<thead>
<tr>
<th>day</th>
<th>drug</th>
<th>dose</th>
<th>route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,4,8,11</td>
<td>bortezomib</td>
<td>1.3 mg/m²</td>
<td>Iv/sc</td>
</tr>
<tr>
<td>1+2, 4+5, 8+9, 11+12</td>
<td>dexamethasone</td>
<td>20 mg</td>
<td>Po</td>
</tr>
</tbody>
</table>

A total of treatment up to 8 cycles should be given with a mid-point assessment. It is probably prudent to administer bortezomib post-dialysis although there is no firm evidence for this. Patients who receive bortezomib/dexamethasone should receive CTD/MPT on relapse.
• If creatinine clearance is above 10 ml/min, CTD/CTDa or MPT as appropriate are reasonable therapies.
  
  o Melphalan dose should be reduced by 25% in the first course if GFR < 30 ml/min and titrated against marrow toxicity in subsequent courses even in patients with severe renal impairment.
  o Cyclophosphamide dose should be reduced by 25% if the GFR is 10–50 ml/min, and of 50% if GFR is <10 ml/min. Thalidomide can be used without dose modification in patients with renal failure. Lenalidomide can be given in patients with renal impairment but dose adjustments as recommended by the manufacturer should be implemented.

• HDT and ASCT may be considered for patients with severe renal impairment (creatinine clearance /GFR < 30 ml/min) but the dose of melphalan should be reduced to a maximum of 140 mg/m². However, HDT for patients on dialysis should be discussed on a case to case basis as the mortality rate is around 20-30%, and some would argue this is too high to consider HDT as a routine standard of care for myeloma patients who are requiring dialysis.
ALGORITHM FOR FIRST LINE TREATMENT OF PLASMA CELL MYELOMA

MYELOMA – newly diagnosed

Renal failure

High dose therapy appropriate?

YES

MYELOMA XI TRIAL intensive arm

CTD or RCD, ± VCD AutoHSCT ± R maintenance

CTD AutoHSCT

NO

MYELOMA XI TRIAL non-intensive arm

CTDa or RCDa ± VCDa ± R maintenance

Intolerant or contraindicated to thalidomide

YES

VMP or VCDa

NO

MPT OR CTDa
### INDICATIONS FOR HAEMOPOIETIC STEM CELL TRANSPLANTATION

The following are indications for haemopoietic stem cell transplantation recommended by the British Society of Blood and Marrow Transplantation (www.bsbmt.org). Updated 2013

**Abbreviations**
- **S** = standard of care
- **CO** = clinical option, can be considered after assessment of risks and benefits
- **D** = developmental, further trials are needed
- **GNR** = generally not recommended

#### Chronic myeloid leukaemia (CML)

<table>
<thead>
<tr>
<th>Stage/Condition</th>
<th>Sibling transplant</th>
<th>MUD transplant</th>
<th>Autograft</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic phase</strong> -TKI refractory1 (after trial of at least 2 TKIs) -TKI tolerant (Grade 2+ toxicity to at least 2 TKIs) -T315I mutation</td>
<td>S</td>
<td>S</td>
<td>GNR</td>
</tr>
<tr>
<td></td>
<td>S</td>
<td>S</td>
<td>GNR</td>
</tr>
<tr>
<td></td>
<td>S</td>
<td>S</td>
<td>GNR</td>
</tr>
<tr>
<td><strong>Accelerated phase</strong> -after initial therapy with TKI</td>
<td>S</td>
<td>S</td>
<td>GNR</td>
</tr>
<tr>
<td><strong>Blast crisis</strong></td>
<td>GNR</td>
<td>GNR</td>
<td>GNR</td>
</tr>
<tr>
<td><strong>2nd chronic phase</strong></td>
<td>S</td>
<td>S</td>
<td>D (if Ph- cells have been stored)</td>
</tr>
</tbody>
</table>

#### Myeloma

<table>
<thead>
<tr>
<th>Stage/Condition</th>
<th>Sibling transplant</th>
<th>MUD transplant</th>
<th>First autograft</th>
<th>Second autograft</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At first response</strong></td>
<td>S</td>
<td></td>
<td>S</td>
<td>CO (Tandem autograft may be considered if no CR after 1st autograft)</td>
</tr>
<tr>
<td><strong>Relapse</strong></td>
<td>CO</td>
<td></td>
<td>S (If not done in first response but patient is considered fit)</td>
<td>S</td>
</tr>
<tr>
<td><strong>Plasma cell leukaemia</strong></td>
<td>S_{15} -If chemo responsive disease -Selected young patients &lt;55 years</td>
<td>CO_{15} -If chemo responsive disease</td>
<td>S - If no suitable donor or unfit for allograft</td>
<td>CO</td>
</tr>
</tbody>
</table>
**General Comments**

1. Generally RIC transplants are performed for patients >45-50 years of age or for patients with significant co-morbidities using the HSCT co-morbidity index or for patients with lymphoma. In the context of certain clinical trials the age for choosing a RIC transplant may be lower. Patients with a score >3 are generally not suitable for any HSCT.

2. For unrelated donor transplants usually either a full 10/10 match at HLA A, B, C and DR is required or a single mismatch.

3. Cord blood transplants are an alternative for patients lacking a sibling or unrelated donor (as defined above). Usually these patients are from ethnic minority.

**Other Plasma Cell Dyscrasias**

<table>
<thead>
<tr>
<th></th>
<th>Sibling transplant</th>
<th>MUD transplant</th>
<th>First autograft</th>
<th>Second autograft</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL amyloid</td>
<td>GNR</td>
<td>GNR</td>
<td>CO</td>
<td>GNR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>As directed by</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>National Amyloid</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Centre in</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>selected cases</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(UKATT trial)</td>
<td></td>
</tr>
<tr>
<td>POEMS</td>
<td>GNR</td>
<td>GNR</td>
<td>CO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Cases discussed</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>with Neurologists</td>
<td></td>
</tr>
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</table>

**Acute myeloid leukaemia**

<table>
<thead>
<tr>
<th></th>
<th>Sibling transplant</th>
<th>MUD transplant</th>
<th>Autograft</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>APL CR1</td>
<td>GNR</td>
<td>GNR</td>
<td>GNR</td>
<td>BCSH Guidelines</td>
</tr>
<tr>
<td>APL CR2 PCR+</td>
<td>S</td>
<td>S</td>
<td>GNR</td>
<td></td>
</tr>
<tr>
<td>APL CR2 PCR-</td>
<td>CO</td>
<td>GNR</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>AML Good Risk CR1</td>
<td>GNR</td>
<td>GNR</td>
<td>GNR</td>
<td></td>
</tr>
<tr>
<td>AML Good Risk CR2</td>
<td>S</td>
<td>S</td>
<td>CO</td>
<td>BCSH Guidelines AML15/16 protocols</td>
</tr>
<tr>
<td>AML Standard Risk CR1</td>
<td>S</td>
<td>S</td>
<td>GNR</td>
<td>AML15/16 protocols</td>
</tr>
<tr>
<td>AML Standard Risk CR2</td>
<td>S</td>
<td>S</td>
<td>CO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sibling transplant</td>
<td>MUD transplant</td>
<td>Autograft</td>
<td>Comments</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>-------------------</td>
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<td>---------------------------</td>
</tr>
<tr>
<td>AML Poor Risk* CR1</td>
<td>S</td>
<td>S</td>
<td>GNR</td>
<td>AML15/16 protocols</td>
</tr>
<tr>
<td>AML Poor Risk* CR2</td>
<td>S</td>
<td>S</td>
<td>CO</td>
<td></td>
</tr>
<tr>
<td>AML not in remission</td>
<td>CO</td>
<td>CO</td>
<td>GNR</td>
<td></td>
</tr>
</tbody>
</table>

*Poor risk defined as either 1. cytogenetics (MRC criteria), 2. secondary or therapy-related AML, 3. failure to achieve CR with standard AML induction therapy

**Acute lymphoblastic leukaemia**

<table>
<thead>
<tr>
<th></th>
<th>Sibling transplant</th>
<th>MUD transplant</th>
<th>Autograft</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1 – Standard Risk</td>
<td>$S^1$</td>
<td>GNR</td>
<td>GNR</td>
</tr>
<tr>
<td>CR1 – Poor Risk</td>
<td>$S^1$</td>
<td>CO$^2$</td>
<td>GNR</td>
</tr>
<tr>
<td>CR2</td>
<td>S</td>
<td>S</td>
<td>GNR$^3$</td>
</tr>
<tr>
<td>Not in remission</td>
<td>GNR</td>
<td>GNR</td>
<td>GNR</td>
</tr>
<tr>
<td>Ph+ ALL</td>
<td>S</td>
<td>S</td>
<td>GNR</td>
</tr>
</tbody>
</table>

1Rowe et al. (2006) Blood (ASH plenary session) 108:127, abstract No 2

2Rowe & Goldstone (2007) Blood 110:2268-2275. Poor risk is defined as adverse cytogenetics, T-ALL with WCC>100x10^9/L, MRD-positive after phase 2.

3Autografts, although inferior to chemotherapy in CR1 patients and inferior to allografts in CR2 patients, may be justified when all other therapeutic options have been explored or the optimal therapy (e.g. chemotherapy) cannot be delivered.

**Lymphoma**

**General comments**

a. An allogeneic stem cell transplant may be considered in any disease category where autologous stem cell harvesting has failed.

b. A MUD should be a 10/10, 8/8 or 9/10 allelic level match.

**Hodgkin lymphoma**

<table>
<thead>
<tr>
<th></th>
<th>Autograft</th>
<th>Sibling transplant</th>
<th>MUD transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1</td>
<td>GNR</td>
<td>GNR</td>
<td>GNR</td>
</tr>
<tr>
<td>CR&gt;1</td>
<td>S</td>
<td>CO$^1$</td>
<td>CO$^1$</td>
</tr>
<tr>
<td>Primary refractory [&lt;PR]</td>
<td>GNRGNR</td>
<td>COD</td>
<td>CO$^D$</td>
</tr>
<tr>
<td>Stable/MR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Refractory</td>
<td>Chemo sensitive</td>
<td>Progressive</td>
<td>Relapse – post-autograft</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-----------------</td>
<td>-------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td></td>
<td>S</td>
<td>GNR</td>
<td>CO</td>
</tr>
<tr>
<td></td>
<td>CO</td>
<td>GNR</td>
<td>GNR</td>
</tr>
<tr>
<td></td>
<td>CO</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

1 Patients considered at high risk of failing an auto in CR1, e.g. CR1<1 y, PET+ post-salvage, less than PR post-salvage, chemorefractory

**Mantle cell lymphoma**

<table>
<thead>
<tr>
<th></th>
<th>Autograft</th>
<th>Sibling transplant</th>
<th>MUD transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1/PR1</td>
<td>S</td>
<td>CO</td>
<td>CO</td>
</tr>
<tr>
<td>CR/PR&gt;1</td>
<td>GNR</td>
<td>GNR</td>
<td>GNR</td>
</tr>
<tr>
<td>Chemorefractory</td>
<td>CO</td>
<td>CO</td>
<td>CO</td>
</tr>
<tr>
<td>Relapse - post-autograft</td>
<td>GNR</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

**Follicular lymphoma**

<table>
<thead>
<tr>
<th></th>
<th>Autograft</th>
<th>Sibling transplant</th>
<th>MUD transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1/PR1</td>
<td>GNR</td>
<td>GNR</td>
<td>GNR</td>
</tr>
<tr>
<td>CR/PR&gt;1</td>
<td>S</td>
<td>CO</td>
<td>CO</td>
</tr>
<tr>
<td>Chemorefractory [&lt;PR]</td>
<td>GNR</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Primary Resistant -sensitive to salvage -resistant</td>
<td>CO</td>
<td>GNR</td>
<td>CO</td>
</tr>
<tr>
<td>Relapse - post-autograft</td>
<td>GNR</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

**Diffuse large B cell lymphoma**

<table>
<thead>
<tr>
<th></th>
<th>Autograft</th>
<th>Sibling transplant</th>
<th>MUD transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1</td>
<td>GNR</td>
<td>GNR</td>
<td>GNR</td>
</tr>
<tr>
<td>PR1 (sensitive to salvage)</td>
<td>CO</td>
<td>CO</td>
<td>CO</td>
</tr>
<tr>
<td>CR/PR&gt;1</td>
<td>S</td>
<td>CO</td>
<td>CO</td>
</tr>
<tr>
<td>Chemorefractory</td>
<td>GNR</td>
<td>GNR</td>
<td>GNR</td>
</tr>
<tr>
<td>Relapse - post-autograft</td>
<td>GNR</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

**Peripheral T cell lymphoma**

<table>
<thead>
<tr>
<th></th>
<th>Autograft</th>
<th>Sibling transplant</th>
<th>MUD transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1/PR1</td>
<td>CO</td>
<td>CO</td>
<td>CO</td>
</tr>
<tr>
<td>CR/PR&gt;1</td>
<td>S</td>
<td>CO</td>
<td>CO</td>
</tr>
<tr>
<td>Chemorefractory [PR]</td>
<td>GNR</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Primary resistant -sensitive to salvage -resistant</td>
<td>S</td>
<td>GNR</td>
<td>S</td>
</tr>
<tr>
<td>Relapse - post-autograft</td>
<td>GNR</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>
### Chronic lymphocytic leukaemia

<table>
<thead>
<tr>
<th></th>
<th>RIC sib allograft</th>
<th>RIC VUD</th>
<th>Auto</th>
<th>UCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high risk CR1&lt;sup&gt;2&lt;/sup&gt;</td>
<td>S</td>
<td>S</td>
<td>GNR</td>
<td>CT*</td>
</tr>
<tr>
<td>High risk CR2&lt;sup&gt;2&lt;/sup&gt;</td>
<td>S</td>
<td>S</td>
<td>CT</td>
<td>CT</td>
</tr>
<tr>
<td>Others CR&gt;2&lt;sup&gt;+&lt;/sup&gt;</td>
<td>CO</td>
<td>CO</td>
<td>CO</td>
<td>CT</td>
</tr>
<tr>
<td>Richter's transformation CR1</td>
<td>S</td>
<td>S</td>
<td>GNR</td>
<td>CT</td>
</tr>
<tr>
<td>T-PLL</td>
<td>S</td>
<td>S</td>
<td>CO</td>
<td>CT</td>
</tr>
<tr>
<td>B-PLL&lt;sup&gt;5&lt;/sup&gt;</td>
<td>CO</td>
<td>CO</td>
<td>CO</td>
<td>CT</td>
</tr>
</tbody>
</table>

**Notes**
- Clinical trial

<sup>1</sup>For most CLL patients, reduced intensity (RIC) conditioning is recommended. However, for some younger patients (<45 years) with very high risk disease and a matched sibling donor then standard intensity conditioning may be preferable (CO).

<sup>2</sup>Very high risk CLL defined as CLL with >20% cells showing del(17p) or purine analogue (PA) refractory. These patients should be treated with p53 independent therapy, such as high dose methylprednisolone and/or alemtuzumab to maximum response and then allografted if possible in CR1.

<sup>3</sup>High risk CLL defined according to EBMT criteria:

1. Relapse within 6 months of PA therapy.
2. Relapse within 2 years of intensive therapy including PA/alkylator combinations, chemoimmunotherapy or autologous transplantation.

<sup>4</sup>Other indications. Include patients not fulfilling criteria 2 or 3 who are in second or subsequent relapse with at least one other commonly recognised adverse features listed below:

1. Bone marrow failure according to Binet criteria
2. Unmutated Vh genes (<98% germline or Vh3.21)
3. ZAP70+ (>20%)
4. CD38+ (>7%)
5. del(11q) or trisomy 12

<sup>5</sup>Approximately 20% of cases of B-PLL are actually mantle cell lymphoma and should be treated accordingly. B-PLL otherwise is rare and should be treated on a case by case basis (CO).

### Aplastic anaemia

<table>
<thead>
<tr>
<th></th>
<th>Matched sibling</th>
<th>MUD</th>
<th>UCB</th>
<th>Autologous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe AA (SAA) &lt; 50 y</td>
<td>S</td>
<td>S if failed IST# and no sibling</td>
<td>CO</td>
<td>GNR</td>
</tr>
<tr>
<td>SAA &gt;50 y&lt;sup&gt;*&lt;/sup&gt;</td>
<td>S if failed IST#</td>
<td>S if failed IST# and no sibling</td>
<td>D</td>
<td>GNR</td>
</tr>
<tr>
<td>Constitutional AA</td>
<td>S</td>
<td>S if no sibling</td>
<td>CO</td>
<td>GNR</td>
</tr>
</tbody>
</table>
If failed one course of immunosuppressive therapy using ATG and ciclosporin
*Also for patients age 50-60 y if good performance status

### Myelodysplastic syndrome (MDS) (adult)

<table>
<thead>
<tr>
<th></th>
<th>Autograft</th>
<th>Sibling allograft</th>
<th>VUD allograft</th>
<th>UCBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPSS score - Low – Int-1</td>
<td>GNR</td>
<td>CO⁺</td>
<td>CO⁺</td>
<td>D²</td>
</tr>
<tr>
<td>IPSS score - Int-2 – High</td>
<td>GNR</td>
<td>S</td>
<td>S</td>
<td>D²</td>
</tr>
<tr>
<td>Therapy-related MDS</td>
<td>GNR</td>
<td>S</td>
<td>S</td>
<td>D²</td>
</tr>
</tbody>
</table>

Reduced intensity conditioning protocols are recommended for patients aged 40-45 years or older, or in patients with pre-existing co-morbidities as defined using the HSCT co-morbidity index (HCT-CI).

¹Allogeneic transplantation in patients with Low or Int-1 disease is generally considered at time of disease progression: progressive cytopenias and transfusion dependance, increasing blast counts, acquisition of adverse cytogenetic markers.

²In view of the limited data on transplantation of adult patients with MDS using umbilical cord blood units, it is recommended that this should be performed within the confines of a clinical research protocol

### Myelofibrosis

<table>
<thead>
<tr>
<th></th>
<th>Sibling allograft</th>
<th>MUD allograft</th>
<th>RIC Allo/MUD</th>
<th>Autograft</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Myelofibrosis (for prognostic score see 1) • Low Risk • Intermediate Risk • High Risk</td>
<td>GNR CO (&lt;45 yrs) S (&lt;45 yrs)</td>
<td>GNR CO (&lt;45 yrs) S (&lt;45 yrs)</td>
<td>GNR CO (&gt;45 yrs) S (&gt;45 yrs) CO (&lt;45 yrs) if clinically unfit)</td>
<td>GNR CO² CO</td>
</tr>
<tr>
<td>Secondary Myelofibrosis • Post-PV MF • Post-ET MF</td>
<td>CO</td>
<td>CO</td>
<td>CO</td>
<td>GNR</td>
</tr>
<tr>
<td></td>
<td>CO</td>
<td>CO</td>
<td>CO</td>
<td>GNR</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>GNR</td>
</tr>
</tbody>
</table>
SECTION 16

BLOOD TRANSFUSION GUIDELINES

THE NATIONAL BLOOD SERVICE (NBS) – contact numbers

NBS Newcastle switchboard 0191 202 4400
Duty Consultant 24/7 0191 202 4500
Dr Cath Chapman 0191 202 4412
Dr Hazel Tinegate 0776 428 0306

SELECTION OF RED CELLS FOR PATIENTS WITH HAEMATOLOGICAL MALIGNANCY

Chronically transfused haematology patients
It is prudent to phenotype as fully as possible prior to transfusion. It may also be reasonable to provide units matched for D, K, C, c, E and e antigens.¹

Recipients of ABO/Rh-mismatched allogeneic haemopoietic stem cell grafts
Approximately 15-25% of HLA identical sibling donor/recipient pairs differ for ABO blood groups. The figure is higher for alternative donor transplants. ABO incompatibility does not affect either graft rejection or GVHD since ABO antigens are not expressed on primitive stem cells.

Click on the link below to access current NBS advice on selecting appropriate products for recipients of such transplants


Patients with autoimmune haemolytic anaemia
Patients should have their correct ABO and D group determined and be tested for the presence of alloantibodies. It may be necessary to refer patients with AIHA to a red cell reference centre in view of the complexity of the investigations required.¹

¹BCSH Guidelines for compatibility procedures in blood transfusion laboratories Transfusion Medicine 2004; 14, 59-73
Indications for platelet transfusions

The recent National Comparative Audit of Platelet transfusions in haematology patients indicated a significant percentage of inappropriate use. Results for your hospital can be accessed through your transfusion team and the generic report can be found at http://hospital.blood.co.uk/library/pdf/Platelet_Re-audit_report-St_Elsewheres_NHS_Foundation_Trust_2010.pdf

The National Comparative Audit team has issued a fact sheet for clinicians, which can be accessed here. It is included as appendix A. Note that prophylactic platelet transfusions are not indicated prior to bone marrow aspirate or trephine. One area of concern is the use of “double dose” platelets.

Platelet refractoriness

This may be due to HLA or HPA alloimmunisation, but is more commonly due to non-immune factors such as sepsis or DIC. An initial clinical assessment should be made, and if no obvious clinical factors are present, tests for HLA antibodies should be carried out. A guide to these tests is found on page 10 at the link below.

If HLA antibodies are detected, HLA matched platelet transfusions should be used.

Use of platelets in suspension medium (PSM)

For this product, the majority of plasma is removed from pooled or apheresis platelets, which are then resuspended in 200 mls of platelet additive solution. The clinical indications are thrombocytopenic bleeding or prophylaxis in a patient who has a history of recurrent severe allergic reactions to plasma-containing components. The shelf life is only 24 hours at present.²

References

¹BCSH guidelines on the use of platelet transfusions

²NBS portfolio of components and guidance for their clinical use, version 3
http://hospital.blood.co.uk/library/pdf/components/SPN_PT1_PR_030_03_Component_Package.pdf
Updated guidance on the use of granulocyte transfusions

From October 2012 a new pooled whole blood derived component is available. The new NHSBT component portfolio name is “Granulocytes, Pooled, Buffy Coat Derived, in Platelet Additive Solution and Plasma, Irradiated” (Replacing where possible the old unpooled component) The NHSBT Components Development Laboratory (CDL) has reported good in-vitro functionality of a purer pooled granulocyte component derived from whole blood donations. The method involved the addition of platelet additive solution but without the need for hydroxyethyl starch or dextran to sediment red cells during processing. As the haematocrit is <20% venesection is unlikely to be required but red cell transfusion requirements may be diminished, and each pack has 2.5 adult therapeutic doses of platelets so platelet transfusion requirements will be significantly diminished.

Although the component contains fewer red cells, a cross match should still be performed. The component should be ordered through your hospital transfusion laboratory, usually using the OBOS online ordering system. Please also discuss with a centre consultant or the duty consultant for the North if local advice is not available.

Dosing

Ten donations are pooled into a final volume of 200-250 ml. Adults may receive up to two packs or 20 donations. Each pack contains approximately $1 \times 10^{10}$ granulocytes

Children <30 kg should receive 10-20 ml/kg up to a maximum of two packs.

CMV negative granulocytes should only be given to CMV negative recipients at risk of CMV disease, i.e. recipients who are at risk of CMV disease (infants, pregnant women, CMV negative recipients of CMV negative allogeneic bone marrow transplants) (see section below)

Full NHSBT information can be accessed at the NHSBT hospitals and science website http://hospital.blood.co.uk/library/pdf/INF276_3.pdf
Indications for CMV-safe cellular blood components

The advisory committee for the safety of blood, tissues and organs has issued a position statement on CMV-tested blood and components in 2012. Its main recommendations are:

- CMV seronegative red cell and platelet components should be provided for intra-uterine transfusions and for neonates (i.e. up to 28 days post expected date of delivery) and therefore all small-sized blood packs and other cellular components intended for neonates should be provided as CMV negative.

- CMV seronegative blood components should be provided where possible for pregnant women, regardless of their CMV sero status, who require repeat elective transfusions through the course of their pregnancy (not labour and delivery). This mainly applies to patients with haemoglobinopathies who are managed in specialist centres. However, CMV negative blood components are not expected to be generally available in all hospitals and therefore for emergency transfusions in pregnant women, leucodepleted components are recommended.

- All blood components, other than granulocytes, now undergo leucodepletion, which provides a significant degree of CMV risk reduction. This measure is considered adequate risk reduction for all patients requiring transfusion (including haemopoietic stem cell transplant patients, organ transplant patients, and immune deficient patients, including those with HIV) without the requirement for CMV negative components in addition.

- CMV PCR monitoring should be considered for all haemopoietic stem cell and solid organ transplant patients (even CMV negative donor/negative recipients) to allow early detection of any possible CMV infection (whether transfusion-transmitted or primary acquired infection)

- Transfusion-transmitted CMV should be reported via the SHOT (Serious Hazards of transfusion) and SABRE (Serious Adverse Blood reactions and Events) systems.

The full guidance can be accessed here and is included as appendix B.
Guidelines on the use of irradiated blood components

BCSH guidance has been updated and can be accessed here http://www.bcshguidelines.com/documents/Irradiation BJH_2011.pdf

The major changes since the last guideline, published in 1996 are:

- **Use of X-irradiation as an alternative to gamma irradiation**
- **Any cases of transfusion-associated GVHD and all episodes where non-irradiated components are transfused to high risk patients should be reported to national haemovigilance systems (e.g. SHOT and SABRE: see above)**
- **Irradiated components are recommended for aplastic anaemia patients receiving immunosuppressive therapy with ATG.**
- **Indication for irradiated components extended to newer purine analogues and related drugs until evidence of their safety is forthcoming (e.g. bendamustine and clofarabine)**

Irradiated components indicated for patients receiving the biological immunosuppressive agent alemtuzumab (anti-CD 52) but not rituximab (anti-CD 20)-regular review will be needed as new biological agents enter clinical practice.

The indications below were in the 1996 guideline and are still current

**Adult and paediatric**

- All transfusions from a first or second degree relative
- All transfusions from a first or second degree relative
- All HLA matched transfusions
- All granulocyte transfusions
- All patients with Hodgkin’s Disease at any stage - life long requirement
- All patients treated with purine analogue drugs (Fludarabine, Cladribine, Deoxycoformycin, Clofarabine *) - life long requirement
- Patients treated with Antilymphocyte immunoglobulin (ALG), Antithymocyte immunoglobulin (ATG) or CAMPATH for 3 months from the last treatment
- All recipients of allogeneic bone marrow transplant from conditioning until GvHD prophylaxis is discontinued or lymphocytes are >1 x 10^6/L^-1 (usually at least 6 months)
- Bone marrow donors and patients undergoing bone marrow harvest - 7 days prior to and during harvest
- All patients undergoing stem cell mobilisation from the commencement of the mobilising chemotherapy regimen until collection completed
- All patients undergoing autologous stem cell transplant, from conditioning until 3 months post transplant, or 6 months if TBI is used.
- Actual or suspected congenital immunodeficiency with defective cell-mediated immunity (e.g. SCID, Di George syndrome, Wiskott Aldrich syndrome, purine nucleoside deficiency, reticular dysgenesis, ADA, Ataxia telanectasia, chronic mucosal candidiasis, MHC class 1 or 2 deficiency)
Paediatric
- All components for intra-uterine transfusions
- All recipients of exchange transfusions (where time permits). If the child has received an intrauterine transfusion the blood must be irradiated.
- Exchange or top-up transfusion in neonates who have had IUT

Storage of irradiated components

Platelets
- Can be irradiated at any time during storage and can then be stored up to their normal shelf life.

Red cells
- Can be irradiated at any time up to 14 days after collection and then be stored for a further 14 days
- Where the patient is at particular risk from hyperkalaemia, e.g. interuterine or neonatal exchange transfusion, it is recommended that red cells should be transfused within 24 hours of irradiation or that the cells are washed

Granulocytes
- All granulocyte components should be irradiated before issue and transfused without delay

Patient Information
Patients at risk of TA-GVHD should be made aware of their need for irradiated blood components and provided with appropriate written information and an alert-card for clinical staff. Initiatives to improve laboratory and clinical information management systems (including IT links with pharmacy and diagnostic services to highlight “at risk” patients should be incorporated into local policies and regularly audited.
Obtaining Consent for blood and component transfusion

It is a general legal and ethical principle that valid consent should be obtained from a patient before they are treated. In 2011, SABTO issued the following recommendations on consent for blood transfusion.

- Valid consent should be obtained and documented in the patient’s clinical record by the healthcare professional.
- There should be a modified form of consent for long-term multi-transfused patients, details of which should be explicit in an organisation’s consent policy
- There should be a standardised information source for clinicians indicating the key issues to be discussed by the healthcare professional when obtaining valid consent from a patient for blood transfusion.
- There should be a standardised source of information for patients who may receive a transfusion in the UK. The current NHSBT information leaflet, “Will I need a blood transfusion?” can be accessed at http://hospital.blood.co.uk/library/pdf/2011_Will_I_Need_English_v3.pdf

The SABTO recommendations can be accessed at http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_130715.pdf
NSSG GUIDELINES FOR TEENAGE AND YOUNG ADULTS

Teenage and Young Adults Peer Review Measures

1. Teenage and Young Adult Pathway for Initial Management

The NSSG has received the document named ‘NECN Teenage and Young Adult Cancer Pathway Guidance Paper’ and agrees to follow the generic TYA Pathway with any site specific variations to be documented. Please see Appendix 1 for pathway.

2. Teenage and Young Adult Pathway for Follow up on completion of first line treatment

The Children and Young Peoples co-ordinating group have produced a pathway for follow up on completion of first line treatment, which was endorsed by the Haematology NSSG. Please see Appendix 2 for more details.

If advice is required regarding the follow up care of a 19-24 year old patient, then the Lead TYA Clinician at the designated hospital or PTC should be contacted. Please see Appendix 3 for contact details.

3. Pathways for cases involving Specialised NHS services (Only Gynae and Sarcoma)

The Gynae NSSG and SAG reviewed and agreed the Specialised NHS Service pathway for patient’s age 16-24 years. This is attached in Appendix 4.
Appendix 1 – Teenage and Young Adult Pathway for initial Management

Teenage and Young Adult Cancer Pathway – 19 to 24 years old

Urgent referral made by GP/DGP/Screening

Emergency Admission

Other source of referral (screening/genetics clinic)

Assess as per local Tumour Site Specific protocol:

May include diagnostic biopsies, but not definitive cancer surgery

Cancer diagnosed or highly suspicious

Patient informed of joint MDT review and place of care options

NS MDT discussion should take place in tumour site specific MDT within PTC/TYA designated hospital AND TYA MDT

Review at TYAMDT

Communication & Liaison between MDTs

Review at PTC/TYA Site Specific haematology-oncology/solid tumour MDT

Joint treatment planning decision agreed, including:

- Diagnosis and treatment modalities/regimen
- Place of treatment delivery, depending on patient age:
  - 16-18 years - PTC facility only (Paediatric & Adolescent Oncology, RVI, Newcastle)
  - 19-24 years - choice of PTC facility (Adult Oncology, NH, Newcastle) or TYA designated hospital
- Named Consultant in charge of each treatment modality
- The arrangements/Referrals to provide age appropriate support if the treatment is delivered outside the PTC facility
- The results of the discussion of fertility issues
- Consider entry into clinical trials
- Consider palliative & supportive care needs
- Identify patient’s key worker

PTC (RVI or Freeman) – treatment and ongoing care (with options for shared care or supportive care)

Designated TYA hospital treatment with option of TYAMDT outreach support 19 – 24 yr

Haematological/Oncological Treatment (first definitive treatment)

Surgery

Chemotherapy

Biological therapy

Radiotherapy

Assess response at site specific haematology-oncology/solid tumour MDT

Consider need for further/consolidation treatment

Relapse or recurrent disease

Yes

No

Long term follow up protocol

Further Treatment

Palliative Care

Abbreviations:

TYA (Teenage and Young Adults)

TYA DH (Teenage and Young Adult Designated Hospitals)

PTC (Principal Treatment Centre, Newcastle upon Tyne hospitals)

TYA Cancer Trial Pathway Map version 1.7

ELT/NIJEST and acknowledgement to Versus Cancer Network

Total Time in Days: 62
Appendix 2 – Pathway for follow up on completion of First line treatment

Completion of first line treatment (including surgery, radiotherapy, chemotherapy, biological or endocrine therapy) Patients aged 19-24 years should have been offered the choice between PTC NuTH and a TYA designated hospital.
<table>
<thead>
<tr>
<th>MDT RESPONSIBILITIES</th>
<th>TUMOUR SITE SPECIFIC MDT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TYA MDT</strong>&lt;br&gt;Location: NUTH&lt;br&gt;Time: Thursdays, 12.00-14.00&lt;br&gt;Lead Clinician: Dr Emma Leathbridge&lt;br&gt;Lead Nurse: Mr David Short&lt;br&gt;Coordinator: Sharon Buckley&lt;br&gt;Phone: 0191 233 6181&lt;br&gt;Email: tru.tr <a href="mailto:TYA@nhs.net">TYA@nhs.net</a>&lt;br&gt;TYA MDT Review end of treatment summary&lt;br&gt;TYA CNS&lt;br&gt;Co-ordination of Clinical care.&lt;br&gt;Acts as point of contact/reference&lt;br&gt;TYA Psychologist&lt;br&gt;Continue to provide level 3-4 support according to need&lt;br&gt;Involvement in end of treatment/ Survivorship clinic/event&lt;br&gt;TYA Social Worker&lt;br&gt;Continue to provide support according to need&lt;br&gt;Introductory letter sent with information and offer of grant at time of diagnosis and relapse&lt;br&gt;More in depth service offered based on assessed need&lt;br&gt;TYA Youth Support Co-ordinator&lt;br&gt;Continue to invite patients to support activities for up to 2 years post first line treatment&lt;br&gt;Involvement in end of treatment/ survivorship clinic/event</td>
<td></td>
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<tr>
<td><strong>SPECIALIST PALLIATIVE CARE MDT</strong>&lt;br&gt;Location: NCCH Freeman Hospital&lt;br&gt;Time: Wednesdays, 09.30-11.30&lt;br&gt;Lead Clinician: Dr M. Comiskey&lt;br&gt;Coordinator: Kerry Halliday&lt;br&gt;Phone: 0191 2138006&lt;br&gt;Email: <a href="mailto:kerry.halliday@nuth.nhs.uk">kerry.halliday@nuth.nhs.uk</a>&lt;br&gt;1. Specialist Palliative Care representation as core member of TYA MDT.&lt;br&gt;2. All sites specific MDT outcomes notified to palliative care lead clinician.&lt;br&gt;3. Patients reviewed at any point along the pathway (diagnosis, relapse, long term follow up, and of life care).&lt;br&gt;4. Holistic needs assessment to include family/Careers.&lt;br&gt;5. Work with patients across the Northern England Strategic Clinical Network, link with other trusts and community palliative care services.&lt;br&gt;MDT outcomes documented on Sunuet.</td>
<td></td>
</tr>
<tr>
<td><strong>TUMOUR SITE SPECIFIC MDT</strong>&lt;br&gt;Location: NUTH&lt;br&gt;Time: Thursdays, 12.00-14.00&lt;br&gt;Lead Clinician: Dr Emma Leathbridge&lt;br&gt;Lead Nurse: Mr David Short&lt;br&gt;Coordinator: Sharon Buckley&lt;br&gt;Phone: 0191 233 6181&lt;br&gt;Email: tru.tr <a href="mailto:TYA@nhs.net">TYA@nhs.net</a>&lt;br&gt;TYA MDT Review end of treatment summary&lt;br&gt;TYA CNS&lt;br&gt;Co-ordination of Clinical care.&lt;br&gt;Acts as point of contact/reference&lt;br&gt;TYA Psychologist&lt;br&gt;Continue to provide level 3-4 support according to need&lt;br&gt;Involvement in end of treatment/ Survivorship clinic/event&lt;br&gt;TYA Social Worker&lt;br&gt;Continue to provide support according to need&lt;br&gt;Introductory letter sent with information and offer of grant at time of diagnosis and relapse&lt;br&gt;More in depth service offered based on assessed need&lt;br&gt;TYA Youth Support Co-ordinator&lt;br&gt;Continue to invite patients to support activities for up to 2 years post first line treatment&lt;br&gt;Involvement in end of treatment/ survivorship clinic/event</td>
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<tr>
<td><strong>TRANSITION TO TYA</strong>&lt;br&gt;Transition to adult&lt;br&gt;Transition into adult services is planned for and discussed with patients well in advance. Transition at a time of crisis, e.g. relapse.&lt;br&gt;Intensive chemotherapy will be avoided wherever possible. Transition will be facilitated by the keyworkers.</td>
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</tbody>
</table>

**YEARS 1-5**
- Clinical surveillance for disease recurrence and treatment toxicity monitoring (including history, clinical examination, laboratory investigations, imaging studies and invasive procedures where indicated according to tumour site specific follow up protocols)

**YEARS 6+**
- Long term follow up for late effects of treatment, consider survivorship issues
- Consider referral to long term follow up/late effects MDT if disease free after 5 years from completion of first line treatment
- Consider extended clinical follow up to 10 years* in selected patient groups as defined by the T30 MDT's (e.g. brain/CNS, seromas, BMT, tests)
# Appendix 3- TYA Designated Hospitals

## List of designated MDTs at Principal Treatment Centre and TYA Designated Hospitals (19-24 years)

<table>
<thead>
<tr>
<th>Name of NHS Trust and designated hospital site</th>
<th>Name of MDT</th>
<th>TYA Lead Clinician</th>
<th>TYA Lead Nurse</th>
<th>Contact Number</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Principal Treatment Centre</strong></td>
<td>All MDTs:</td>
<td>Dr Emma Lethbridge</td>
<td>David Short</td>
<td>0191 2448858 (Decc98858)</td>
</tr>
<tr>
<td></td>
<td>Breast</td>
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<td></td>
<td>Colorectal</td>
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<tr>
<td></td>
<td>Gynaecology (diagnostic)</td>
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<td></td>
<td>Haematology</td>
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<td></td>
<td>Head &amp; Neck</td>
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<td></td>
<td>Lung</td>
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<tr>
<td></td>
<td>Neuroendocrinology (Brain/Spine, Pituitary, Skull Base)</td>
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<td></td>
<td>Sarcoma</td>
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<td></td>
<td>Specialist Skin</td>
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<td></td>
<td>Specialist pancreatic</td>
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<tr>
<td></td>
<td>SPC T-cell Lymphoma</td>
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<td></td>
<td>Teenage and Young Adult MDT</td>
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<td>Testicular</td>
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<td>Thyroid</td>
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<td></td>
<td>Specialist Upper GI</td>
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<tr>
<td></td>
<td>Specialist Urology</td>
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<tr>
<td><strong>Gateshead Health NHS Foundation Trust - at Queen Elizabeth Hospital</strong></td>
<td>Specialist Gynaecology</td>
<td>Ms Christine Ang</td>
<td><a href="mailto:helen.manderville@ghnt.nhs.uk">helen.manderville@ghnt.nhs.uk</a></td>
<td>0191 4456148</td>
</tr>
<tr>
<td><strong>City Hospitals Sunderland NHS Foundation Trust - at Sunderland Royal Hospital</strong></td>
<td>Haematology</td>
<td>Dr Scott Marshall</td>
<td>Faye Laverick <a href="mailto:faye.armstrong@chsft.nhs.uk">faye.armstrong@chsft.nhs.uk</a></td>
<td>0191 5666256</td>
</tr>
<tr>
<td></td>
<td>Specialist Urology (testicular only)</td>
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<tr>
<td><strong>North Tees and Hartlepool NHS Foundation Trust - at University Hospital of North Tees</strong></td>
<td>All MDTs: fishman Lekkreddy</td>
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<td></td>
<td>Haematology</td>
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<td>Local Urology</td>
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<td>Thyroid</td>
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<td>Lung</td>
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<td></td>
<td>Local Upper GI</td>
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<tr>
<td><strong>South Tees Hospital NHS Foundation Trust - at James Cook University Hospital</strong></td>
<td>All MDTs: fishman Lekkreddy</td>
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<td></td>
<td>Specialist Gynaecology</td>
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Appendix 4 – NHS Specialised Services Pathway

NHS Specialised Services - Referral Pathway for Primary Malignant Bone Cancer for patients age 16-24 years within the North of England

Paediatrician → GP → Radiology/Incidental Finding

Referral to Sarcoma Service at Freeman Hospital Newcastle (FRH)
See Sarcoma pathway for contact details

If age 16-18 years refer to PTC paediatric & adolescent MDT at RVI and Bone & Soft Tissue MDT at FRH

All patients to be discussed at the TYA MDT (see TYA pathway for contact details)

If age 19-24 years refer to Bone & Soft Tissue MDT at FRH

Necessary to refer to National Ewing’s Sarcoma MDT for discussion?

Yes → Submit electronic MDT proforma and link in via WebEx.

Please see Bone & Soft tissue site specific pathway and/or paediatric & adolescent pathway for detail

No → 5 years post treatment for patients age 16-24 years

Age 16-18 at time of diagnosis refer to long term follow up clinic/MDT

Age 19-24 yrs at time of diagnosis follow up on adult protocol

Primary Bone Cancer Pathway DRAFT
Toni Hunt NECN Version 0.3 Aug 2012
NHS Specialised Services
Referral Pathway for Hydatidiform Mole / Gestational Trophoblastic Neoplasm / Choriocarcinoma
Weston Park Hospital, Sheffield

Gynaecologist / Antenatal dept perform U/S or histology from failed pregnancy confirms hydatidiform mole
Post Pregnancy, ectopic pregnancy or miscarriage confirms choriocarcinoma on histology or high clinical suspicion

Patient referred to Weston Park Hospital Sheffield. Histology reviewed and patient registered on national programme

Hydatidiform mole diagnosis confirmed on histology

Choriocarcinoma diagnosis confirmed on histology or further staging needed to confirm

hCG levels return to normal

Patient bloods & urine monitored by Sheffield copies to GP and referring gynaecologist

Complete follow up protocol
Discharge

hCG levels do not return to normal

Outpatient visit at Sheffield
Staging scan, blood tests, prognosis score, treatment plan at Sheffield

Discuss at Sheffield GTN MDT

Outpatient visit at Sheffield for staging and treatment plan

Patients age 16-24 yrs refer to TYAMDT @ Sheffield

Low risk: methotrexate chemo can be given at local hospital under direction of Sheffield. If age 16-18 years this should be on teenage unit (RTVI). If age 19-24 this should be on Young Adult unit at Newcastle (Freeman) or TYA Designated Unit at James Cook, Middlesbrough

All Treatment delivered at Sheffield

All follow up carried out by Sheffield (OPC, phone, email & text)

hCG monitoring will be for life via Sheffield. Copies sent to GP and referring gynaecologist

Choriocarcinoma Pathway
Toni Hunt NECN Version 0.4 Aug 2012
## List of Contributors

<table>
<thead>
<tr>
<th>Section</th>
<th>Topic</th>
<th>Name / s</th>
<th>Page</th>
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<tbody>
<tr>
<td>1.</td>
<td>NEHODS</td>
<td>Peter Carey, Gavin Cuthbert</td>
<td></td>
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<tr>
<td>2.</td>
<td>Guidelines for Genetic Analysis in Haematological Malignancies</td>
<td>Peter Carey, Gavin Cuthbert</td>
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<td>3.</td>
<td>Guidelines and Indications for PET CT</td>
<td>Dr George Petridis</td>
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<td>4.</td>
<td>Guidelines for Management of Acute Myeloid Leukaemia (AML)</td>
<td>Dr Gail Jones</td>
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<td>Guidelines for Management of Myelodysplastic Syndromes</td>
<td>Dr Mari Kilner</td>
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<td>6.</td>
<td>Guidelines for Management of Acute Lymphoblastic Leukaemia</td>
<td>Dr Tobias Menne</td>
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<td>7.</td>
<td>Guidelines for Management of Chronic Myeloid Leukaemia</td>
<td>Professor Steve O’Brien</td>
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<td>8.</td>
<td>Guidelines for Management of Myeloproliferative Disorders</td>
<td>Dr Yogesh Upadaye</td>
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<td>9.</td>
<td>Guidelines for Management of Chronic Lymphocytic Leukaemia (CLL) and Lymphoproliferative Disorders</td>
<td>Dr Scott Marshall, Dr Victoria Hervey</td>
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<td>10.</td>
<td>Guidelines for the Management of Low-Grade Non-Hodgkin Lymphoma</td>
<td>Dr George Holmes</td>
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<td>11.</td>
<td>Guidelines for the Management of Waldenstroms Macroglobulinaemia</td>
<td>Dr Jamie Maddox</td>
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<td>12.</td>
<td>Guidelines for the Management of Mantle Cell Lymphoma</td>
<td>Dr Victoria Hervey</td>
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<td>13.</td>
<td>Guidelines for the Management of High-Grade B Cell Non-Hodgkin Lymphoma</td>
<td>Dr Anne Lennard</td>
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<td>Guidelines for the Management of Nodular Lymphocyte Predominant Hodgkin Lymphoma</td>
<td>Dr Victoria Hervey</td>
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<td>15.</td>
<td>Guidelines for Management of Hodgkin Lymphoma</td>
<td>Dr Wendy Osborne</td>
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<td>16.14</td>
<td>Guidelines for Management of Plasma Cell Myeloma</td>
<td>Dr Simon Lyons</td>
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<td>15</td>
<td>Indications for Haemopoietic Stem Cell Transplantation</td>
<td>Dr Erin Hurst</td>
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<tr>
<td>16</td>
<td>Blood Transfusion Guidelines</td>
<td>Dr Andrew Charlton</td>
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