
Pan-London Haemato-Oncology Clinical Guidelines

Acute Leukaemias and Myeloid Neoplasms
Part 2: Acute Myeloid Leukaemia

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Disclaimer

These guidelines should be read in conjunction with the latest NICE guidance, and all applicable national/international guidance. The prescribing information in these guidelines is for health professionals only. It is not intended to replace consultation with the Haematology Consultant at the patient's specialist centre. For information on cautions, contra-indications and side effects, refer to the up-to-date prescribing information. While great care has been taken to see that the information in these guidelines is accurate, the user is advised to check the doses and regimens carefully and if there is any uncertainty about the guidance provided, you should discuss your queries with a Haematology Consultant or Senior Pharmacist. No set of guidelines can cover all variations required for specific patient circumstances. It is the responsibility of the healthcare practitioners using them to adapt them for safe use within their institutions and for the individual needs of patients.

Contact us

The writing cycle for the guidelines will be from May-July each year. If you wish to be part of the writing group, please contact us through the following link: [Pan London Blood Cancer](https://panlondonbloodcancer.org.uk) (or via uclh.panlondonbloodcancer@nhs.net).

If you wish to report errors or omissions that require urgent attention please contact us via the same email addresses.

1 Introduction

Acute myeloid leukaemia (AML) is an uncommon and heterogeneous clonal haematopoietic neoplasm. It represents around 40% of all leukaemias in adults; the incidence rises sharply in adults over the age of 50.

Overall, AML can be cured in approximately 30–45% of patients who are fit enough to withstand intensive chemotherapy. For those who are cured, there is a modest increased risk of secondary cancers and cardiovascular disease due to the adverse effects of treatment.

The heterogeneity of AML extends not only to the disease phenotype, but also to the many molecular aberrations that are associated with leukaemogenesis, making the diagnostic and treatment monitoring pathway particularly specialised and targeted to the AML sub-type.

Patients diagnosed with AML should be cared for by haemato-oncology subspecialists in a BCSH (British Committee for Standards in Haematology) at least Level 2 Haemato-Oncology Unit (2a or 2b, dependent on intensity of chemotherapy to be given) which participates in clinical trials for patients with AML.

These guidelines have been derived in part from the European Leukaemia Net Consensus Guidelines on the diagnosis and management of AML, the original BCSH AML guidelines, and incorporating further details on clinical trials and diagnostic/treatment options relevant to London and the UK.^{1, 2} The guideline is not designed to be exhaustive, but should act as a guide.

All new cases of AML should be discussed at the multidisciplinary team (MDT) meeting to agree the treatment pathway.

Treatment for AML is quite regimented and driven by well-defined protocols within a clinical trial set-up. This guideline will not recapitulate these clinical trials but is a general guide to treatment strategies for new and relapsed patients. The main considerations are:

- AML may be a curable disease in young and older fit patients. It becomes harder to treat with age; fewer patients are cured as age advances and therapeutic complications are increasingly common.
- All patients should be treated with therapy adjusted to performance status and AML risk stratification.
- Since the disease is rare and treatment is complicated, there are many areas of controversy where best practice is not defined. **Patients should be treated within a clinical trial wherever possible.**
- Experienced specific and supportive care is required in at least a BCSH Level 2 unit which offers clinical trials.

2 Referral Pathways

Patients with suspected AML should be referred to a haematologist for assessment on the same day on a 2 week wait pathway.

Patients with severe neutropenia, thrombocytopenia or blasts in peripheral blood picked up on a routine blood test via the laboratory and suspected AML should be urgently referred to an A&E department or directly to a haematology inpatient unit which treats AML (BCSH Level 2–3), following discussion with a haematologist.

All new patients should be referred to the MDT for confirmation of diagnosis, prognosis and management plan, taking into account their performance status, needs and co-morbidities.

The following patients should be brought to the MDT:

- All new patients with AML in order to confirm the diagnosis and treatment plan.
- All patients where a new line of therapy needs to be considered.
- All patients with a re-staging assessment of response to treatment.
- All patients in whom an allogeneic stem cell transplant is a consideration.

Perhaps we should amend this slightly: Patients with AML should be discussed within two weeks of diagnosis. In some cases it may be safe to wait for genetic test results before initiating treatment, whilst in others treatment may have commenced prior to the MDT discussion based on clinical urgency.

The MDT outcome should be documented and communicated to primary care and secondary care referring centre (where relevant).

New patients should be discussed with the MDT AML lead or the MDT lead at presentation for urgent agreement on management plan prior to formal MDT discussion.

Those who are newly diagnosed should have access to specialist haemato-oncology rehabilitation teams, i.e. physiotherapist, occupational therapist, speech and language therapist and dietitian. Where there are not currently specialist haemato-oncology teams, they should be able to access oncology specialists or, at a minimum, rehabilitation teams with access to support and advice from haemato-oncology specialists.

Planning for an allogeneic stem cell transplant should begin at the time of diagnosis in conjunction with the transplant centre. Patients should be HLA typed at the time of diagnosis. A joint approach with elderly care physicians and palliative care teams may be appropriate in patients with poor prognosis disease, poor performance status and who are not eligible for transplant.

Patients who fail to respond to first-line therapy, lose response or experience disease progression may be discussed with a centre offering a clinical trial for relapsed patients (see [section 12: Research/Clinical Trials](#)), especially if they progress through second-line treatment.

Patients considered for haematopoietic stem cell transplantation need to be referred early in their treatment (as soon as is practical and at the latest after recovery from cycle 1 induction) to a JACIE-accredited centre.

3 Investigation and Diagnosis

Patients may present with infection, bleeding, symptoms of anaemia or hyperviscosity, constitutional symptoms, bone pain, central nervous system (CNS) symptoms and/or cytopenias with or without hepatosplenomegaly.

For most patients, the diagnosis is made on the basis of an abnormal FBC/film. In elderly patients (the most common age group for AML), a blood test (FBC) should be performed for those presenting with symptoms of anaemia, infection or bruising/bleeding. At specialist centres, a blood film, BMAT with immunophenotyping and cytogenetics can be undertaken to assess for a clonal abnormality. Where a BMAT is declined by a patient, or is inappropriate based on performance status, peripheral blood immunophenotyping/cytogenetics/FISH may be informative.

When the diagnosis of AML is suspected, a full history and examination should be undertaken and all co-morbidities should be assessed to aid treatment selection and a management plan.

The following tests should be undertaken as appropriate:

- FBC, differential and film
- Retics and DAT
- Haematinics (vitamin B12, folate, ferritin)
- Coagulation screen
- Blood group and antibody screen
- Renal/liver/bone profiles
- Glucose
- LDH/uric acid
- CRP
- Serum immunoglobulins/SPEP
- HLA-typing
- HAV, HBV (HBV sAg, HBV sAb, HBV cAb), HCV, HIV, CMV (total antibody – IgG & IgM) serology
- G6PD screen
- ECG
- CXR
- ECHO/MUGA
- Creatinine clearance
- BMAT (see details on page 7)
- Pregnancy test (if relevant)
- MRSA screening swabs (per Trust policies)
- Urinalysis
- Infection screen (cultures or urine/blood, as clinically indicated)
- For patients with features suggestive of CNS disease consider MRI or CT head/spine +/- lumbar puncture.

3.1 Fertility

Consideration of fertility preservation should be made for those of reproductive age. The options for fertility preservation should be discussed and the patient referred to a fertility specialist for sperm cryopreservation, and egg harvesting or fertilised embryos if appropriate. Prior to induction chemotherapy, the latter will not be available to patients, but may be an option if a stem cell transplant is being contemplated later in the course of treatment.

3.2 Pathology

Careful attention must be paid to the labelling of forms and samples before sending to the SIHMDS and trial centre. Samples are unlikely to be processed unless clearly and correctly labelled.

3.2.1 Bone marrow aspirate and trephine (BMAT)

Refer to local SIHMDS guidelines for sample collection for morphology, immunophenotyping, cytogenetics and molecular genetics and bone marrow trephine.

3.3 Imaging

Patients with neurological symptoms at diagnosis (or during treatment) should undergo MRI brain (with gadolinium) and whole spine. In the presence of a high blast count and/or low platelet count, if a bleed is suspected, an urgent non-contrasted CT can be done prior to further imaging/investigations.

All patients should have a baseline chest X-ray.

3.4 Core diagnostic criteria

The diagnosis of AML requires compatible morphology and immunophenotyping. The requisite blast percentage for a diagnosis of AML is $\geq 20\%$ myeloid blasts in bone marrow according to World Health Organization (WHO) criteria 2016. The categories of disease with the presence of t(8;21)(q22;q22), inv16(p13q22) or t(16;16) (p13q22) and t(15;17)(q24;q21) (latest HUGO terminology) are considered as AML regardless of the blast percentage documented. According to the WHO criteria, cases of therapy-related AML/MDS may have the balanced translocations as above, but should be categorised as **therapy-related AML** with the associated genetic abnormality noted, rather than AML with recurrent genetic abnormalities.

AML can present in the **peripheral blood** only, in **bone marrow +/- blood** and in **soft tissues (myeloid sarcoma)**. Regardless of site of presentation, all tissue samples (peripheral blood, bone marrow and any relevant involved soft tissue) should be assessed for involvement (see subsections below for details).

For presentation in the **peripheral blood**, required investigations include:

- Peripheral blood and bone marrow morphology – as per WHO classification
- Flow cytometry
- Cytogenetics/FISH
- Molecular analysis.

For presentation in the **bone marrow**, required investigations include:

- Morphology of bone marrow aspirate and peripheral blood (as per WHO)
- Flow cytometry
- Immunohistochemistry panel on trephine
- Cytogenetics/FISH
- Molecular analysis (including WGS for eligible patients).

For presentation in tissue, i.e. **myeloid sarcoma**:

- Morphology of bone marrow aspirate, peripheral blood and tissue
- Immunohistochemistry panel on tissue (same as for trephine)
- Cytogenetics/FISH on tissue aspirate or paraffin sections (optional).

All patients with AML who will undergo treatment should have a bone marrow test performed at presentation, and during therapy, for monitoring of response/minimal residual disease (MRD). Diagnosis may be made using peripheral blood alone if the diagnosis is definite based on typical features/tests, and the patient's performance status precludes remission-induction treatment or effective disease modification.

3.4.1 Peripheral blood film

It is recommended that a film be examined routinely in conjunction with the bone marrow for blasts and any other atypical features, e.g. evidence of haemolysis.

3.4.2 Bone marrow aspirate

It is recommended that at least 400 cells are evaluated and a particulate smear/film examined using a May-Grunwald-Giemsa stain or Wright-Giemsa stain in order to assess leukaemic blast percentage. The presence of leukaemic blasts $\geq 20\%$ is diagnostic of AML. If acute promyelocytic leukaemia (APML) is suspected by morphology, the presence of PML-RARA should be established urgently so that full APML-targeted therapy can be initiated.

If APML is suspected, all-trans-retinoic acid (ATRA) treatment should be started while awaiting results.

3.4.3 Cytochemistry

These tests are now rarely employed since immunophenotyping via flow cytometry is readily available. (Note that absent MPO by cytochemistry does not rule out a myeloid lineage leukaemia as early myeloblasts and monoblasts may lack MPO.) Non-specific esterase staining may be useful to assign monocytic lineage.

3.4.4 Flow cytometry

Immunophenotyping using flow cytometry in an SIHMDS laboratory should be employed in the diagnostic work-up of all new acute leukaemias. This is a mandatory test as it will identify the leukaemic clone and will be valuable for MRD detection. A standard acute leukaemia panel will include pan-B and -T combinations and markers for AML (Tables 1 and 2; Figure 1). A minimalist panel (Table 1) could be followed, or a Euroflow recommended panel (Table 2 and Figure 1):

Table 1: Minimalist approach for the diagnosis of AML

Panel/population	Markers*
Myeloid	CD13/CD15/CD33/CD117/HLADR/CD34/cytMPO
Monocytic/dendritic cell	CD4/CD11c/CD14/CD64
Erythroid	Glycophorin A (CD235a)
Megakaryoblastic	CD41/CD61
Lymphoid	CD2/CD7/cytCD3
	CD10/CD19/CD22/cytCD79a/cytIgM
Early markers	CD34/TdT

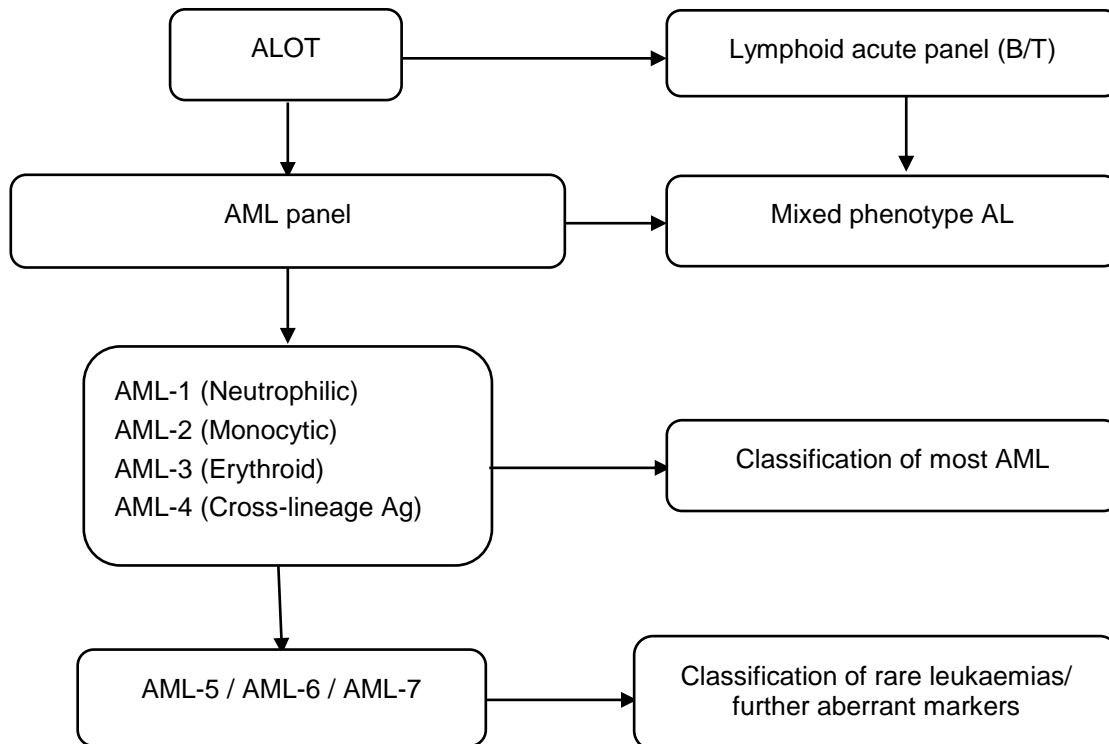
* Discretionary/optional markers: CD235a for AML M6; CD41/CD61 for AML M7

Table 2: Euroflow recommended panel

Tube	pacB/V450	pacO/V500	FITC	PE	PerCPcy5.5	PECy7	APC	APCH7
ALOT	cyCD3	CD45	cyMPO	cy79a	CD34	CD19	CD7	smCD3
AML-1	HLA-DR	CD45	CD16	CD13	CD34	CD117	CD11b	CD10
AML-2	HLA-DR	CD45	CD35/CD36	CD64	CD34	CD117	CD300e	CD14
AML-3	HLA-DR	CD45	CD15/CD36	CD105	CD34	CD117	CD33	CD71
AML-4	HLA-DR	CD45	NucTdT	CD56	CD34	CD19	CD7	CD38

Extended panel

Tube	pacB/V450	pacO/V500	FITC	PE	PerCPcy5.5	PECy7	APC	APCH7
AML-5	HLA-DR	CD45	CD15	NG2	CD34	CD117	CD22	CD38
AML-6	HLA-DR	CD45	CD42a/61	CD203c	CD34	CD117	CD123	CD4
AML-7	HLA-DR	CD45	CD41	CD25	CD34	CD117	CD42b	CD9
'mast-cell'	HLA-DR	CD45	CD2	CD25	CD34	CD117	CD33	CD9

Figure 1: Potential strategy for AML diagnosis using flow cytometry (Euroflow)

Intermediate phenotypes can occur and are acceptable to define myeloid lineage. Where possible a marker pattern characteristic of the clonal cells should be defined which is suitable for MRD monitoring by flow cytometry.

Cases of APML are typically CD34+/-, CD13-hetero+, CD33-homo+++, CD117+, CD15-, HLA-DR-, MPO+++. Staining for nuclear PML protein can be performed – a microparticulate pattern supports diagnosis of APML. Rapid FISH testing for PML-RARA can also be used for diagnostic purposes.

All patients should have PB/BM samples sent to their designated SIHMDS laboratory for a baseline to guide molecular MRD monitoring (30mls EDTA PB and 10mls BM in heparinised culture media). Local SIHMDS laboratories should have provision in place to ensure samples are directed to the relevant MRD laboratories if they do not provide this service.

3.4.5 Cytogenetics

G-banding and FISH analysis is usually done on a bone marrow aspirate sample, although they may also be undertaken on peripheral blood if marrow is not available.

At least 20 metaphases should be evaluated for non-random chromosomal abnormalities and reported.

Interphase FISH may supplement standard analysis and is particularly useful where conventional G-banding fails. It can detect targeted chromosomal abnormalities such as RUNX1-RUNX1T1, CBFB-MYH11, PML-RARA, Inversion 3 and related abnormalities, KMT2A (MLL) rearrangements and chromosome 5 or 7 abnormalities or other gene fusions as dictated by clinical/morphological or immunophenotypic findings.

- **Essential:** G-banding; FISH for t(15;17) (PML-RARA), inv16 (CBFB-MYH11), t(8;21) (RUNX1-RUNX1T1), MLL rearrangement.
- **Extended:** FISH for chromosome 5 or 7 abnormalities or other gene fusions as dictated by clinical/morphological or immunophenotypic findings, these are particularly important where AML-MRC is suspected. Staining for nuclear PML protein can be performed by fluorescence microscopy – a microparticulate pattern supports diagnosis of APML.

3.4.6 Molecular assessment

All samples should be tested for clinically actionable mutations (e.g. FLT3, NPM1, CEPBA) with rapid turnaround times sufficient to allow the use of target therapies such as midostaurin. The repertoire of actionable mutations is likely to expand with the advent of novel therapies and prognostic tools, however the cancer test directory currently recommends testing for NPM1, CEBPA, RUNX1, FLT3, IDH1, IDH2, KIT, WT1, ASXL1, SRSF2, STAG2, RAD21, TP53, KRAS, NRAS, MLL-PTD.

Samples should be sent to a SIHMDS laboratory service proficient in the test at diagnosis. MRD assessments for CBF leukaemias using the fusion transcript can be useful for response monitoring.

NHSE plans to roll out whole genome sequencing for AML in the near future. This may assist in treatment stratification and/or trials of targeted therapies but a standard pathway is not yet established.

3.4.7 Bone marrow trephine (and other tissues, i.e. myeloid sarcoma)

This test will assess marrow cellularity, topography and blasts, and immunocytochemistry for lineage markers to complement immunophenotyping/morphologic assessment on the aspirate. It should be done at diagnosis and after recovery from the first chemotherapy cycle – thereafter, it is optional dependent on clinical need, outcome after cycle 1 and type of AML.

Immunohistochemistry panels on the trephine:

- **Suggested:** CD34/CD117/MPO/CD42b/Glycophorin C/HLA-DR/CD68R/TdT/CD20/CD3/PAX5/CD10.
- **Extended:** CD13/CD16/CD15/CD33/CD163/CD79a.

3.5 AML classification

This should be done as per WHO 2016. ([Table 3](#)).⁴

Table 3: AML WHO classification (2016)**AML with recurrent genetic abnormalities**

AML with t(8;21)(q22;q22.1);RUNX1-RUNX1T1

AML with inv(16)(p13.1;q22) or t(16;16)(p13.1;q22);CBFB-MYH11

APL with PML-RARA

AML with t(9;11)(p21.3;q23.3);MLLT3-KMT2A

AML with t(6;9)(p23;q34.1);DEK-NUP214

AML with inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2);GATA2, MECOM

AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);RBM15-MKL1

Provisional entity: AML with BCR-ABL1

AML with mutated NPM1

AML with biallelic mutations of CEBPA

Provisional entity: AML with mutated RUNX1

AML with myelodysplasia-related changes**Therapy-related myeloid neoplasms****AML, NOS**

AML with minimal differentiation

AML without maturation

AML with maturation

Acute myelomonocytic leukemia

Acute monoblastic/monocytic leukemia

Pure erythroid leukemia

Acute megakaryoblastic leukemia

Acute basophilic leukemia

Acute panmyelosis with myelofibrosis

Myeloid sarcoma**Myeloid proliferations related to Down syndrome**

Transient abnormal myelopoiesis (TAM)

Myeloid leukemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm

4 Risk Stratification at Diagnosis

Risk stratification includes the well-established risk factors such as increasing age, cytogenetic findings, WCC at presentation, molecular genetics, type of AML (i.e. *de novo* versus secondary), etc. This guideline will briefly summarise key cytogenetic factors and three validated molecularly prognostic aberrations associated with AML: FLT3-ITD, NPM1 and CEBPA mutations.

4.1 Cytogenetic abnormalities in AML

Conventional cytogenetic analysis at the time of diagnosis is the most important independent prognostic factor in adult AML, with regard to rates of complete remission (CR) and survival.^{5, 6}

Cytogenetic groups have historically been divided into three main categories: favourable risk, intermediate risk and adverse risk disease. Hierarchical cytogenetic clustering has defined three distinct groups with regard to remission rates, time to relapse and overall survival (OS).⁷ The favourable group, consisting of the 'Core Binding Factor' (CBF) leukaemias, t(8;21)(q22;q22) and inv(16)(p13q22)/t(16;16)(p13;q22), and the distinct disease entity of APML displayed, in general, a favourable outcome with regard to the achievement of an initial CR and superior OS. This is in contrast to the adverse risk group, comprising individuals with a complex karyotype (in this study defined as >3 unrelated abnormalities), -5/del5q, -7, del7q, certain KMT2A (MLL) rearrangements or 3q abnormalities, who displayed an increased risk of death during induction therapy, a higher incidence of primary resistant disease and a poorer OS.

Frequent features of complex karyotype AML are chromosome 17p abnormalities +/- TP53 gene deletions/mutations. The standard or intermediate risk group is comprised of those with a 'normal karyotype' on conventional G-banding analysis and abnormalities not classified as favourable or adverse; in this particular cohort these included +8, +21, +22, del 7q, del 9q, 11q23 anomalies and any other miscellaneous structural or numerical chromosomal anomalies. Diagnostic cytogenetic findings have hence been used to drive therapeutic stratification in major AML trials ([Table 4](#)).

For the purpose of classification, this guidance will follow the MRC definition of complex cytogenetics which is >3 chromosomal abnormalities.

4.1.1 Focus on core binding factor leukaemias

Altogether, these leukaemias consist of approximately 15% of all *de novo* younger adult (under 60) AML patients. The two hallmark cytogenetic findings are the presence of the t(8;21)(q22;q22) translocation or the inv(16)(p13q22)/t(16;16)(p13;q22). Although it is historically common to group together the core binding factor (CBF) leukaemias with regards to prognosis, important differences do exist between these two disease entities (clinic-pathological features, molecular heterogeneity and prognosis).⁹

KIT mutations have been described in 17–47% of individuals with t(8;21) and 22–38% of those with inv(16)/t(16;16)(21,22). The presence of KIT mutations, most commonly within exon 17, is associated with inferior clinical endpoints with regards to the cumulative incidence of relapse (CIR), event free survival (EFS) and OS in those with the t(8;21) translocation.^{10, 11} In the case of inv(16)/t(16;16), discrepancies exist between studies regarding the effect of KIT mutations on clinical outcome, although a Cancer and Leukaemia Group B (CALGB) study demonstrated that the CIR was higher in the mutated KIT group compared to the wild-type group, in particular those

with KIT exon 17 mutations (5 Year CIR; 80% vs 29%, $p=0.002$).¹⁰ However, response monitoring via qPCR based MRD assays for the fusion gene may provide a better indicator at an individual level of the risk of relapse.

In terms of treatment, all patients with CBF leukaemias should receive gemtuzumab ozogamicin as part of induction chemotherapy due to significant survival benefit (Hills et al [Lancet Oncol](#). 2014 Aug;15(9):986-96). It is accepted that CBF leukaemias benefit from multiple cycles of high-dose cytarabine (HiDAC) consolidation.

Table 4: AML MRC cytogenetic risk stratification – Grimwade et al 2010

Genetic group	Subsets
Favourable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 t(15;17)(q22;q21)
Intermediate	Cytogenetic abnormalities not classified as favourable or adverse
Adverse	abn(3q) (excluding t(3;5)(q21~25;q31-35) inv(3)(q21q26) or t(3;3)(q21;q26) -5 or del(5q); add(5q) -7; add(7q)/del(7q) t(6;11)(q27;q23); KMT2A rearranged t(10;11)(p11~13.q23); KMT2A rearranged t(11q23)(excluding t(9;11)(p21-22;q23) and t(11;19)(q23;p13) t(9;22)(q34.1;q11.2); BCR-ABL1 -17/abn(17p) Complex karyotype (≥ 4 unrelated abnormalities)

4.2 Molecular stratification

An increasing amount of data have become available concerning the molecular heterogeneity within AML, particularly within the CN-AML category. As ever-increasing numbers of prognostic factors are identified, the translation of these data into a clinically meaningful, composite scoring system for risk stratification becomes increasingly complex. The ultimate aim is to identify molecular classifiers that have enhanced prognostic power above that of conventional risk-stratifiers (Table 5).

Genetic group	Subsets
Favourable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 Mutated NPM1 without FLT3-ITD or with FLT3-ITDlow†

Genetic group	Subsets
	Biallelic mutated CEBPA
Intermediate	Mutated NPM1 and FLT3-ITD ^{high†} Wild-type NPM1 without FLT3-ITD or with FLT3-ITD ^{low†} (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); MLLT3-KMT2A [‡] Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); <i>DEK-NUP214</i> t(v;11q23.3); <i>KMT2A</i> rearranged t(9;22)(q34.1;q11.2); <i>BCR-ABL1</i> inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); <i>GATA2,MECOM(EVI1)</i> -5 or del(5q); -7; -17/abn(17p) Complex karyotype, [§] monosomal karyotype Wild-type NPM1 and FLT3-ITD ^{high†} Mutated RUNX1 [¶] Mutated ASXL1 [¶] Mutated TP53 [#]

Source: Dohner H *et al. Blood* 2017; **129**:424-447.

Frequencies, response rates, and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.

* Prognostic impact of a marker is treatment-dependent and may change with new therapies.

† Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5); semiquantitative assessment of *FLT3*-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve “*FLT3*-ITD” divided by area under the curve “*FLT3*-wild type”; recent studies indicate that AML with *NPM1* mutation and *FLT3*-ITD low allelic ratio may also have a more favourable prognosis and patients should not routinely be assigned to allogeneic HCT.

‡ The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.

§ Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.

|| Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).¹¹⁶

¶ These markers should not be used as an adverse prognostic marker if they co-occur with favourable-risk AML subtypes.

TP53 mutations are significantly associated with AML with complex and monosomal karyotype.

4.2.1 FLT3 mutations in AML

FLT3 mutations are among the most commonly detected genetic aberrations occurring in AML. Two main types of activating mutations occur: internal tandem duplications (ITDs), and tyrosine kinase domain (TKD) point mutations. About 25–30% of individuals with AML possess FLT3-ITDs, which mainly occur in the highly conserved juxtamembrane (JM) region producing ‘in-frame’ transcripts and a protein with constitutive activation.

The incidence of FLT3-ITDs appears to be particularly high in CN-AML and also in APL, although it can be found across a broad spectrum of AML subtypes. It is well accepted that the presence of a FLT3-ITD mutation conveys a poor prognosis in AML, but does not have an impact on outcomes in APL.^{13, 14}

The other group of well-documented FLT3 point mutations occurs in the 'activation-loop' region of the second TKD. These mutations occur in between 4 and 10% of adult AML cases and at least half involve residue D835 (D835Y).¹⁵ The significance of TKD mutations is not yet completely clear but they do not appear to be associated with a poor outcome.

4.2.2 NPM1 mutations

The NPM1 gene is located on chromosome 5q35. In AML, specific NPM1 mutations can occur leading to abnormal blast cell cytoplasmic accumulation of the mutant NPM protein – this is termed 'cytoplasmic dislocated-NPM1' (NPMc+). Although it is clear that the vast majority of *NPM1* mutations occur in the CN-AML category, studies of large cohorts of patients have demonstrated the presence of these mutations in combination with other karyotypic alterations, such as AML with trisomy 8 or trisomy 4, deletions and monosomies such as –Y. It appears to be mutually exclusive to the presence of the t(15;17) translocation.^{16, 17}

In general, NPM1 mutations in AML have been associated with a higher white cell count, CD34 negative blasts, a 'cup-sign' on morphology and increased percentage of blasts at diagnosis. Although described in all FAB types apart from the M3 promyelocytic group, it is significantly associated with myelomonocytic or monocytic morphology.¹⁷

The prognostic importance of the presence of the NPM1 mutation appears dependent on the presence or absence of co-operating gene mutations such as the *FLT3*-ITD. In brief, considering the mutation status of NPM1 and FLT3, the CN-AML NPM1 mutated/FLT3-ITD negative group displays favourable CR rates, EFS, RFS and OS in multivariate analyses. The high risk, poor prognostic group consists of those individuals with an *FLT3*-ITD mutation who are NPM1 wild-type.^{17, 18}

4.2.3 CEBPA mutations in AML

The transcription factor CCAAT/enhancer binding protein- α , encoded by CEBPA, plays an important functional role in normal granulopoiesis and sporadic CEBPA mutations have been found to occur in around 8% of adult AML cases. In younger adults with CN-AML and mutated CEBPA, there appears to be an associated favourable prognosis but this is restricted to patients with biallelic (double) CEBPA mutations.¹⁹ The favourable prognosis is negated by the presence of a FLT3-ITD.

4.3 Other prognostic factors

High white cell count ($>100 \times 10^9/L$) at presentation, male sex, secondary disease and age as well as refractory status at the end of cycle 1 ($>15\%$ blasts) also portend higher risk disease and should be considered in their entirety with the cytogenetic and molecular stratification of risk. Current NIHR AML trials incorporate a risk score into treatment randomisation strategies following cycle 1 of treatment.

4.4 Acute promyelocytic leukaemia (APML)

APML has particular cytogenetic, morphological and clinical characteristics. It is considered separately from other AML subtypes in terms of prognosis and treatment modalities. The hallmark feature of this disease is the balanced translocation t(15;17)(q24;q21), with the fusion of the promyelocytic gene (PML) on chromosome 15 and the retinoic acid receptor gene (RAR α) on chromosome 17. Rare variants of the disease are characterised by alternative translocations involving RAR α and other genes such as nucleophosmin (NPM), Signal Transducers and Activators of Transcription (STAT)5b, the nuclear mitotic apparatus gene (NuMA) and the Promyelocytic Leukaemia Zinc Finger (PLZF) gene.²⁰

The treatment of APML has been revolutionised by the use of all-trans-retinoic acid (ATRA), arsenic trioxide (ATO) and anthracycline-based chemotherapy.²⁰ This section will concentrate on the management of the PML-RAR α associated APML. Induction mortality used to be a considerable problem in the management of individuals with APML, in particular prior to the ATRA-anthracycline treatment era – predominantly due to haemorrhagic complications, in addition to infectious complications and occurrence of the ATRA differentiation syndrome. The differentiation syndrome is often characterised by dyspnoea, pyrexia, pulmonary infiltrates and weight gain, accompanied by a rising WCC.

Significant predictors of haemorrhage include increased WCC at presentation, abnormal renal function and deranged coagulation.²¹ The treatment of *de novo* APML with the ‘chemo-free’ ATRA/ATO combination therapy ‘upfront’ has also been found to induce a high remission rate and an excellent five-year RFS.

Despite the favourable post-induction prognosis of patients with APML, relapses can occur after chemotherapy+ATRA and hence MRD monitoring for these patients is recommended. Patients treated up front with ATO combinations have a very low relapse rate, obviating the need for routine MRD monitoring following treatment completion. It is generally accepted that the presence of PML-RAR α fusion transcripts at the end of induction does not correlate with clinical outcome. However, persistence of reverse transcriptase (RT)-PCR detectable PML-RAR α transcripts at the end of consolidation treatment is associated with future relapse.²² The adoption of quantitative RT-PCR (RQ-PCR) techniques for MRD monitoring, via sequential monitoring of fusion transcripts following the end of the consolidation treatment phase is therefore standard of care.

MRD monitoring with a bone marrow aspirate should be undertaken at least every three months after the end of therapy for the first three years in chemotherapy+ATRA treated patients. If MRD remains negative, monitoring can be stopped at that point as relapse thereafter is unlikely. If MRD becomes positive during this period, a repeat sample to confirm MRD is required and salvage therapy should be initiated (usually with ATRA + ATO dependent on first-line treatment and length of CR). The patient should be discussed at the MDT with a JACIE-accredited transplant centre for HSCT options, but there are emerging data that patients initially treated with chemotherapy+ATRA and salvaged with ATO containing regimens have excellent outcomes without HSCT.

5 Response Criteria

Remission status is determined after each cycle of treatment and discussed at the MDT with the restaging bone marrow. The marrow should be reassessed by day 35 of the treatment cycle (day 1 is the first day of chemotherapy on that cycle) unless confirmed to be in CR after cycle 1 and not requiring further MRD monitoring – this should be decided at the MDT. The following definitions of remission are standard, based on the percentage of leukaemic cells/blasts on morphologic assessment of the marrow aspirate film, and should be agreed during the MDT in order to define the management plan:

- **Complete remission (CR):** the marrow is regenerating normal haematopoietic cells and contains <5% blast cells by morphology on the aspirate film. ANC $\geq 1.0 \times 10^9/L$; platelet count $\geq 100 \times 10^9/L$
- **CR with incomplete hematologic recovery (CR_i):** All CR criteria except for residual neutropenia (<1.0 $\times 10^9/L$) or thrombocytopenia (<100 $\times 10^9/L$)
- **Partial remission (PR):** the marrow is regenerating normal haematopoietic cells with ANC $\geq 1.0 \times 10^9/L$ and platelet count $\geq 100 \times 10^9/L$ and there is a decrease of bone marrow blast percentage to 5% to 25%; and a decrease from pre-treatment bone marrow blast percentage by at least 50%
- **Resistant disease (RD):** the marrow contains >25% leukaemic cells.

The definition of MRD does not necessarily comply with the definitions of remission by morphologic assessment and needs to be assessed on a case-by-case basis at the MDT.

Re-staging and follow-up investigations on peripheral blood and/or bone marrow samples to determine MRD (as dictated by the original presentation):

- Morphology: As per WHO classification.
- Flow cytometry panels: these may be targeted based on leukaemia-associated phenotype. An accomplished understanding of normal BM pattern of expression of these markers is also invaluable for MRD monitoring.
- Immunohistochemistry panel on trephine: this should be based on the presentation phenotype.
- Cytogenetics/FISH: Based on findings at presentation.
- Molecular investigations: qPCR for PML-RARA for APL cases. All other mutations, such as NPM1 and CBF fusions dependent on remission status and treatment intent/clinical trial.

6 Patient Information and Support

If the diagnosis of AML is certain, patients should be informed by appropriately trained staff that AML is a cancer of the blood, bone marrow and immune system. Their prognosis, based on the bone marrow cytogenetics (when available), and other co-morbidities should be discussed along with possible treatment options and clinical trials or research studies currently available.

All patients must have access to a key worker. This is usually (but not always) the clinical nurse specialist (CNS). The CNS/key worker should be present at diagnosis and at any significant discussion where treatment changes and outcomes are discussed. In the absence of the CNS, a senior nurse may deputise. Discussions should be documented in the patient's notes and/or on the electronic patient record (EPR). Where it is not possible for the CNS or a deputy to be present, patients should be given the CNS's contact numbers. The clinician leading the consultation should advise the CNS, who should then arrange to make contact with the patient.

The CNS should ensure that all patients are offered a Holistic Needs Assessment (HNA) at key pathway points, including within 31 days of diagnosis, at the end of each treatment regime and whenever a person requests one. Following HNA, the patient should be offered a written care plan, which should be developed with the patient and communicated to all appropriate healthcare and allied healthcare professionals.

The Bloodwise (formerly Leukaemia & Lymphoma Research) and Macmillan Cancer Support AML or APML information booklets are good sources of patient information at diagnosis and are available for download on the following websites:

<https://bloodwise.org.uk/info-support/acute-myeloid-leukaemia/what>

<https://bloodwise.org.uk/info-support/acute-promyelocytic-leukaemia/what>

www.macmillan.org.uk/Cancerinformation/Cancerinformation.aspx

7 Treatment

Formal written consent should be obtained for all patients before commencing any cytoreductive therapy.

The BCSH suggested levels of care suitable to provide the facilities and resources required for the management of AML are:

Level 2a: Non-intensive management of AML only, i.e. without curative intent

Level 2b and Level 3: Management of AML with curative intent. All patients between 16 and 24 years of age should be referred to the Teenage and Young Adult (TYA) MDT at the relevant Principal Treatment Centre (PTC) – University College Hospital for North Thames and Royal Marsden Hospital for South Thames. Patients aged between 16 and 18 years must be treated at a TYA PTC. Patients between 19 and 24 should be offered the choice between treatment at a TYA PTC or at a TYA designated hospital.

If AML is suspected or definitively diagnosed, ensure that the patient is transferred immediately for treatment to at least a BCSH Level 2 haematology unit (Level 2b–3 for those who will undergo intensive treatment). This can be discussed with the AML lead or MDT lead in your haematology MDT if needed. Please ensure transfer is undertaken as soon as AML is suspected, so that the patient can have appropriate Level 2–3 nursing and supportive care, and that appropriate clinical trials are considered and enrolment/treatment can occur in a timely fashion. Ideally, a BMAT should be undertaken at the leukaemia unit after transfer if clinically appropriate.

Treatment for AML follows strict protocols and most patients are enrolled onto the current AML clinical trial on the National Portfolio of Clinical Studies (see [section 12: Research/Clinical Trials](#)). These protocols will therefore not be outlined in this guideline.

All patients should be offered entry into appropriate national trials where available.

Treatment for AML is quite regimented and driven by well-defined protocols within the trial set-up. This guideline will not recapitulate these clinical trials, but is a general guide to treatment strategies for new and relapsed patients. The main considerations are:

- AML may be a curable disease in young and older fit patients. It becomes harder to treat with age; fewer patients are cured as age advances and therapeutic complications are increasingly common.
- All patients should be treated with therapy suitable for their performance status and AML risk stratification.
- Since the disease is rare and treatment is complicated, there are many areas of controversy where best practice is not defined. Patients should be treated within a clinical trial wherever possible.
- Experienced specific and supportive care is required in a BCSH at least Level 2 unit which offers clinical trials.

7.1 Age- and risk-specific therapeutic approach

7.1.1 First-line treatment

All patients regardless of age should be offered the opportunity to participate in a clinical trial or research study.

The aim of induction chemotherapy is to induce a complete remission (CR). Consolidation chemotherapy and/or haematopoietic stem cell transplantation is necessary to prevent relapse and increase the chance of cure.

In the absence of a clinical trial, the following guideline is recommended for the treatment of AML (except APML – see below):

Induction therapy (cycles 1 and 2)

The cornerstone of induction treatment in AML patients deemed fit for intensive therapy is a daunorubicin and cytarabine-based schedule (Excluding APML). A number of recent NICE technology appraisals have approved additional adjuncts to conventional regimens and alternative formulations. Early decision making based on available morphological, cytogenetic and molecular results is critical in order to offer the best regimen on a case by case basis.

In general, those under 60 years (or older patients deemed fit for intensive therapy at clinician discretion) should undergo the current standard induction therapy consisting of daunorubicin and Ara-C (DA), 3+10 (cycle 1) and 3+8 (cycle 2). The recommended daunorubicin dose in the first cycle is 60mg/m². FLAG-Ida for cycles 1 and 2 may also be considered if patients are young and already known to be high risk.

Patients with CD33-positive AML with favourable or intermediate risk cytogenetics (table 2), or where cytogenetic results are unavailable at the time of initiating treatment may receive gemtuzumab ozogamicin in addition to daunorubicin and cytarabine as per NICE guidance [TA545, 2018]. In cases where Gemtuzumab ozogamicin is started prior to knowing the cytogenetic results, it should not continue if subsequent results indicate poor prognosis karyotype.

Patients with therapy-related AML, or AML with myelodysplasia-related changes (AML-MRC, defined by a history of pre-existing MDS or MDS/MPN, cytogenetic abnormalities consistent with a presumptive diagnosis of pre-existing MDS (ELN) or dysplasia in at least 50% of cells in at least 2 lineages (WHO)) may receive liposomal cytarabine-daunorubicin (L-DA, Vyxeos). For induction remission the dose is daunorubicin 44mg/m² and cytarabine 100mg/m² day 1, 3 and 5 for course 1 and daunorubicin 44mg/m² and cytarabine 100mg/m² day 1 and 3 for a subsequent induction course if needed (NICE TA552, 2018).

Patients with mutations in FLT3 (either ITD or TKD) are now eligible to receive the TKI midostaurin as part of their treatment programme (NICE TA523, 2018). Midostaurin is started 24 hours after the last dose of chemotherapy and continued for 14 days in induction and each of subsequent consolidation cycles. Midostaurin can then be continued as single agent maintenance for up to 48 weeks. It should be stopped 48 hours prior to starting transplant conditioning.

It should be noted that only patients treated with conventional daunorubicin plus cytarabine induction regimens and high-dose cytarabine consolidations are eligible for treatment with midostaurin or gemtuzumab ozogamicin (GO, Mylotarg), and that these adjuncts are

reimbursed in a mutually exclusive manner. Therefore rapid cytogenetic and FLT3 mutation testing should be available in order to aid decision making prior to initiating treatment.

Consolidation therapy (cycles 3 +/- 4)

The MRC AML12 and 15 trials did not find any benefit of five over four cycles of therapy. Consolidation with HiDAC is standard of care currently – 1.5gm/m² is not inferior to 3gm/m² and may be preferred, especially in older patients due to potential neurotoxicity. For younger patients with adverse-risk cytogenetics, consolidation with MACE/MIDAC is preferred if there are delays to planned HSCT or if patients are not fit for allograft (**Burnett et al JCO 2013 figure 4**).

Patients who received gemtuzumab ozogamicin (Mylotarg) may receive 3mg/m² on upto 2 courses of consolidation (addition of gemtuzumab to maximum of 3 courses of conventional treatment in total).

Patients with FLT3 mutated AML may continue to receive midostaurin in consolidation cycles as above, and as maintenance for 48 weeks.

For patients treated with liposomal cytarabine-daunorubicin (Vyxeos), consolidation continues at a dose of daunorubicin 29mg/m² and cytarabine 65mg/m² on days 1 and 3 for a maximum of 2 course.

If patients are to proceed to an allogeneic stem cell transplant, the procedure should be undertaken as soon as a CR is achieved and the donor is readily available and prepped. One or two cycles of consolidation can be given as a 'holding' measure until the transplant can be performed, but the risks of toxicity and prolonged cytopenia need to be taken into consideration.

Haematopoietic stem cell transplantation (HSCT)

All potential allogeneic HSCT (AlloSCT) candidates should be discussed with a JACIE-accredited stem cell transplantation unit at the earliest opportunity. A critical factor contributing to outcome in HSCT is appropriate referral, planning and timing of SCT. Adequate time is needed to identify the most suitable donor and to obtain a stem cell product. In general, all high-risk and most intermediate-risk patients with AML receiving chemotherapy with curative intent should be referred to explore transplant options early.

It should be noted that the risk stratification of AML is dynamic and increasingly complex due to the increasing availability of molecular markers. A complete guide to SCT for AML is outside the remit of this guideline and all potential cases should be discussed.

However, the following general points can be applied.

- In general, there is no indication for SCT in favourable risk AML in CR1.
- AlloSCT should, if feasible, be performed in those with poor risk AML in CR1. This is defined as those with unfavourable cytogenetics (MRC criteria), with unfavourable molecular genetics (FLT3-ITD and NPM1 wild type), therapy-related or secondary AML in CR1, and those who fail to achieve CR to standard induction therapy. Patients with NPM mutations should also proceed to transplant if they remain NPM MRD positive after cycle 2 of chemotherapy. Equally MRD monitoring of fusion transcripts in CBF-leukaemias can also be informative for selecting those at high risk of relapse that may benefit from upfront alloSCT.
- With regards to those with intermediate-risk AML, this is a very heterogeneous group. The AML17 'high-risk' score can help to indicate those who may benefit from AlloSCT within this

cohort. The majority of transplant physicians will consider transplant consolidation in this group of individuals, although the supporting data are mixed. Decisions regarding AlloSCT should be made on an individualised, case-by-case basis.

- All patients who achieve CR2 should be referred for AlloSCT.
- All potential transplant candidates should have CMV status and HLA Class I and II typing performed at the earliest opportunity.

7.1.2 Poor-risk, refractory or relapsed patients (second-line treatment)

All suitable patients should be discussed with the transplant team to consider stem cell transplantation. Patients without an HSCT option should be offered a clinical trial for novel agents, if available (see [section 12: Research/Clinical Trials](#)).

Primary refractory AML

A lack of response, or only a partial response, to induction chemotherapy is associated with a poor prognosis in general. The general approach is to escalate to 1–2 cycles of FLAG-(Ida) chemotherapy in an attempt to gain CR prior to a potential allogeneic HSCT if a suitable donor is identified. Alternative salvage regimens pre-allograft are offered in the treatment algorithm ([Figure 2](#)), and early phase clinical trial or access to compassionate use programs of novel agents should be considered.

Relapsed AML

The management of patients who relapse is complex and often the outcome is unsatisfactory. In deciding upon the most appropriate salvage therapy, many factors need to be taken into consideration, including induction protocols used, the patient's age, performance status, cytogenetics, the length of initial CR achieved, the potential for consolidation with an allogeneic HSCT (or indeed second HSCT and/or DLI therapy) and patient preference. In younger and/or more fit patients, treatment is planned with a view to proceeding to an HSCT.

The most commonly used regimen is up to two cycles of FLAG-(Idarubicin) in an attempt to gain a second CR prior to proceeding to HSCT. Cumulative anthracycline exposure should be determined to ensure that the patient has not reached the maximum doses. Other salvage regimens chosen are dependent on previous lines of therapy, performance status and risk profile. All cases should be discussed at the MDT.

If a suitable trial is open, all patients relapsing or refractory to FLAG-based chemotherapy should be considered. Other salvage options are included in the treatment algorithm ([Figure 2](#)). Low dose continuous infusion Ara-C (either 10 or 20mg/m²) / 24-hour infusion for 21 days or access to compassionate use programs of novel agents may also be considered to attempt remission pre-allograft.

If a new remission is achieved (CR2) then AlloSCT is the preferred method of consolidation. In those who undergo further relapse post-transplant, in the absence of active GVHD, immunosuppression should be discontinued and consideration given to donor lymphocyte infusions. Consideration should be given to the use of azacitidine in selected patients, in particular those with low blast counts. In those younger, fitter patients who relapse more than 12 months after an AlloSCT, consideration should be given to a second allograft following salvage chemotherapy.

An estimate of long-term survival has been suggested by a simplified risk stratification for those patients younger than 60 in first relapse (Table 5).²³

Table 5: Simplified prognostic score (0–14 points) for AML age <60 at first relapse (non-APML)

Duration of CR	Points	Cytogenetics at diagnosis	Points
>18 months	0	Inv 16 or t(16;16)	0
7–18 months	3	t(8;21)	3
<6 months	5	Other [†]	5
Age at first relapse		SCT pre-relapse	
<35	0	No SCT	0
36–45	1	Prior SCT	2
>45	2		
Risk	Index score in points	Survival probability %	
		At 1 year	At 5 years
Favourable (9% of patients)	0–6	70	46
Intermediate (25% of patients)	7–9	49	18
Unfavourable (66% of patients)	10–14	16	4

[†] Normal, intermediate, unfavourable and unknown cytogenetics.

7.1.3 Management of elderly patients with AML

Outcomes for elderly patients with AML are inferior to those of younger patients. In general, there is often a higher rate of induction deaths and drug resistance, and poorer RFS and OS. These data are confounded by co-morbid medical conditions and a reluctance to stratify those aged over 60 to appropriate risk-adapted therapy. Even in those deemed fit enough for intensive chemotherapy, although initial CR rates of up to 50% in some studies can be obtained, relapses are common and overall survival is poor. There is no ‘standard’ post-remission therapy. Fitter elderly AML patients suitable for intensive therapy and potential RIC allogeneic HSCT should be discussed with the transplant team at a JACIE-accredited centre. Recent reports have suggested that age alone, at least up until the age of 70, does not alter the outcome in RIC transplantation.

Elderly patients with complex cytogenetics have a low rate of CR.

Of note in a study of 5'-Azacitidine therapy in AML with 20–30% blasts, patients deemed unfit for standard induction chemotherapy were randomised between conventional care regimens (CCR; BSC, LD Ara-C and HC) and azacitidine. In the 113 patients studied, patients with low BM blast count WHO-defined AML (previously classified as RAEB-t using FAB criteria) clearly benefited from azacitidine treatment compared with CCR, with half of patients in the azacitidine group still alive at two years, compared with only 16% in the CCR group.²⁴ There was a reduction in hospital inpatient days and a higher proportion achieved RBC transfusion independence. Azacitidine can be of benefit and induce remissions even in patients with poorer-risk disease and should be considered in those patients with a blast count 20–30% if a clinical trial is not available or preferred.

Stratification of the elderly AML patient

The Wheatley criteria define three risk groups with regards to outcomes in elderly AML, derived from retrospective analysis of the patients enrolled in the AML11 trial.²⁵ These are performance status, *de novo* versus secondary AML, age, cytogenetics and WBC count at presentation. These prognostic factors were validated in the AML14 trial. The three prognostic groups had one-year survival rates of 53%, 43% and 16% respectively (Table 6).

Table 6: Simplified risk score

Parameter	Score
Cytogenetic group	1 = favourable/intermediate, 5 = adverse, 2 = unknown
WBC group	1 = <10.0, 2 = 10.0–49.9, 3 = 50–99.9, 4 = 100+ ($\times 10^9/L$)
Performance status	Performance status score: 0, 1, 2, 3, 4
Age group	1 = 60–64, 2 = 65–69, 3 = 70–74, 4 = 75+ (years)
AML type	1 = <i>de novo</i> , 3 = secondary
Total	Score (cytogenetic group) + Score (WBC group) + Score (performance status) + Score (age group) + Score (AML type)
Risk group (1-yr survival)	4–6 = Good (53%) 7–8 = Standard (43%) 9+ = Poor (16%)

Rollig *et al* reported recently on 909 elderly patients enrolled in the AML 96 trial and were able to distinguish four prognostic groups: ‘favourable risk’, ‘good-intermediate risk’, ‘adverse-intermediate risk’, and ‘high risk’ based on favourable and adverse cytogenetics and a stratification of those with an intermediate risk karyotype based on CD34 expression ($\leq 10\%$), LDH and *NPM1* status (mutated versus non-mutated).²⁶ In summary, these scoring systems can aid identification of those who may benefit from standard therapy, and those who will not and may warrant more investigational therapy.

Recommendations for treatment in elderly AML

All patients should be offered the opportunity to enter a clinical trial or research study (see [section 12: Research/Clinical Trials](#)).

In the absence of a clinical trial, the following guideline is recommended for the treatment of AML (except APML – see [section 7.2](#)):

For elderly patients with no co-morbidities and a PS <2, consider standard induction chemotherapy. Cytogenetic and molecular investigations should be carried out as for younger patients. Those with standard or favourable risk cytogenetics are eligible to receive DA plus gemtuzumab and those with FLT3 mutations should be considered for DA plus midostaurin. For those with adverse cytogenetics, the outcome is poor and consideration should be given to investigational drugs. A RIC HSCT should be considered.

For those not deemed fit for intensive therapy, consider:

- investigational agents (especially if adverse cytogenetics)

- azacitidine if meets NICE criteria (especially if adverse cytogenetics and blasts 20–30%)
- LD Ara-C SC BD or by continuous infusion
- best supportive care.

7.2 APML treatment

Also see [section 9: Supportive Care](#).

APML is a haematological emergency and, if suspected on review of the blood film or bone marrow aspirate, ATRA should be commenced at a dose of 45mg/m² in divided doses ASAP prior to confirmatory test results.

An emergency supply of ATRA should be available at all centres with a Level 2–3 haematology unit. The diagnosis should be confirmed and treatment commenced within 24 hours (see [section 7.2.1](#)).

In APML, appropriate supportive care (especially during induction) is just as important as the administration of chemotherapy and strict guidelines/protocols should be followed in a Level 2–3 unit experienced in such protocols. The main cause of early mortality is uncontrolled haemorrhage due to disseminated intravascular coagulation (DIC).

Diagnosis is based on the haemorrhagic clinical manifestations, typical morphology of the leukaemic cells, laboratory evidence of DIC and characteristic antibody staining and cytogenetics.

7.2.1 Key points in APML management

- ATRA should be started as soon as the diagnosis is suspected, at a dose of 45mg/m²/day fractionated into two doses (NB: contraindicated if allergic to soya or peanuts).
- Diagnostic and follow-up BM and PB samples should be sent for baseline investigation and subsequent MRD.
- At least once daily clotting screen should be done during induction therapy. Maintain plts >50 x 10⁹/L, fibrinogen >2 with cryoprecipitate and correct APTT and PT with FFP.
- Leukapheresis in high WCC patients should be avoided – there is a high risk of exacerbating fatal haemorrhagic outcome.
- Beware of ATRA syndrome and treat promptly (prophylaxis may be considered if patients present with high WBC at diagnosis).

All patients should be offered the opportunity to enter a clinical trial or research study (see [section 12: Research/Clinical Trials](#) section).

Non-trial patients

See [Figure 3](#).

Patients with low/intermediate risk APML as defined by a presenting white cell count below 10 x 10⁹/L are now eligible to receive arsenic trioxide (ATO) and ATRA as front line therapy (NICE TA526, 2018) and this is the treatment of choice, although idarubicin-based regimens still remain a clinical option. For patients with a presenting WCC > 10 x 10⁹/L, the established therapy is based

upon the PETHEMA protocol of ATRA and idarubicin, which achieves >90% remission rates.²⁷ ATRA should be commenced as soon as the diagnosis is suspected at a dose of 45mg/m²/day fractionated into two doses (NB: contraindicated if allergic to soya or peanuts). At least daily clotting screen during induction therapy should be done. Maintain platelet count >50, fibrinogen >2 with cryoprecipitate and correct APTT and PT with FFP. Leukapheresis in high WCC patients should be avoided at risk of exacerbating fatal haemorrhagic outcome (see [section 9: Supportive Care](#) and [section 8: Management of Disease and Treatment-related Complications](#)).

If the WCC is >10 x 10⁹/L at presentation, the first dose of idarubicin of AIDA may be brought forward by 24 hours (i.e. administer on day 1). Patients who present with a WBC >10 x 10⁹/L should be considered for dexamethasone 10mg 12-hourly for the first 3–5 days as prophylaxis against ATRA syndrome. NB: failure to achieve haematological CR after 60 days of ATRA equates to high-risk disease and treatment options need to be reviewed. This is a very rare occurrence in practice.

Treatment should only proceed with each cycle when neutrophils >1.5 and platelets >100. If cytopenias are thought to be due to disease, discuss with consultant in charge of care and with expertise in APML treatment.

7.2.2 APML in the elderly

Patients with low/intermediate risk APML (as defined by a presenting white cell count below 10 x 10⁹/L) should receive arsenic trioxide (ATO) and ATRA (NICE, 2018). For high risk patients, experience from the PETHEMA group suggests that the ATRA/anthracycline combination can be used in the elderly with success, although there is higher remission-induction mortality, particularly in those >70 years of age. In the original protocol, for those over 70 years, the fourth dose (i.e. day 8) of idarubicin was omitted.

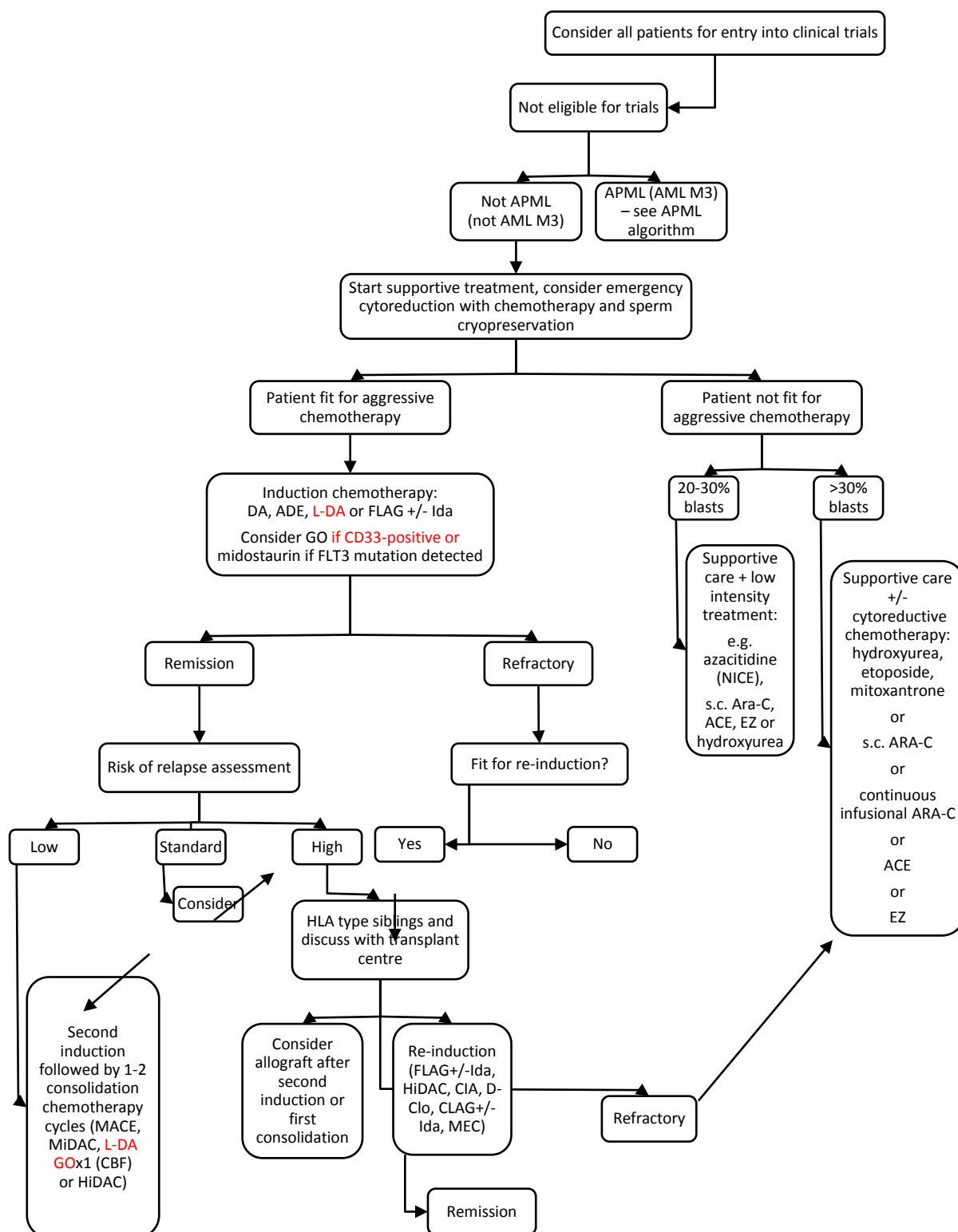
7.2.3 Clinical or molecular relapsed APML or persistent MRD+

Relapsed APML needs re-induction therapy in an attempt to gain molecular-negativity. Arsenic trioxide (ATO) is at present the drug of choice and is licensed in the UK for relapsed/refractory APML. All cases of relapsed APML should be investigated for CNS disease.

The ATO chemotherapy script/proforma should be consulted for key issues regarding electrolyte replacement and QT intervals prior to administration. Patients should have an ECG assessment before and up to twice weekly during treatment to ensure that the QT interval does not exceed 460msec. Drugs which can prolong the QT interval should be avoided. During therapy the serum potassium must be kept above 4mmol/l and the serum magnesium above 0.8 mmol/l.

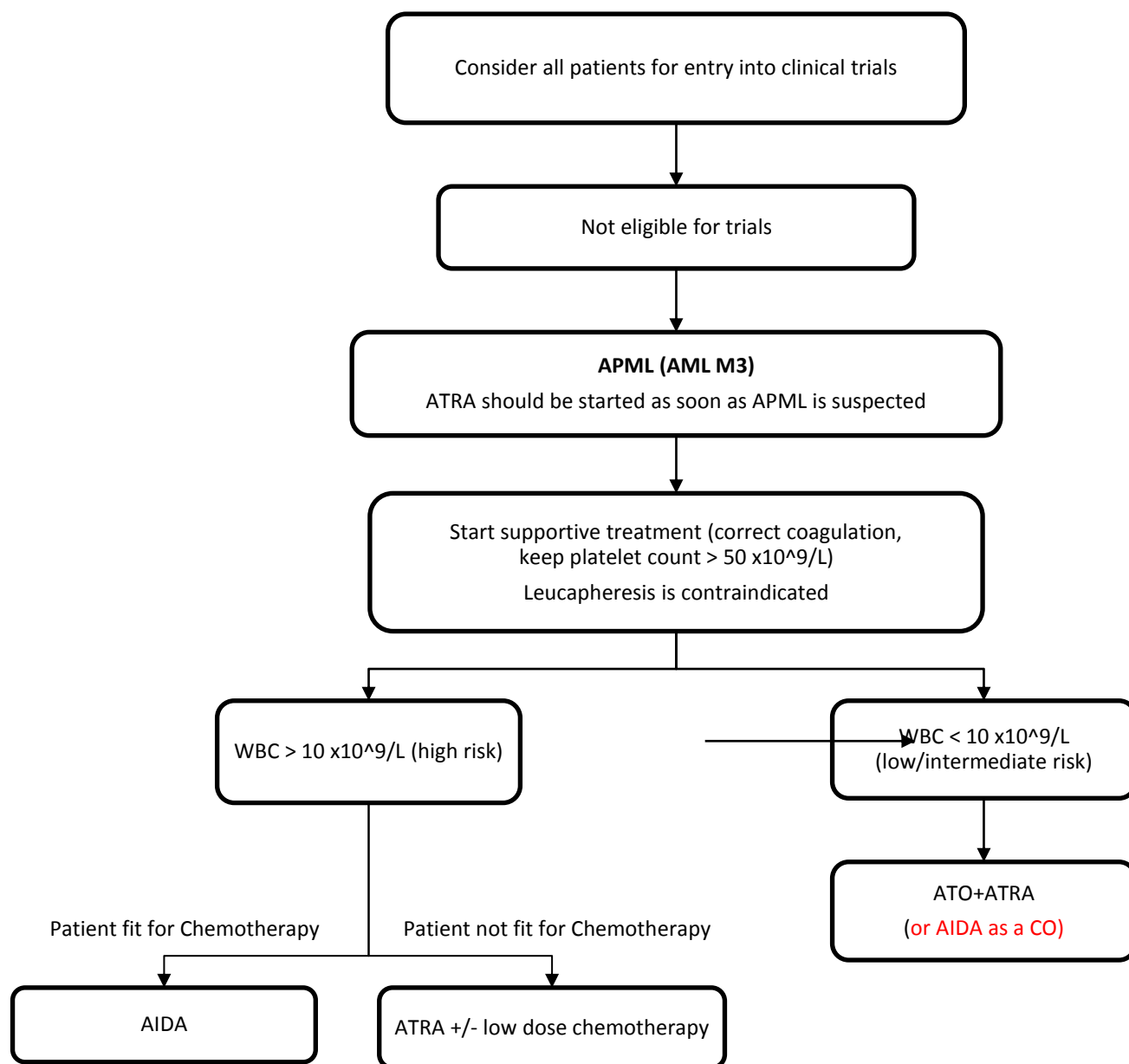
Re-induction therapy will require either further arsenic or HSCT as a consolidation measure. If molecular negativity has been achieved, this could be an autologous HSCT (CR2) or an allogeneic HSCT if MR is not achieved and in high-risk disease.

APML relapse patients must have a lumbar puncture to check for CNS relapse, a common feature at clinical relapse of disease.



DA, daunorubicin and cytarabine, L-DA, Liposomal daunorubicin and cytarabine (Vyxeos), GO, gemtuzumab ozogamicin (Myelotarg), FLAG-Ida, Fludarabine, cytarabine, GCSF, and idarubicin, ADE cytarabine daunorubicin and etoposide, ARA-C, cytarabine, HiDAC, High-dose cytarabine, MACE, Amsacrine, cytarabine, etoposide, MiDAC, Mitoxantrone and cytarabine, CIA, Clofarabine, idarubicin, cytarabine, DClo, Daunorubicin, clofarabine, CLAG-Ida, Cladribine, cytarabine, idarubicin, EZ, etoposide, idarubicin, ACE, A220, quizartinib / alternative FLT3 inhibitor.

Figure 3: Treatment algorithm – APML



8 Management of Disease and Treatment-related Complications

8.1 Anaemia

Appropriate blood transfusion support should be provided for patients with AML. Red cell transfusions should be avoided if there is any risk of leukostasis. Irradiated blood should be given if the patient is going to proceed to an allogeneic stem cell transplant within the month, or if regimens with fludarabine, cladribine or clofarabine are used.

8.2 Severe neutropenia

Patients with AML are often neutropenic on presentation and this worsens with initiation of therapy. The standard neutropenic precautions regarding infection control, use of single rooms as well as prophylaxis are mandatory (see [section 9.6](#)). All healthcare professionals should employ the highest level of infection control.

The use of G-CSF is highly dependent upon the context of the disease and the chemotherapy protocol in which it is being used. G-CSF is used to hasten recovery of the neutrophil count, decrease risk of infection and reduce hospital stay. However, evidence supporting improved survival with G-CSF is lacking. It may be used in patients who have a definite CR and are in at least the second cycle of chemotherapy – use should be initiated only after discussion with a consultant and only when absolutely clinically indicated. It may also be used in the context of specific chemotherapy regimens (e.g. FLAG-Ida, CLAG-Ida).

8.3 Neutropenic sepsis

Patients with neutropenic pyrexia or sepsis should be treated according to local protocols for neutropenic sepsis, including taking of blood culture samples.

In addition, the following may be considered:

- Urinalysis
- Midstream specimen of urine
- Chest X-ray
- Swabs: throat (bacterial and viral), CVAD site if present and any other focal lesions as appropriate
- Sputum and stool culture
- CMV, EBV, Adeno PCR if indicated.

8.4 Severe thrombocytopenia

Platelets should be transfused when the platelet count is $\leq 10 \times 10^9/L$, or $\leq 20 \times 10^9/L$ in the setting of sepsis. If the patient is bleeding, aim for higher platelet counts, dependent on the extent and site of blood loss. Platelets should be $\geq 50 \times 10^9/L$ for a lumbar puncture.

Irradiated blood products should be requested for patients on protocols containing fludarabine, cladribine and clofarabine and for those planned to proceed to an allogeneic stem cell transplant.

Consider tranexamic acid in order to maintain haemostasis in patients who have bleeding that is difficult to manage only if the patient is in CR (and if the urine dipstick is negative for blood). See [section 9.1: Transfusions](#).

8.5 Thrombosis/haemostasis

Patients with AML are at high risk of bleeding complications. Every patient should have a clotting screen at diagnosis and clotting abnormalities corrected. Anticoagulation should be avoided unless there is clear documentation of a thrombotic event. In this case, advice should be sought from a coagulation specialist.

Haemorrhagic complications can be especially problematic in patients with APML. In APML, platelets should be maintained $\geq 50 \times 10^9/L$ with apheresis platelet transfusions during induction cycle 1 of therapy (until disease is in a haematological CR). PT, aPTT and fibrinogen should also be corrected (to an INR and/or aPTTR level < 1.5 and fibrinogen $> 1-2g/L$) with FFP 12–15ml/kg and cryoprecipitate 10-pk units as clinically indicated. Coagulation (PT/aPTT, fibrinogen and FBC) should be measured twice daily until coagulation normalises, and thereafter once daily until remission confirmed. There is no role for the routine use of heparin or tranexamic acid in APML.

Ensure that patients have good control of blood pressure (if they are known to be hypertensive) and avoid aspirin/NSAIDs and IM injections. Avoid arterial blood gases unless absolutely necessary – ensure platelets $> 50 \times 10^9/L$.

8.6 Hyperleukocytosis/hyperviscosity syndrome

Hyperleukocytosis/hyperviscosity syndrome occurs due to an elevated leukaemic blast cell number in the peripheral blood circulation; the increased viscosity causes leukostasis within vulnerable capillary regions and ischaemia of tissues with occasional infiltration of leukaemic cells into the tissues themselves, causing organ compromise.

Symptoms of leukostasis occur at different blast cell count thresholds, depending on the leukaemic subtype. In AML, the blast count is typically greater than $50 \times 10^9/L$ when symptoms occur, although it can occur at any level of WBC count especially in acute monoblastic leukaemia (even $10 \times 10^9/L$).

Urgent leukapheresis can be undertaken if high counts are causing symptoms of hyperviscosity. Cyto-reductive therapy must be initiated or optimised simultaneously. Transfusion and dehydration should be avoided in patients with hyperviscosity syndrome and aggressive hydration should be instituted.

8.7 Hyperviscosity syndrome

Urgent leukapheresis can be undertaken if high counts are causing symptoms of hyperviscosity. Cyto-reductive therapy must be initiated or optimised simultaneously. See [section 8: Management of Disease and Treatment-related Complications](#).

8.8 Leukapheresis

The need for leukapheresis is determined by symptoms and risk stratification – a high leukocyte count is not in itself an indication for urgent leukapheresis. Patients with features (even very early) of leukostasis (e.g. pulmonary infiltrates, hypoxia, CNS changes, renal failure, cardiac ischaemia, priapism, severe retinopathy) should however be considered for leukapheresis. Leukapheresis is contraindicated in APML.

8.9 Tumour lysis syndrome (TLS)

See [Annex 1](#).

Patients with aggressive disease may already be in tumour lysis prior to the initiation of chemotherapy. Tumour lysis is indicated by a high LDH, uric acid, hyperkalaemia, hyperphosphataemia, hypocalcaemia and renal failure (see [Annex 1](#) and [Annex 2](#)). The mainstay of treatment is avoidance by aggressive IV hydration from diagnosis, and especially at the start of cytoreductive therapy, rasburicase as per protocol (if G6PD is normal), followed by allopurinol. If TLS does occur, patients undergoing intensive therapy must be supported with appropriate fluid and electrolyte management and, if necessary, ICU transfer with haemofiltration until TLS resolves and renal function improves.

8.10 Hyperuricaemia

See [Annex 2](#).

Patients should be treated with allopurinol or rasburicase according to local protocols and patient-specific factors (e.g. renal failure, WBC count, level of LDH/uric acid). All patients should be well hydrated and receive allopurinol 100–300mg daily (dependent on renal function). This should continue for at least the first two cycles of induction treatment unless an allergy develops. Allopurinol should be re-initiated for relapsed disease.

8.11 Myeloid sarcomas

Myeloid sarcomas (MS) – either *de novo*, coincidental with AML or secondary – are rare extramedullary tumours which are included in the current WHO classification of AML. Patients should be managed systemically in exactly the same fashion as those presenting with AML. The selective use of either radiotherapy or surgical debulking is adjunctive therapy only in certain specific situations such as spinal cord compression, and is not considered ‘stand-alone’ definitive therapy for those with MS.

8.12 CNS disease

Patients with AML may present or relapse with CNS involvement. A typical presentation is ‘numb-chin syndrome’ or ‘sub-mental/mental neuropathy’. Such patients should have an urgent MRI brain/whole spine and LP with CSF for protein/glucose/microbiology and cytology with immunophenotyping. Intrathecal chemotherapy should be administered at the same time as the first LP (see [section 7: Treatment](#)).

Patients with relapsed APML should have a diagnostic LP, as CNS involvement is common at relapse.

CNS disease at presentation in AML occurs in <1% of all adult patients. Management of CNS disease at any stage should follow the suggestions encompassed in the current clinical trial.

If a patient with AML presents with signs +/- symptoms suggestive of CNS disease, they should have a diagnostic LP performed (following a brain CT/MRI scan) to obtain samples for cytospin and flow cytometry, with concomitant administration of intrathecal cytosine arabinoside (Ara-C) 50mg. If cytospin/flow cytometry confirms CNS disease then treatment with Ara-C 50mg should continue three times/week until clearance of the blasts and the majority of centres continue weekly for up to six weeks. Systemic therapy would also continue as planned.

8.13 Pregnancy and AML (adapted from ELN/BCSH guidelines)

This specific situation requires joint management with the haematologist and obstetrician. Therapy for AML must be balanced between the mother's health and the immediate and potentially long-term effects on the developing foetus; treatment delays can adversely affect maternal outcome. Leukaemia in pregnancy has been associated with increased rates of spontaneous abortion, intra-uterine growth retardation and perinatal mortality.

The risks of teratogenicity are documented as highest between 2 and 8 weeks post-conception. The option of early termination should be offered to the mother in the first trimester. The risks of chemotherapy in the second and third trimester need to be discussed with the mother at the time of consent. Consideration should be given to early induced labour between cycles of chemotherapy. Due to postulated increased placental transfer of idarubicin, daunorubicin is the anthracycline of choice during induction. ATRA is contraindicated in the first trimester, but can be administered in the second and third trimesters. Arsenic trioxide is contraindicated at any point during pregnancy and lactation. Supportive therapies should also be adjusted according to teratogenic effects and the potential of the drug to cross the placenta.

8.14 Initial cytoreduction with hydroxyurea

For patients with high WBC counts, with symptoms (or at risk) of leukostasis, treatment with hydroxyurea/hydroxycarbamide (HU) should be started as a matter of urgency until definitive cytoreductive chemotherapy can be administered. Treatment may be started with HU 2 grams 1–4 times per day, dependent on WBC count, to aim for rapid reduction of blasts together with rasburicase (see [Annex 2](#)) administered as a once daily 30 minute intravenous infusion in 50ml of a sodium chloride 0.9% solution (or allopurinol 300mg/day orally if rasburicase contraindicated, e.g. G6PD deficiency), and adequate hydration.

If rasburicase cannot be used, saline hydration with additional bicarbonate to alkalinise urine may be instituted, with forced diuresis if necessary, to reduce the symptoms of leukostasis and to reduce the adverse effects of tumour lysis. Aggressive supportive measures (as indicated by the patient's performance status prior to the diagnosis of leukaemia) are advised. This may include ventilatory and dialysis support until definitive cytoreduction can be accomplished, and thereafter as deemed appropriate.

8.15 Ara-C-induced conjunctivitis

To prevent conjunctivitis during high-dose cytarabine ($\geq 1\text{g/m}^2$), all patients should be given prednisolone 0.5% eye drops in each eye every two hours during waking hours (some centres may also use betamethasone 0.1% eye ointment at night starting the day before) and continuing until five days after the last dose of cytarabine.

8.16 Ara-C (CYSTAR) syndrome

This side effect is rare and generally seen with higher doses of the drug.

8.16.1 Clinical features

- Occurs within 6–12 hours of administration of the drug.
- Characteristic features include fever, myalgias, arthralgias, bone pain, occasional chest pain, maculopapular rash and conjunctivitis.

8.16.2 Action

Most patients respond to withdrawal of the drug or, if treatment needs to be continued, by the addition of corticosteroid therapy.

8.17 ATRA (tretinoin) syndrome

ATRA syndrome is a life-threatening complication of uncertain pathogenesis that can occur during treatment of patients with APML using ATRA.

8.17.1 Characteristics

- Typical onset in first 1–2 weeks of ATRA treatment
- Incidence 10–15%
- Risk greater if presentation WCC $>5 \times 10^9/L$ occurs as WBC is usually rising
- Occurrence of ATRA syndrome associated with lower event-free survival/overall survival
- Respiratory distress with pulmonary infiltrates
- Pleural and pericardial effusion
- Fever
- Weight gain
- Hypotension
- Renal failure.

8.17.2 Management

- Stop ATRA
- High dose IV dexamethasone 10mg bd for three days initially
- Furosemide as clinically required
- Ventilation and/or haemodialysis may be required.

8.18 Anthracycline-related myocardial damage

Although the cumulative dose of anthracycline is the most important risk factor for myocardial damage during intensive treatment, cardiomyopathy may occur at any dose of anthracycline, in particular in those patients with other CVS risk factors. There is no standard treatment strategy to prevent such effects. An adequate EF (>50 – 55%) should be ensured prior to initiation of anthracycline treatment and repeat ECHO or MUGA should be done during treatment if there is any suspicion of cardiac damage.

Cardioxane (dexrazoxane) may be an option at some centres, although it is not standard of care currently – it has the potential to reduce the risk of anthracycline-related myocardial damage. Each case should be discussed with the consultant prior to writing the prescription and the name of the drug should be included in the consent for chemotherapy form. Its use should be considered in the following types of patient:

- Aged over 60 or under 18
- Significant cardiac history

- Left ventricular ejection fraction <50%
- Previous anthracyclines to equivalent of 300mg doxorubicin
- Other CVS risk factors (HTN, DM, strong family history, high cholesterol).

Dose

Daunorubicin: 20mg cardioxane/mg anthracycline

Idarubicin: 50mg cardioxane/mg anthracycline

Delivered in 250 mls Ringer's lactate (sodium lactate) over 15 minutes (~30 minutes before anthracycline). Total dose of dexrazoxane not >1000mg/m² with a single dose of anthracycline – to be given with each dose of anthracycline. ECG and MUGA scan or doppler echocardiogram pre-treatment and at one month and six months post-treatment.

Mitoxantrone may also result in myocardial damage at cumulative doses above 160mg/m², but the mechanism of damage is thought to be different from that of other anthracyclines. Dexrazoxane may have a protective effect against mitoxantrone-induced cardiotoxicity, but this is not well established. If dexrazoxane is prescribed, the dose recommended at present is 80mg cardioxane/mg mitoxantrone.

9 Supportive Care

Supportive care is very important for all patients with AML. Patients should be nursed in isolation rooms with appropriate and monitored air and water filtration systems (at least neutral-pressure or positive-pressure isolation rooms with *en suite*) as per BCSH Level 2–3 measures, dependent on the intensity of treatment. Clean, neutropenic diets should be instituted (although the evidence for these is limited) and appropriate infection control measures should be undertaken. Prophylaxis and treatment of infection from presentation should be instituted based on local protocols, with antibiotic choice largely dependent on local microbiological flora. For patients who will undergo intensive treatment schedules, a central venous access device (PICC line, Hickman line) should be inserted as soon as is safely possible.

9.1 Transfusions

Transfusion triggers should be chosen in advance for patients, dependent on co-morbidities. For patients with no co-morbidities or bleeding risk, and in those who do not lead active lifestyles, it would be reasonable to aim for a target Hb > 80g/L.

Red cell transfusions should be avoided if there is any risk of leukostasis.

Platelets should be transfused when the platelet count is $<10 \times 10^9/L$, or $<20 \times 10^9/L$ in the setting of sepsis.

Irradiated blood products should be requested for patients on protocols containing fludarabine, cladribine and clofarabine and for at least the one month prior to a planned stem cell transplant.

9.2 Haemostasis and thrombosis

Platelet transfusions should be administered as per guidelines in [section 8.8](#).

9.3 Hyperviscosity syndrome

Urgent leukapheresis can be undertaken if high counts are causing symptoms of hyperviscosity. Cyto-reductive therapy must be initiated or optimised simultaneously. See [section 8.10](#).

9.4 Hyperuricaemia

See [Management of Disease and Treatment-related Complications, section 8.13](#).

9.5 Tumour lysis syndrome

See [Management of Disease and Treatment-related Complications, section 8.12](#).

9.6 Infection prophylaxis

During intensive treatment regimens in induction and consolidation, patients should receive routine prophylaxis for fungal infections (usually with an extended triazole such as posaconazole or itraconazole) and be considered for anti-bacterial prophylaxis according to local flora and sensitivities and as per local protocols on neutropenic sepsis.

G-CSF may be used to hasten recovery of the neutrophil count, decrease the risk of infection and reduce hospital stay only in those patients who have had a confirmed CR and in defined clinically-adverse situations (i.e. severe sepsis, invasive aspergillosis, etc) and under the guidance of a

consultant experienced in such treatment protocols. Evidence supporting improved survival with G-CSF is lacking. For neutropenic sepsis, use G-CSF to encourage neutrophil recovery if clinically appropriate (and only on the advice of a consultant haematologist).

In order to avoid infective complications, constipation should be avoided. Rectal examination, suppositories and enemas should be avoided in neutropenic patients.

A neutropenic diet should be followed until counts recover. Patients should be nursed in a neutral-pressure or positive-pressure isolation room with appropriate air and water filtration systems during inpatient stays and at least during the first cycle of induction. For patients who live close to the Level 2–3 unit, are dependable, have a supportive infrastructure at home (i.e. able to bring the patient to hospital urgently when ill) and for those units who have immediate access to an appropriate haemato-oncology bed, outpatient therapy/follow-up may be considered during the neutropenic phases, after recovery from initial induction therapy.

9.7 Mouth care

Frequent (usually 4–5 times per day) mouthwashes and gentle tooth-brushing with a soft bristle (or children's toothbrush) during treatment cycles (and with a mouth sponge from an oral-care pack when gums are bleeding) should be used as per local protocols in all patients during treatment.

9.8 Control of menstruation

In young menstruating females undergoing treatment, norethisterone 5mg po tds should be administered in order to prevent normal menses and bleeding complications. Breakthrough bleeding should be allowed once intensive treatment is completed. Alternatively, progesterone pessaries 200-400mg daily can be used if LFTs deranged to suppress menstruation OR both if breakthrough bleeding OR consider increasing dose of norethisterone. Continue medication until platelets $>100 \times 10^9/L$ with recovery.

9.9 Weight loss

A screening tool for the assessment of dietary issues may be completed weekly for inpatients and, if issues are identified, a referral should be made to a specialist dietitian. Referral for specialist dietetic input should be made in the following instances:

- Any patient with neutropenia should be provided with information and education on the neutropenic diet and be referred to a specialist dietitian.
- If artificial feeding is being considered, a referral to the specialist dietitian should be made.
- Weight loss/malnutrition should be identified through weekly screening of inpatients.

9.10 Complex symptom management

Discuss with specialist palliative care team for advice on symptom management, e.g. pain, mucositis, when there is no/poor response to standard interventions. If appropriate, referral can be made to the specialist palliative care team.

10 End-of-treatment Information

10.1 End of treatment

The MDT outcome form and clinic letters will serve to communicate new lines of treatment to the GP.

End of treatment is defined as the end of primary remission induction therapy and/or when there are any significant changes in treatment.

10.2 Treatment summary and care plan

There are two related but distinct documents which patients should be given at the end of treatment:

- A treatment summary provides a summary of the cancer treatments received by the end of the first treatment, planned follow-ups (including mechanisms for these), and signs and symptoms of which to be aware. Their aim is to provide information not only to the patient, but also to the GP about possible consequences of cancer and its treatment, signs of recurrence and other important information.
- A care plan is generated as a result of an HNA and is the agreed plan between the patient and healthcare professional about how the identified areas of concern will be addressed. This may cover provision of information (e.g. through an information prescription), onward referral for specialist assessment and intervention (e.g. breathlessness management), or things which the patient themselves can do (e.g. contact their HR department about graduated return to work options).

Recommendation

An end of treatment consultation should be offered to every patient. This should include an end of treatment HNA and associated written care plan, and should also include the discussion and provision of a comprehensive treatment summary.

11 Follow-up Arrangements

Patients on treatment will need inpatient admission during induction therapy. Some centres have the capacity and day care facilities to enable patients to be discharged during the neutropenic phases of intensive chemotherapy after induction treatment. Such patients usually need to meet the following criteria:

- are in a documented CR
- have had a relatively uncomplicated previous cycle of treatment
- have a stable and controlled home environment with supportive and reliable family/carers
- live near to the Level 2–3 centre
- have immediate access to an inpatient bed in the Level 2–3 haematology unit if needed, 24/7.

Patients not fit for intensive treatment and on non-intensive treatment protocols will have therapy aimed towards quality of life and outpatient therapy as much as possible. Such care is highly dependent on availability of chemotherapy in the community (e.g. for s.c. Ara-C), especially after induction treatment (at least some of which may need to be given as an inpatient dependent on risks of tumour lysis) and if allowed by the current clinical trial protocols for such patients. When discharged, frequent monitoring is required and is dependent on the therapeutic phase of treatment and the degree of supportive care required.

Patients may have shared care between a specialist site and the local treating hospital based on local preference. These arrangements must be clearly outlined so that the patient is clear where to attend in an emergency and understands the pathways of communication between the sites.

Patients who have completed chemotherapy will be followed up at least every three months in the first two years, then every four months in the next two years, and six-monthly in the final year.

12 Research/Clinical Trials

All patients should be considered for a clinical trial wherever possible.

For patients with long distances to travel to the trial centre, the option of shared care may be considered. For those centres wishing to participate in shared care, clear documentation of shared care arrangements must be undertaken with communication to both centres, the GP and the patient.

Bio-banking of diagnostic material may be considered if appropriate approvals (ethics/R&D permission) are in place at the referring site. Alternatively, patients can be referred directly.

13 End-of-life Care

For older patients and in those with poor performance status and/or high-risk disease, discussions regarding prognosis and treatment options should also include discussions on end-of-life care. These are to facilitate transitions between active disease-modifying therapy to clinical trials, or supportive care only at the time of disease progression/non-response. Care may be required from specialist palliative care teams.

The named clinical nurse specialist/key worker, patient, family members and palliative care teams, as well as members of the inpatient ward team, may be involved. Clear documentation of the discussion with guidance to the treating teams is helpful in communicating these discussions and outputs to the wider team that may care for the individual.

14 Data Requirements

Accurate data collection is essential to monitor outcomes, and the collection of this information, particularly clinical data, remains the responsibility of the members of the multidisciplinary team with support from a data manager. Haematology services are required to submit data to nationally mandated datasets for all patients diagnosed with haematological cancer; further details on these datasets are available in [Annex 4](#).

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Annex 1: Guideline for the Management of Tumour Lysis Syndrome (TLS)

To be read in conjunction with rasburicase protocol (see [Annex 2](#)).

TLS is life-threatening. Rapid lysis of tumour cells leads to the release of cellular contents into circulation resulting in hyperkalaemia, hyperphosphataemia, hyperuricaemia and hypocalcaemia which may lead to acute oliguric renal failure and cardiac arrhythmias. TLS can occur spontaneously in tumours with a very high proliferative rate, and/or during induction treatment. It can be classified as laboratory TLS (no clinical manifestations) or clinical TLS (life-threatening clinical abnormalities). Symptoms during TLS include fever, haemolysis, headaches, vomiting, diarrhoea, rash and hypersensitivity reactions.

Prevention of TLS

1. Standard care is hydration and allopurinol and these help prevent TLS.
2. Check urate, renal function and LDH prior to starting chemotherapy and hydrate with 3L/m² over 24 hours.
3. For high risk patients rasburicase should be considered.

Management (see separate rasburicase protocol): Rasburicase is to be used immediately prior to and during treatment-induction for the indications below and when authorised by a consultant haematologist.

TLS Screen is to be ordered 1–4 times per day according to patient's clinical condition until resolves: Urea, creatinine, uric acid, phosphate, potassium, corrected calcium and LDH (FBC if AML/ALL/CML/MPN).

Risk Group	Diagnosis	Preventative Strategies
High	Burkitt lymphoma Burkitt-type ALL AML or ALL with WBC >100 x 10 ⁹ /L	1. IVF (~3L/m ² /day, to maintain UOP >100ml/m ² /hr) or aggressive hydration as per chemotherapy protocols. 2. Rasburicase* as per rasburicase protocol
Moderate	AML with WBC > 50 x 10 ⁹ /L Other ALL High grade NHL with bulky disease CML accelerated/blast phase, or where rapid response to therapy expected	1. IVF (~3L/m ² /day, to maintain UOP >100ml/m ² /hr) or aggressive hydration as per chemotherapy protocols. 2. Rasburicase* as per rasburicase protocol
Minor	Other AML Myeloma Other lymphoma/CLL Other CML and MPN	Use allopurinol. Use rasburicase* where clinically indicated (high risk): High LDH (>ULN) Renal failure High proliferation index High uric acid (>420 umol/L or 7mg/ml)

* No dose adjustment in renal/hepatic impairment. Ensure normal G6PD level prior to rasburicase (if low, use aggressive hydration & allopurinol).

References:

- Cairo MS, Bishop M. Tumour lysis syndrome: New therapeutic strategies and classification. *Br J Haematology*. 2004;**127**: 3–11.
- Coiffier B, Altman A, Pui CH, *et al*. Guidelines for the management of paediatric and adult tumour lysis syndrome: an evidence-based review. *Journal of Clinical Oncology*. 2008;**26**:2767–78.
- Howard SC, Jones DP and Pui CH. The tumor lysis syndrome. *NEJM*. 2011; **364**(19):1844–54.
- Hummel M, Reiter S, Adam K, *et al*. Effective treatment and prophylaxis of hyperuricemia and impaired renal function in tumor lysis syndrome with low doses of rasburicase. *Eur J Haematol*. 2008;**80**:331–6.
- Jones GL, Will A, Jackson GH, *et al*. Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. *Br J Haematol*. 2015;**169**(5):661–71.
- NHS Economic Evaluation Database, NIHR Centre for Reviews and Dissemination. The University of York, 2012.

Annex 2: Guidelines for Use of Rasburicase in Adult Haematology and Oncology Patients

Criteria for use

Rasburicase may be used only for the following indications, when authorised by a consultant haematologist or oncologist:

Urate oxidase (rasburicase) is an enzyme which catalyses the oxidation of uric acid to allantoin, which is more easily excreted in the urine.

Used in the treatment of:

- hyperuricaemia associated with high grade haematological malignancies
- prevention of complications of tumour lysis syndrome

Indications (see also separate guideline):

- Induction or salvage therapy of AML, ALL, high grade lymphoma, high grade multiple myeloma with
 - High LDH (>ULN)
 - Renal failure
 - High proliferation index (Ki67>80%; consider if Ki67>50%)
 - High uric acid (>420 $\mu\text{mol/L}$ or 7mg/ml)

Further to the above, consider using rasburicase in those patients unable to tolerate aggressive hydration.

Protocol for use:

1. Ensure patient (male or female) is G6PD negative prior to use (if positive, use aggressive hydration with allopurinol – consider higher doses based on risk of TLS and creat level).
2. Ensure aggressive hydration as per chemotherapy protocols.
3. At initiation of treatment, for uric acid levels of:
 - a) < 420 $\mu\text{mol/L}$ (7mg/L), give a single 3mg dose of rasburicase.
 - b) >420 $\mu\text{mol/L}$ (7mg/L), give a single 6mg dose of rasburicase.
4. Local policies should be followed with regard to collecting blood samples and laboratory monitoring.
5. Start allopurinol as per protocols the morning after rasburicase given.
6. Measure uric acid levels as per tumour lysis (TLS) protocols and at least daily until TLS resolved.
7. During TLS monitoring, if uric acid levels >20 $\mu\text{mol/L}$ (>0.3 mg/L), or renal failure worsens, give another 1.5–6 mg rasburicase, as indicated by level and clinical parameters of TLS.

References:

NHS Economic Evaluation Database, NIHR Centre for Reviews and Dissemination. The University of York, 2012.

Trifilio SM, Pi J, Zook J, *et al.* Effectiveness of a single 3-mg rasburicase dose for the management of hyperuricemia in patients with haematological malignancies. *Bone Marrow Transplantation*. 2011;**46**:800–805.

Hummel M, Reiter S, Adam K, *et al.* Effective treatment and prophylaxis of hyperuricemia and impaired renal function in tumor lysis syndrome with low doses of rasburicase. *Eur J Haematol*. 2008;**80**:331–6.

Trifilio S, Gordon L, Singhal S, *et al.* Reduced-dose rasburicase (recombinant xanthine oxidase) in adult cancer patients with hyperuricemia. *Bone Marrow Transplant*. 2006;**37**:997–1001.

Hutcherson DA, Gammon DC, Bhatt MS and Faneuf M. Reduced-dose rasburicase in the treatment of adults with hyperuricemia associated with malignancy. *Pharmacotherapy*. 2006;**26**:242–7.

Special warnings and precautions for use

Allergic reactions may occur with this product, patients should be closely monitored and full resuscitation facilities should be at hand. Should any serious allergic or anaphylactic reaction occur treatment should be immediately discontinued and appropriate resuscitation given.

Caution should be exercised in patients with a history of atopic allergies.

Administration of rasburicase decreases serum uric acid to below normal levels, **but has no direct effect in reversing hyperphosphataemia, hyperkalaemia and hypocalcaemia. If severe these abnormalities should be corrected following standard treatment guidelines.**

There are limited data available to recommend the sequential use of rasburicase and allopurinol.

To ensure accurate measurement of uric acid plasma level during treatment with rasburicase, a strict sample handling procedure must be followed to minimise ex vivo degradation of the analyte. Local policies should be followed with regard to collecting blood samples and laboratory monitoring.

Annex 3: Monitoring of Long-term Survivors of Chemotherapy

Haematopoietic Stem Cell Transplantation (HSCT), Acute Leukaemia, Lymphoma

Survivors of Childhood & Adult Leukaemias/Lymphomas have increased risks of secondary cancers, CVS disease and other chronic illnesses, largely secondary to therapy.

For adult survivors of leukaemia (especially those treated in childhood):

- A treatment summary from the treating haematologist should be requested.
- If cranial radiotherapy was a component of treatment, there is an increased risk of secondary tumours, stroke, growth hormone deficiency, ocular & neurocognitive defects.
- Check BMI, BP & lipids – survivors of ALL have ↑ risk of obesity & metabolic derangements.
- Consider gonadal assessment (FSH/LH/testosterone) & referral to fertility specialist.
- Consider DEXA scan – peak bone density reduced after childhood exposure to high-dose steroids and other therapies.
- Screen for LV dysfunction in survivors who received anthracyclines, especially if patient received a high cumulative dose or treated before the age of 5 years.
- Screen for transfusional iron overload – commence venesection programme if ferritin >1000 and patient is male or non-menstruating female.
- Consider ophthalmology review annually for assessment of early cataract formation.
- Dental pathology is common and survivors should have annual check-ups.

For haemato-oncology survivors after the 5 year ‘cure’ milestone of follow-up:

Patients should undergo annual review for complications of chemotherapy which should consist of:

- Thorough review of systems & physical examination.
- Ensure appropriate monitoring for secondary cancers is being undertaken (skin, breast, cervical, uterine/ovarian, prostate, colorectal, haematologic, sarcomas).
- Monitor for secondary effects and refer back to GP as appropriate:
 - LDL/HDL, TG, Glc, HbA1c, TSH, AIS & ESR, Igs & SPEP, FBC/film, LFTs, U&Es.
- For those who received anthracyclines or involved field radiotherapy to the chest area, check ECHO every 5 years and ECG annually.
- For those who received radiotherapy to the chest (e.g. IF Mantle RT) below age 30, screening at local Breast Screening Service (use dedicated referral form) to commence at age 30 or 8 years post RT, whichever later:
 - Age 30–39 Annual MRI
 - Age 40–49 Annual MRI +/- Mammo
 - Age 50+ Annual Mammo +/- MRI.
- For those who received steroids, consider DEXA scan – every 3–5 yrs.

- For those who received cranial XRT, assess for early cataracts at least once every 5 years.
- Lifestyle advice (stop smoking, EtOH/stress ↓, fitness, protection against sun exposure, etc.).
- All survivors of HSCT should receive endocarditis prophylaxis for dental procedures.

References:

Diller L. Adult primary care after childhood acute lymphoblastic leukemia. *N Engl J Med*. 2011;**365**:1417–24.

Majhail NS, *et al*. Special Report: Recommended screening and preventative practices for long-term survivors after hematopoietic cell transplantation. *Bone Marrow Transplantation*. 2012;**47**;doi:10.1038/bmt.2012.5.

Annex 4: Data Requirements

Haematology oncology services are required to submit data to the following nationally mandated datasets for all patients diagnosed with haematological cancers.

The Cancer Outcomes and Services Dataset (COSD)

The core dataset for all tumour types including haematological cancers is mandated from January 2013, and the site-specific dataset is mandated from July 2013. Details of the dataset can be found on the National Cancer Intelligence Network website:

www.ncin.org.uk/collecting_and_using_data/data_collection/cosd.aspx

The local cancer registry will be collating this dataset using Trust data feeds which should include all these items. The feeds are:

- Trust PAS
- Trust pathology
- Trust radiology
- Trust multidisciplinary team (MDT) feed.

In line with the requirements set out in Provider Trust contracts, this data should be submitted within 25 working days of the end of the month in which the activity took place.

Three groups of haematological cancers are considered stageable by the Registry:

- Lymphomas, using Ann Arbor (or Murphy St Jude for children)
- Myelomas, using ISS
- CLLs, using Rai and Binet

For the purposes of COSD, any other haematological cancers are not counted as stageable.

For CLL both Rai (0-IV) and Binet (A-C) stages need to be recorded and submitted to COSD to be considered “fully staged”

MGUS does not need to be recorded and submitted as is not defined as an invasive tumour

Systemic Anti-Cancer Therapy dataset (SACT)

Provider Trusts that provide chemotherapy to patients are required to submit data to the SACT dataset. Details of the audit and the dataset requirements are available on the dataset homepage:

www.chemodataset.nhs.uk/home.aspx

Radiotherapy Dataset (RTDS)

Provider Trusts that provide radiotherapy to patients are required to submit data to the RTDS dataset. Details of the audit and the dataset requirements are available on the dataset homepage:

www.canceruk.net/rtservices/rtds/

Cancer Waiting Times dataset

Trusts are required to submit data to the Cancer Waiting Times dataset, which includes details of all patients who are referred as a 2 week wait (2ww) referral, and all patients who are treated for cancer. Trusts are required to submit this data within 25 working days of the month of either when the patient was first seen for the 2ww target, or when the patient was treated. The cancer waiting times dataset can be found at:

www.datadictionary.nhs.uk/data_dictionary/messages/clinical_data_sets/data_sets/national_cancer_waiting_times_monitoring_data_set_fr.asp

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