Greater Manchester Cancer Haemato-Oncology Pathway

Guidelines for the Management of Acute Myeloid Leukaemia

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1. Introduction

These guidelines were drafted and agreed by the working group of AML for the Greater Manchester Cancer Haemato-Oncology Pathway Board. They have in part been derived from the BSH and ELN guidelines on the management of AML in adults and further developed to incorporate recent NICE guidance, clinical data and trials specifically relevant to the area.

Appropriate setting for therapy
Recommendations from the National Institute for Clinical Excellence should be followed (http://www.nice.org.uk). Patients should be managed by a multi-disciplinary team serving a population of at least 500,000, with induction therapy only carried out in centres treating at least five patients per year.

Adolescent patients
All patients aged 16-18 should be referred to the regional adolescent unit at Christie NHSFT for management, patients aged 19- 24 should be made aware of the adolescent facility at diagnosis although may elect for shared care, or for their primary treatment centre to be another centre designated to treat teenage and young adults.

2. Diagnosis of Acute Myeloid Leukaemia

2.1 Classification

The World Health Organisation (WHO) system for the diagnosis and classification of AML was first developed in 2001 and superseded the modified FAB classification. The WHO system has been revised and updated in 2008[1], 2016[2] and most recently in 2022[3].

The 5th edition (WHO2022) divides AML into two categories: AML with defining genetic abnormalities (DGA) and AML defined by differentiation. Important changes from the 4th edition include the elimination of the 20% blast cutoff for many entities in the category of AML with DGA, and the removal of dysplastic morphology alone as a diagnostic criterion for “AML, myelodysplasia-related”.

Simultaneously in 2022, the International Consensus Classification (ICC) was released as an alternate classification system[4]. Both the WHO2022 and the ICC heavily incorporate molecular data for diagnostic classification of AML, but differ in significant ways, most importantly the blast percentage cutoffs for AML diagnosis which is summarised in table 4. Other notable differences are that the ICC includes the entities of “MDS/AML” (10-19% blasts) and “AML with mutated TP53”, requires bZIP domain mutations (irrespective of mono- or biallelic nature) for the diagnosis of CEBPA-mutated AML, and no longer recognises “therapy-related myeloid neoplasm” (known as “myeloid neoplasms post-cytotoxic therapy” in WHO2022) as a distinct AML entity.

Table 1: WHO2022 classification of myeloid neoplasms – Acute myeloid leukaemia

Acute myeloid leukaemia, defined by differentiation
Acute myeloid leukaemia with minimal differentiation
Acute myeloid leukaemia without maturation
Acute myeloid leukaemia with maturation
Acute basophilic leukaemia
Acute myelomonocytic leukaemia
Acute monocytic leukaemia
Acute erythroid leukaemia The diagnosis of AEL supersedes AML-MR. AEL is a distinct AML type characterized by neoplastic proliferation of erythroid cells with features of maturation arrest and high prevalence of biallelic TP53 alterations. Diagnostic criteria include erythroid predominance, usually ≥80% of bone marrow elements, of which ≥30% are proerythroblasts.
Acute megakaryoblastic leukaemia
Myeloid sarcoma

Acute myeloid leukaemia with defining genetic abnormalities
Acute promyelocytic leukaemia with *PML*::*RARA* fusion
Acute myeloid leukaemia with *RUNX1*::*RUNX1T1* fusion
Acute myeloid leukaemia with *CBFB*::*MYH11* fusion
Acute myeloid leukaemia with *DEK*::*NUP214* fusion
Acute myeloid leukaemia with *RBM15*::*MRTFA* fusion
Acute myeloid leukaemia with *BCR*::*ABL1* fusion
Acute myeloid leukaemia with *KMT2A* rearrangement
Acute myeloid leukaemia with *MECOM* rearrangement
Acute myeloid leukaemia with *NUP98* rearrangement
Acute myeloid leukaemia with *NPM1* mutation
Acute myeloid leukaemia with *CEBPA* mutation
Acute myeloid leukaemia, myelodysplasia-related - Defining cytogenetic abnormalities or somatic mutations - **OR** history of MDS or MDS/MPN <u>Defining cytogenetic abnormalities:</u> - Complex karyotype (3+ abnormalities) - 5q deletion or loss of 5q due to unbalanced translocation - Monosomy 7, 7q deletion, or loss of 7q due to unbalanced translocation - 11q deletion - 12p deletion or loss of 12p due to unbalanced translocation - Monosomy 13 or 13q deletion - 17p deletion or loss of 17p due to unbalanced translocation - Isochromosome 17q - Idic(X)(q13) <u>Defining somatic mutations:</u> - ASXL1 - BCOR - EZH2 - SF3B1 - SRSF2 - STAG2 - U2AF1 - ZRSR2
Acute myeloid leukaemia with other defined genetic alterations

Table 2: WHO2022 classification of myeloid neoplasms – Acute leukaemias of mixed or ambiguous lineage

Acute leukaemia of ambiguous lineage with defining genetic abnormalities
Mixed-phenotype acute leukaemia with *BCR*::*ABL1* fusion Mixed-phenotype acute leukaemia with *KMT2A* rearrangement Acute leukaemia of ambiguous lineage with other defined genetic alterations Mixed-phenotype acute leukaemia with *ZNF384* rearrangement Acute leukaemia of ambiguous lineage with *BCL11B* rearrangement
Acute leukaemia of ambiguous lineage, immunophenotypically defined
Mixed-phenotype acute leukaemia, B/myeloid Mixed-phenotype acute leukaemia, T/myeloid Mixed-phenotype acute leukaemia, rare types Acute leukaemia of ambiguous lineage, not otherwise specified Acute undifferentiated leukaemia

Table 3: WHO2022 classification of myeloid neoplasms – Subtypes of myeloid neoplasms associated with germline predisposition

Myeloid neoplasms with germline predisposition without a pre- existing platelet disorder or organ dysfunction
Germline *CEBPA* P/LP variant (CEBPA-associated familial AML) Germline *DDX41* P/LP variant Germline *TP53* P/LP variant (Li-Fraumeni syndrome)
Myeloid neoplasms with germline predisposition and pre-existing platelet disorder
Germline *RUNX1* P/LP variant (familial platelet disorder with associated myeloid malignancy, FPD-MM) Germline *ANKRD26* P/LP variant (Thrombocytopenia 2) Germline *ETV6* P/LP variant (Thrombocytopenia 5)
Myeloid neoplasms with germline predisposition and potential organ dysfunction
Germline *GATA2* P/LP variant (GATA2-deficiency) Bone marrow failure syndromes o Severe congenital neutropenia (SCN) o Shwachman-Diamond syndrome (SDS) o Fanconi anaemia (FA) Telomere biology disorders RASopathies (Neurofibromatosis type 1, CBL syndrome, Noonan syndrome or Noonan syndrome-like disorders) Down syndrome Germline *SAMD9* P/LP variant (MIRAGE syndrome) Germline *SAMD9L* P/LP variant (SAMD9L-related Ataxia Pancytopenia Syndrome) Biallelic germline *BLM* P/LP variant (Bloom syndrome)

P/LP = Pathogenic/Likely pathogenic

Table 4: Differences between the 5th edition WHO (WHO2022) and the ICC classifications in classification and blast cutoff for diagnosis of genetically-defined AML

WHO2022		**ICC**	
Classification	**Blast cutoff**	**Classification**	**Blast cutoff**
APML with *PML*::*RARA* fusion	**-**	APL with t(15;17) (q24.1;q21.2)/*PML::RARA* APL with other *RARA* rearrangement	**≥10%**
AML with *RUNX1*::*RUNX1T1* fusion	**-**	AML with t(8;21) (q22;q22.1)/*RUNX1::RUNX1T1*	**≥10%**
AML with *CBFB*::*MYH11* fusion	**-**	AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*	**≥10%**
AML with *DEK*::*NUP214* fusion	**-**	AML with t(6;9) (p23;q34.1)/*DEK::NUP14*	**≥10%**
AML with *RBM15*::*MRTFA* fusion	**-**	Classified in AML with other rare recurring translocations	**≥10%**
AML with *KMT2A* rearrangement	**-**	AML with t(9;11) (p21.3;q23.3)/*MLLT3::KMT2A* AML with other *KMT2A* rearrangement	**≥10%**
AML with *MECOM* rearrangement	**-**	AML with inv(3)(q21.3q26.2) or t(3;3) (q21.3;q26.2)/*GATA2*;*MECOM*(*EVI1*) AML with other *MECOM* rearrangement	**≥10%**
AML with *NUP98* rearrangement	**-**	Classified in AML with other rare recurring translocations	**≥10%**
AML with *NPM1* mutation	**-**	AML with mutated *NPM1*	**≥10%**
AML with *BCR*::*ABL1* fusion	**≥20%**	AML with t(9;22)(22) (q34.1;q11.2)/*BCR::ABL1*	**≥20%**

AML with *CEBPA* mutation	**≥20%**	AML with mutated bZIP *CEBPA*	**≥10%**
AML with other defined genetic alteration	**≥20%**	AML with other rare recurring translocations • AML with t(1;3) (p36.3;q21.3)/*PRDM16::RPN1* • AML with t(3;5)(q25.3) (q25.3;q35.1)/*NPM1::MLF1* • AML with t(8;16) (p11.2;p13.3)/*KAT6A::CREBBP* • AML with t(1;22) (p13.3;q13.1)/*RBM15::MRTF1* • AML with t(5;11) (q35.2;p15.4)/*NUP98:NSD1* • AML with t(11;12) (p15.4;p13.3)/*NUP98::KMD5A* • AML with *NUP98* and other partners AML with t(7;12) • (q36.3;p13.2)/*ETV6::MNX* AML with t(10;11)(p12.3);q14.2)/*PICA* • *LM::MLLT10* • AML with t(16;21) (p11.2;q22.2)/*FUS::ERG* • AML with t(16;21)(q24.3;q22.1)/*RUNX 1::CBFA2T3* • AML with inv(16)(p13.3;q24.3)/*CBFA 2T3::GLIS2*	**≥10%**
AML, myelodysplasia-related *Defining cytogenetic abnormalities:* • Complex karyotype (≥ 3 abnormalities) • 5q deletion or loss of 5q • monosomy 7, 7q deletion, or loss of 7q 11q deletion • 12p deletion or loss of 12p • Monosomy 13 or 13q deletion • 17p deletion or loss of 17p • isochromosome 17q • idic(X)(q13) *Defining somatic mutations:* • *ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2*	**≥20%**	AML with myelodysplasia-related cytogenetic abnormalities *Defining cytogenetic abnormalities:* • Complex karyotype (≥ 3 abnormalities • del(5q)/t(5q)/add(5q) • -7/del(7q) • +8 • del(12p)/t(12p)/add(11p) • i(17q), -17/add(17p) or del(17p) • del(20q) • idci(X)(q13) AML with myelodysplasia-related gene mutations • *ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2, RUNX1*	**10-19% (MDS/AML)** **≥20% (AML)**

2.2 Diagnosis

All samples should be requested using the HODS system and send to its central reception at Manchester Foundation Trust. As a minimum, the following samples should be taken when treatment is intended:

- FBC and blood film
- Bone marrow aspirate (morphology)
- Bone marrow trephine
- Flow cytometry/immunophenotyping
- Cytogenetics sample (for karyotype and FISH)
- Molecular/genomics sample for (rapid molecular and panel-based testing)
- RNA/DNA extraction and store is recommended for all new cases
- Clinical trial samples (if relevant)

2.2.1 Morphology

All patients should have a bone marrow aspirate and trephine biopsy. These may be omitted if the peripheral blast count is high and the patient is for palliative treatment only. A trephine biopsy is essential in cases of a dry tap or aparticulate aspirate, and also if the aspirate is dilute. The trephine may reveal fibrosis and/or multilineage dysplasia.

2.2.2 Immunophenotyping

Performed to confirm cell lineage and to identify acute leukaemias of ambiguous lineage. Aberrant expression of lymphoid markers such as CD7, CD19 or CD2 is also a well-recognised finding in AML, as is high CD33 and low CD34 expression.

2.2.3 Cytogenetics/ FISH

Conventional cytogenetic analysis is mandatory in the evaluation of AML. A rapid karyotype may be useful in urgent cases. Fluorescence in situ hybridization (FISH) is useful to detect or confirm specific abnormalities - for example, core-binding factor (CBF*) AML, KMT2A and MECOM rearrangements and APML. It may also be useful when karyotyping fails, alongside a SNP microarray.

* CBF AML: AML with t(8;21)(q22;q22) or inv(16)(p13q22)/t(16;16)(p13;q22) and/or the corresponding molecular rearrangements RUNX1::RUNX1T1 and CBFB::MYH11.

2.2.4 Diagnostic Molecular & Genomic Studies

2.2.4.1 Rapid Molecular Testing

Rapid molecular testing for NPM1, FLT3-ITD and FLT3-TKD should be requested on all new cases of AML to aide in immediate prognostication and therapy selection. The anticipated turnaround time is within 3 working days. Fusion gene panels may also provide additional and rapid information in addition to cytogenetic studies.

2.2.4.2 Myeloid NGS panels

A myeloid gene panel is now the standard of care for all new diagnoses of AML. This can be performed on peripheral blood or bone marrow. Repeat myeloid panels after

diagnosis are not routinely indicated. A targeted AML gene panel including IDH1/ IDH2 and TP53 with a faster turnaround time for new and urgent cases is under development.

2.2.4.3 Whole Genome Sequencing

Whole genome sequencing is not routinely indicated and no longer NHS commissioned but may provide further information where there is diagnostic uncertainty or an appropriate clinical context.

If clinician and patient wish to proceed with WGS please ensure a tumour sample (1-4ml EDTA marrow or blood containing >20 blasts) has been sent via the HODS service to the regional Genomic Laboratory Hub at 6th Floor St Mary's Hospital Manchester. A germline sample (3-4 mm skin punch biopsy or Saliva sample in Orange DNA collection tube) should also be sent for WGS to proceed. A "tumour first" pathway may be requested to prioritise diagnostic WGS testing where it is not possible or timely to send a germline sample immediately.

2.2.4.4 Consideration toward germline predisposition

Increasing numbers of patients are being recognised as having a familial predisposition syndrome to haematological malignancy. A finding of such may impact clinical management in multiple areas including donor selection for allogeneic transplant, counselling and potential testing of relatives, and possibly health surveillance of those who share a causative germline variant.

A thorough family history of malignancy (both haematological or solid tumour) should be obtained at diagnosis. A patient's historical blood counts should be reviewed, in particular for thrombocytopenia. Other germline disorders may display specific clinical phenotypes (eg. GATA2 haploinsufficiency and bone marrow failure syndromes).

Germline variants involving DDX41, RUNX1, CEBPA and TP53 may be detected on the routine myeloid NGS panel. A variant with a VAF of close to 50% should prompt consideration of a germline origin. Germline origin of a variant should ideally be confirmed on a germline sample thereby excluding somatic mutations in hematopoietic cells.

Sending a paired germline sample at diagnosis would be recommended in cases of high clinical suspicion. Specific consent for testing should be obtained from the patient beforehand. Formal genetic counselling of the patient and their relatives should be considered depending on the findings.

2.2.4.5 Minimal residual disease (MRD) assessment

MRD assessment and monitoring is now an important part of AML management and has strong prognostic value and treatment implications. This includes patients treated with less-intensive therapy.

Routine molecular MRD monitoring should be performed in cases where a marker is present. These include NPM1-mutated AML, CBF-AML (RUNX1-RUNX1T1 or CBFB-MYH11), KMT2A-rearranged AML, AML with DEK-NUP214, AML with BCR-ABL and APL.

MRD for common NPM1 mutation transcripts and CBF-AML MRD can be performed locally, with others requiring a send-away test.

A baseline sample should be sent at diagnosis. Routine MRD monitoring should be continued for up to 2 years after consolidation. See later section on MRD monitoring and relapse.

2.2.5 Risk Stratification

The ELN guidelines risk stratify AML into three risk categories based on the genetic profile. The 2022 update notably removed the use of FLT3-ITD allelic ratio as a prognosticator and includes NPM1 mutated AML with additional adverse-risk cytogenetic abnormalities in the adverse category.

Table 5: Risk stratification (ELN 2022)

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 • bZIP in-frame mutated *CEBPA*
Intermediate	• Mutated *NPM1* with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A* • Cytogenetic and/or molecular abnormalities not classified as favourable or adverse
Adverse	• t(6;9)(p23.3;q34.10)/*DEK::NUP214* • t(v;11q23.3)/*KMT2A*-rearranged • t(9;22)(q34.1;q11.2)/*BCR::ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)* • t(3q26.2;v)/*MECOME*(*EVI1*)-rearranged • -5 or del(5q); -7; -17/abn(17p) • Complex karyotype, monosomal karyotype • Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and/ or *ZRSR2* • Mutated *TP53*

In 2024, the ELN recommended a risk classification for adults with AML receiving less-intensive therapies, which includes hypomethylating agent monotherapy or with venetoclax or ivosidenib (in IDH1 mutated AML). This classification does not apply to patients who have received prior treatment with a hypomethylating agent.

Table 6: ELN 2024 risk stratification for adults with AML receiving less-intensive therapies

Favourable	• Mutated *NPM1* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt}) • Mutated *IDH2* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt}) • Mutated *IDH1* (*TP53*^{wt})[#] • Mutated *DDX41* • Other cytogenetic and/or molecular abnormalities* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})
Intermediate	• Other cytogenetic and molecular abnormalities* (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})
Adverse	• Mutated *TP53*

[#]Applies specifically to patients treated with azacitidine+ivosidenib

*For many cytogenetic and molecular abnormalities, single or as co-aberrations, no data are currently available; they are tentatively categorized as favourable and intermediate-risk depending on the absence or presence of activating signalling gene mutations.

2.3 Assessment of Fitness

In addition to the past medical history, assessment of performance status, and co-morbidities should be taken into consideration. This is important to aid a decision if intensive chemotherapy would be suitable. Increasing age is an adverse prognostic factor[5], even after accounting for disease specific prognostic factors, and performance status. Despite this, age should not be the sole determinant of suitability for intensive therapy. A careful evaluation of co-morbidities should be undertaken so that patients suitable for intensive treatment may receive it. Co-morbidity indices such as the HCT-CI have been validated for predicting outcomes in AML patients[6]. To assist in evaluating their fitness for treatment, older adults should ideally have a multidimensional geriatric assessment of their physical function, cognition, mental health, social support, nutrition, polypharmacy, comorbidities and performance status[7].

Mandatory investigations			
FBC and film	Retics and DAT	Blood group and antibody screen	Haematinics
Renal/ liver/ bone profile	Coagulation screen and fibrinogen	CXR	Echo/ MUGA
Urate/ LDH	Urinalysis	ECG	Virology: hepatitis B/C and HIV-1
Glucose	CRP	Serum immunoglobulins	G6PD screen
Additional Investigations			
Pregnancy test		Semen cryopreservation (all potentially fertile patients)	
HLA class I and II (potential transplant patients)		CMV serology (potential transplant patients)	

Infection screen (as indicated)	MRI/ CT head+/- LP if features of CNS disease

2.4 Patient Support

All patients should be appointed a key worker and should be offered a 'Holistic Needs Assessment' (HNA) at key points in their patient pathway.

Several useful resources are available to the patient and are listed below:
https://bloodcancer.org.uk/understanding-blood-cancer/
https://www.macmillan.org.uk/cancer-information-and-support

3. Treatment

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

3.1 Clinical Trials

Where possible patients should be offered participation in a clinical trial. There is evidence of improved outcome for patients who have entered clinical studies and increasingly in the management of acute leukaemia, there are further investigations which can improve diagnosis, stratification, monitoring and access to new agents which strongly support this as a potential standard of care. A list of actively open trials can be accessed via the CRUK website. (https://find.cancerresearchuk.org/clinical-trials?size=n_20_n&filters%5B0%5D%5Bfield%5D=cancer_types&filters%5B0%5D%5Bvalues%5D%5B0%5D=Acute%20myeloid%20leukaemia%20%28AML%29&filters%5B0%5D%5Btype%5D=all)

3.2 Off Trial: Young patients (< 60 years) and older patients deemed fit for intensive therapy

3.2.1 Induction therapy (cycles 1 and 2)

- ***The standard of care is daunorubicin with cytarabine (DA3+10: daunorubicin 60mg/m^2 on days 1, 3, 5 plus cytarabine 100mg/m^2 12-hourly on days 1-10) for cycle one and daunorubicin with cytarabine (DA 3+8) for cycle 2.***
- ***Consideration should be given as to the addition of midostaurin, quizartinib, gemtuzumab ozogamicin or substitution with CPX351 as per NICE guidance (3.2.3 - 3.2.6)***
- ***FLAG-Ida for cycles 1 and 2 may be considered if patients are young (< 60 years) with secondary disease, already known to have high risk disease or have mixed phenotype acute leukaemia (MPAL).***

Alternative anthracyclines have been compared including idarubicin[8] and mitoxantrone[9] at comparable doses with no improvement in overall survival. High doses of cytarabine with daunorubicin have also been studied, including by the SWOG group, with no

increase in CR but a demonstrable increase in toxicity[10]. Recent data comparing daunorubicin doses of 90mg/m^2 versus 60mg/m^2 did not show any difference in early response, remission rate or survival outcomes[11].

3.2.2 Post-Remission / Consolidation

- ***The standard of care is high-dose Cytarabine 1.5-3g/m^2 12-hourly on days 1, 3, 5 (or 1,2,3) if < 60yrs, or 1.0-1.5g/m^2 12-hourly on days 1, 3, 5 if >60yrs.***

A landmark study by the CALGB has demonstrated that 4 cycles of high-dose Cytarabine [3g vs. 400mg vs. 100mg] leads to a survival advantage in patients with CBF leukaemia[12]. Variable availability of Amsacrine and trial evolution had established the standard consolidation as high-dose Cytarabine 3g/m^2 BD on days 1, 3, 5 if < 60yrs old or 1.5g/m^2 BD on days 1, 3, 5 if >60yrs.

A reduced dose of 1.5g/m2 BD Cytarabine may be considered as the AML15 study did not find a difference in outcome between this dose and 3g/m2 BD[13]. A reduced dose is recommended in the 2022 ELN guidelines[14].

Consecutive administration on days 1 to 3, rather than on alternate days (days 1, 3, and 5) may hasten blood count recovery and reduce health resource consumption[15-17].

The optimal number of cycles of therapy continues to be investigated within clinical trials; current published evidence suggests this consists of 3-4 cycles in total.

Patients with poor risk disease have a dismal outcome with conventional consolidation[18] and should be considered for allogeneic transplantation. In general, allogeneic HCT should be considered when the relapse probability without the procedure is predicted to be 35% to 40%[19]. If a patient is to proceed to an allogenic stem cell transplant, the transplant should occur once in CR and the donor is ready. One or two cycles of chemotherapy can be given while awaiting transplant, but toxicity risks must be considered.

3.2.3 Midostaurin

- ***NICE approved for patients with FLT3-ITD mutation at diagnosis***
- ***Midostaurin at 50mg orally twice daily can be added to induction (DA) and consolidation (high-dose Cytarabine) chemotherapy, commenced 24 hours after chemotherapy and given for 14 days after completion of chemo).***
- ***Patients in complete remission can continue with midostaurin maintenance for up to 12 cycles (28-days).***
- ***If patient is proceeding to a transplant, midostaurin should be stopped 48 hours prior to starting conditioning.***

The CALGB 10603 (RATIFY) study was the basis for NICE recommendations and demonstrated an improvement in survival at 4 years (55.7% vs 63.7%) when used with induction DA 3+7 and consolidation with high-dose cytarabine followed by maintenance[20].

3.2.4 Quizartinib

- ***NICE approved for newly diagnosed FLT3-ITD-positive AML***
- ***Quizartinib can be added to standard induction (DA) and consolidation (high-dose cytarabine)***
    - ***Quizartinib 35.4mg PO once daily is added for 14 days after completion of cytarabine in each cycle. For patients concomitantly receiving a strong CYP3A4 inhibitor, the dose is reduced to 17.7 mg/day.***
- ***Patients in complete remission can continue with quizartinib monotherapy as maintenance treatment up to 3 years. This includes patients who have had an allogeneic stem cell transplant and sufficient count recovery and without GVHD. (The drug is started 30-120 days post-transplant)***
    - ***Quizartinib is given starting at 26.5mg PO once daily and increased to 53mg once daily if the QTc (Fredricia) measured midway during the first cycle is <450ms. (For patients concomitantly receiving a strong CYP3A4 inhibitor, the starting dose is reduced to 17.7 mg/day and increased to 26.5mg/day if QTcF is <450ms).***

The QUANTUM-First study was the basis for NICE recommendations[21]. This was a randomised, double-blind, placebo-controlled phase III trial including 539 patients with newly diagnosed FLT3-ITD positive AML. When compared to placebo, quizartinib improved median OS (31.9 months vs 15.1 months, HR 0.78, 95% CI 0.62–0.98, p=0.032). This study included patients up to 75 years old. Quizartinib is a type II FLT3 inhibitor and is inactive against FLT3-TKD; these patients were excluded from the trial.

3.2.5 Mylotarg (Gemtuzumab Ozogamicin/GO)

- **NICE approved for patients with de novo CD33+ AML (no APML) and favourable / intermediate risk cytogenetics (or unknown at time of treatment initiation)**
- **Mylotarg is given at 3mg/m^2 on days 1, 4, 7 during induction with DA 3+7. For patients in complete remission Mylotarg can be given at 3mg/m^2 on days 1 & 4 with up to two consolidation DA chemotherapies**

Results of the MRC AML15 and 16 trials have shown that the use of Mylotarg as part of induction chemotherapy does reduce the relapse risk in CBF leukaemia and to a lesser extent in standard risk disease, where there is a non-statistically significant trend to benefit[22,23]. There are now at least 5 randomised studies published. Mylotarg was NICE approved using the ALFA 0701 schedule[24]. In cases where Mylotarg is started prior to knowing cytogenetic results, it should be stopped if subsequent results indicate poor prognostic karyotype.

3.2.6 CPX-351/Vyxeos (Liposomal cytarabine and daunorubicin)

- ***NICE approved for newly diagnosed therapy-related AML or AML with myelodysplasia-related changes***

CPX-351 is a dual-drug liposomal encapsulation of daunorubicin and cytarabine in a synergistic 1:5 molar ratio. CPX-351 was studied in an open-label, randomized, phase III trial, where 309 patients aged 60-75 years with newly diagnosed high-risk/sAML received one to two induction cycles of CPX-351 or 7+3 followed by consolidation therapy of the same. CPX-351 significantly improved median overall survival when compared to the standard of care (9.56 v 5.95 months, HR 0.69; 95% CI, 0.52-0.90; one-sided P = 0.003)[25]. The AML19 study showed similar outcomes of CPX-351 when compared to FLAG-Ida in younger patients with adverse karyotype AML and high risk MDS, with a subgroup of patients with MDS-related gene mutations demonstrating improved survival with CPX-351[26].

3.2.7 Oral azacitidine maintenance after intensive chemotherapy

- ***NICE approved for patients who are in complete remission (or complete remission with incomplete count recovery) after induction therapy with or without consolidation treatment and cannot have (or do not want to have) a haematopoietic stem cell transplant***

The QUAZAR AML-001 study is the basis for the NICE recommendation[27]. It was a phase 3 double-blind, randomised controlled trial comparing oral azacitidine versus placebo in 472 adults >55 years old with AML who were in complete remission after intensive induction chemotherapy and unable to have a stem cell transplant. 85% of patients randomised received two or more cycles of chemotherapy (including induction) and the median time to randomisation was 3 months. Oral azacitidine maintenance improved overall survival (24.7 months vs 14.8 months, P = <0.001) and relapse-free survival (10.2 months vs 4.8 months, P = <0.001) compared to placebo. The benefit of oral azacitidine maintenance in CBF-AML is unclear.

3.3 Older patients (> 60 years) or patients not deemed fit for intensive chemotherapy

The prognosis worsens with advancing age and such patients are more likely to demonstrate resistance and suffer death to initial therapy[28]. Several studies however confirm a better quality of life and survival advantage for low intensity induction therapy compared to supportive care only[5].

- ***Consider intensive chemotherapy if good performance status in absence of both significant comorbidities and poor risk/complex cytogenetics.***
- ***Consider venetoclax and azacitidine or venetoclax and low-dose cytarabine if patient unsuitable for an intensive chemotherapy approach. top after two cycles if no response as the vast majority of responses occur within the first two cycles.***
- ***If IDH1 positive, consider ivosidenib and azacitidine if patient is unsuitable for intensive chemotherapy.***
- ***Consider azacitidine for those with poor performance status and/or comorbidities with poor risk/complex cytogenetics and <30% blasts***

Assuming a performance status of up to 2 and no significant comorbidity or cytogenetic complexity standard induction therapy can be undertaken with an expectation of a CR

rate of 50% and a treatment related mortality of up to 15%[28]. There is limited data to properly evaluate the effect of post remission therapy. The MRC AML11 study confirmed no advantage to a total of 4 versus 3 cycles of therapy[29] thus shortened consolidation is standard. The overwhelming majority of these patients will relapse and should be evaluated for alternative therapy such as consolidation such as reduced intensity allogeneic transplantation.

3.3.2 Venetoclax in combination with azacitidine

- ***NICE approved for adults with untreated AML when intensive induction chemotherapy is unsuitable.***

The data for the use of venetoclax and azacitidine is from the VIALE-A trial, where venetoclax/azacitidine was compared to azacitidine/placebo[30]. The median overall survival was 14.7 months in the treatment arm versus 9.6 in the control arm (hazard ratio for death, 0.66; 95% confidence interval, 0.52 to 0.85; P<0.001).

Admission to hospital and monitoring for tumour lysis syndrome during the dose ramp-up of cycle one is recommended. Dosing is as follows:

Cycle 1
Azacitidine 75 mg/m2 SC once daily for the first 7 working days of 28 day cycle *and* Venetoclax 100 mg PO on Day 1, 200 mg PO on Day 2, 300mg PO on Day 3, then 100 mg* PO once daily on Days 4-28 (with the addition of concomitant azole antifungal prophylaxis).
Cycle 2 onwards
Azacitidine 75 mg/m2 SC once daily for the first 7 working days of 28 day cycle *and* Venetoclax 100 mg* PO once daily on Days 1-28 continuously.

*Note venetoclax dose should be adjusted depending on the degree of CYP3A4 interaction with azole antifungal prophylaxis.

A bone marrow biopsy for disease response is recommended around Day 21 of the first cycle[14]. At this time point, if blasts clearance <5% (i.e. morphological leukaemia-free state) is acheived, venetoclax can be stopped until blood counts recover. The next cycle can then be commenced once blood counts sufficiently recover. If disease persists (blasts remain >5%), venetoclax should be continued for the remainder of the first cycle and the next cycle commenced, regardless of blood counts.

Consider adjustments of venetoclax (+/- azacitidine) dosing and duration in subsequent cycles according to delays in count recovery. Consider regular G-CSF use if there are significant issues with neutropenia and blast clearance has been achieved.

Most disease responses occur in the first two cycles. Treatment can continue for as long as the patient derives benefit, or until disease progression or unacceptable drug toxicity.

3.3.4 Venetoclax in combination with low-dose cytarabine

- ***NICE approved for adults with untreated AML with >30% blasts when intensive induction chemotherapy is unsuitable. This should preferably only be used in NPM1-mutated cases where outcomes appear similar with venetoclax-azacitidine.***

The VIALE-C trial was the basis for NICE recommendations[31]. It was a phase 3, randomised, placebo-controlled trial comparing venetoclax or placebo in combination with low-dose cytarabine in 211 patients with newly diagnosed AML ineligible for intensive chemotherapy. Patients receiving venetoclax + LDAC had higher rates of CR/CRi compared to LDAC alone (48.3% vs 13.2%) and higher median OS at 2-year follow-up (8.4 vs 4.1 months). Long term 5-year followup continued to show OS benefit, with 31% of CR/CRi remaining in remisison for >2 years[32]. Recent analysis of a real-world UK cohort showed comparable outcomes compared to venetoclax-azacitidine in the NPM1 mutated subgroup[33].

3.3.5 Ivosidenib in combination with azacitidine

- ***NICE approved for adults with untreated AML with an IDH1 R132 mutation who cannot have standard intensive induction chemotherapy.***
- ***Ivosidenib 500mg PO once daily is given in combination with azacitidine 75mg/m² SC once daily days 1-7 in 28-day cycles.***
- ***Treatment can continue for as long as patient derives benefit, or until disease progression or unacceptable drug toxicity.***

The AGILE study was the basis for NICE recommendations[34]. It was a phase III randomised, placebo-controlled trial investigating the use of azacitidine in 146 patients with newly diagnosed IDH1-mutated AML ineligible for intensive induction chemotherapy. Compared to placebo, ivosidenib improved event-free survival (HR 0.33, 95% CI 0.16-0.69, P=0.002) and overall survival (24 months vs 7.9 months, HR 0.44 95% CI 0.27-0.73, P=0.001).

Venetoclax in combination with azacitidine also shows significant activity in IDH1-mutated AML and remains a reasonable choice, as there have not yet been head-to-head comparisons between azacitidine +ivosidenib and azacitidine+venetoclax.

3.3.6 Azacitidine

- ***Consider azacitidine (75mg/m² sc once daily days 1-7 with weekend breaks, 28-day cycles until progression) for those with poor performance status/ comorbidities, poor risk/complex cytogenetics and <30% blasts***

A phase 3 randomised trial has demonstrated a survival advantage for patient with int-2 and high risk MDS[35]. A third of these patients now have AML as defined by the WHO and may have a survival benefit over conventional care (2-year OS 50 vs 16%), although these may be a particular group of patients with non-proliferative disease. Recent data has

been published demonstrating a benefit in patients with blasts >30% compared to standard therapy but this was not approved by NICE for use in the NHS.

3.3.7 Low-dose Cytarabine

- ***Consider low-dose Cytarabine for those not suitable or eligible for Azacitidine or intensive chemotherapy***

Is considered the standard of care for those patients not suitable for intensive chemotherapy. The MRC AML14 study has demonstrated a survival advantage for low-dose Cytarabine 20mg BD SC for 10 days, repeated every 28 days, when compared to hydroxycarbamide[36]. Although there was no survival benefit for patients with adverse cytogenetics, these patients should be considered for investigational approaches.

3.4 Primary Refractory Disease

- ***Consider intensive chemotherapy with FLAG-Ida followed by allogeneic Stem Cell transplant or clinical trial***

Primary refractory disease is defined as failure to obtain a complete remission after exposure to two courses of intensive induction. However, failure to respond to the first cycle of induction therapy is a major predictor of a poor outcome[37] and conventional chemotherapy then offers virtually no prospect of long term DFS. Consideration of the patients' age, response to initial therapy, nature of initial therapy should be considered. In general terms escalation of treatment is indicated for patients under the age of 60. With FLAG IDA (Fludarabine 30mg/m2 on days 2-6, Cytarabine 2g/m2 over 4 hours on days 2-6, Idarubicin 8mg/m2 days 4-6, GCSF sc od days 1-7) remission can be achieved in up to 50% of such patients, and may be reasonable if there is a potential for allogeneic transplantation. MACE (Amsacrine 100mg/m^2 1-hour infusion days 1-5, Cytarabine 200mg/m^2 by continuous IV infusion days 1-5, Etoposide 100mg/m^2 4-hour infusion days 1-5) is an alternative to FLAG IDA. Patients who are not suitable for allogeneic transplantation should be considered for investigational therapy of novel agents.

3.5 Minimal residual disease (MRD) monitoring during and after treatment

MRD monitoring should routinely be monitored where possible. This may be done via molecular MRD monitoring in cases with a suitable marker, or otherwise with multiparametric flow cytometric (MFC) MRD. MRD assessment is especially prognostic at specific timepoints during treatment in certain cases. MRD monitoring should be routinely continued for up to 2 years after completion of consolidation therapy and may also be used after allogeneic stem cell transplantation[38]. In cases of MRD persistence, progression or relapse, patients should be considered for closer monitoring, allogeneic stem cell transplantation or further therapy (e.g. venetoclax-based treatment, salvage chemotherapy, or donor lymphocyte infusions with azacitidine).

NPM1 mutated AML

In NPM1-mutated AML, MRD should be assessed preferentially in peripheral blood (PB) after 2 cycles of chemotherapy, in BM at the end of consolidation, and in BM every 3 mo for 24 mo after the end of consolidation. (Alternatively, MRD may be assessed from PB every 4 to 6 wk during follow-up for 24 mo)[38]. NPM1 PCR positivity in PB after 2 cycles of chemotherapy is a strong negative prognostic marker for disease relapse and inferior outcomes[39], and should warrant consideration of an allogeneic stem cell transplant in first complete remission[40].

CBF-AML

In RUNX1-RUNX1T1, and CBFB-MYH11 mutated AML MRD should be assessed preferentially in PB after 2 cycles of chemotherapy, in BM at the end of consolidation treatment, and in PB every 4 to 6 wk for 24 mo after the end of consolidation[38].

APML

In APML, the most important MRD end point is BM PCR negativity for PML-RARA at the end of consolidation[38]. In high-risk APML, consider continuing regular monitoring for 2 years beyond the end of treatment.

4. Allogeneic Stem Cell Transplantation (SCT)

4.1 Non-Trial Patients suitable for transplant

MRD guided	Intermediate risk AML	Poor risk AML	Relapsed/ refractory
NPM1+ Molecular MRD+ve in PB after 2 induction cycles	FLT3-ITD+/ NPM1-	As per ELN criteria	In 2nd or higher remission
Molecular relapse of NPM1 or CBF AML	FLT3-ITD-/ NPM1- (no MRD marker)		

The decision to perform allogeneic HCT during first remission depends on the risk-benefit ratio (ie, nonrelapse mortality [NRM] and disability/reduction in relapse risk) based on cytogenetic and molecular genetic features of disease at presentation and response to initial therapy, as well as patient, donor, and transplant factors. Allogeneic SCT as a post remission therapy is associated with the lowest rates of relapse. It combines chemo +/- radiotherapy with immunotherapy through a potent graft versus leukaemia (GVL) effect. However, the benefits of allogeneic SCT have been offset by the high non-relapse mortality (NRM) of the procedure. A meta-analysis of clinical trials that assigned allo SCT versus alternative consolidation therapies on an intent-to-treat donor versus no-donor basis show that allogeneic SCT offers significant benefit for patients with intermediate

and high risk AML[41]. Therefore, allogeneic SCT may specially be applied to patients with a high risk of relapse and a relatively low risk of NRM. Thus, for individual decision making, it is important to take into account both the disease risk, as defined by the cytogenetic and molecular genetic profile of the leukaemia and the risk associated with the transplant procedure as assessed by the co-morbidity score and other transplant-related risk indices.

For patients with favorable-risk disease, allogeneic HCT in CR1 is generally not recommended except for those with inadequate clearance of MRD. Molecular positivity for NPM1 after the second cycle of chemotherapy is predictive of higher relapse risk and CR1 allogeneic SCT should be considered[40].

4.2 General recommendations

All patients of childbearing age undergoing SCT should be offered the opportunity of preserving fertility prior to treatment, unless there are overriding clinical reasons not to do so. Contact St Mary's Hospital tel. 0161 276 6430.

Patients who are potential candidates for allogeneic SCT should be discussed with and referred to one of the regional transplant centres (Manchester Royal Infirmary and Christie Hospital). A donor search should be initiated as soon as possible; good practice would be for all suitable patients to HLA type the patient and siblings at time of diagnosis and refer to a transplant centre as early as possible.

5. Relapse

In general the prognosis for patients who relapse is poor irrespective of therapy. Consideration should be given to the patients' previous treatment, age, performance status, karyotype and specifically the duration of CR1. Patients who are not fit for allogeneic will generally not be suitable for intensive salvage therapy.

5.1 Salvage chemotherapy

- ***FLAG or FLAG-I or MACE followed by allogeneic SCT***
- ***Experimental therapy or clinical trial if not suitable for SCT***

For young and fit patients who relapse after completion of chemotherapy, consideration should be given to high dose ARA-C based salvage chemotherapy (e.g. FLAG, FLAG-Ida, MACE) followed by consolidation with an allogeneic SCT. Early consideration should be given to any available clinical trials.

Patients who relapse after allogeneic SCT are only eligible for 2nd allogeneic SCT after salvage chemotherapy if their relapse occurred after 1 year of initial SCT.

5.2 Gilteritinib

Gilteritinib monotherapy is recommended as an option in relapsed or refractory FLT-3 mutation positive AML. The evidence for gilteritinib in this setting comes from the ADMIRAL trial, where treatment with gilteritinib increased median overall survival compared to salvage chemotherapy from 5.6 months to 9.3 months (hazard ratio 0.68; 95% CI 0.53% to 0.88, p=0.0013)[42].

5.3 Investigational therapy

Patients who have relapsed within 12 months post-transplant or are not fit for transplant may be suitable for investigational therapy.

6. Supportive care

Advances in supportive care have resulted in improvements in survival as evidenced by individuals with AML recruited to clinical trials.

The recommendations set out below offer guidance and an evidence base where available to allow local/unit policies to be developed. Individualised policies recognise the importance of identifying locally prevalent infectious organisms and drug resistance patterns.

6.1 Antibiotic prophylaxis

- ***Prophylactic Ciprofloxacin 500mg bd or Levofloxacin 500mg od***

The use of prophylactic antibiotics in induction chemotherapy and in neutropenic individuals undergoing consolidation chemotherapy remains controversial. The results of a large meta-analysis Cochrane review however do demonstrate that the use of prophylactic antibiotics when compared to placebo is effective in reducing overall mortality and infection related mortality in neutropenic patients[43]. This effect is most marked in individuals receiving quinolone antibiotics[44]. Guidance by the European Leukamia Net recommends their use[45]. Therefore, a prophylactic quinolone antibiotic is appropriate for prophylactic use in neutropenic individuals with AML.

6.2 Antifungal prophylaxis

- ***Posaconazole tablets 300mg od PO (24hr loading 300mg bd)***

Fungal infections are a major cause of morbidity and mortality in the AML population; overall incidence rates of IFI were around 12% (mould 7.9% and yeast 4.4%). Death rates attributable to invasive mould or yeast infection were documented to be 38% and 35% respectively.

The use of anti-fungal prophylaxis has been shown to reduce the fungal infection related mortality when compared to placebo[46]. Prophylaxis with a drug active against Aspergillus species is required given the epidemiology of IFI in this patient group.

ECIL 2018 guidelines[47] recommend posaconazole as first choice where baseline incidence of mould is high and there is overall consensus on its routine use in patients on AML therapy. In 2022, EHA published a consensus statement on antifungal prophylaxis with novel targeted therapies for AML[48]. Caution for drug-drug interactions with novel agents should be taken and dose reductions of venetoclax, ivosidenib and quizartinib are recommended when used concomitantly with strong CYP3A4 inhibitors.

The initiation of prophylaxis should be in parallel with induction of cytotoxic chemotherapy in order to ensure maximal effect at time of severe neutropenia and mucosal barrier breakdown. To be administered until neutrophil recovery of >0.5x10^9/L for 2 consecutive days.

6.3 Antiviral prophylaxis

This is not routinely required however can be considered in individuals receiving fludarabine/clofarabine-containing regimens and with previous herpetic virus reactivation.

6.4 Pneumocystis carinii/jerovii prophylaxis

Individuals receiving fludarabine/clofarabine-containing regimens should receive prophylaxis against PCP/PJP infections with either cotrimoxazole with alternatives of azithromycin or dapsone if not tolerated.

6.5 Tumour lysis syndrome

- **Allopurinol prophylaxis 300mg od PO**
- **Rasburicase prophylaxis for high WCC AML**

Metabolic derangements can occur with tumour breakdown following the initiation of cytotoxic therapy. The tumour lysis syndrome is most commonly seen in tumours with a high proliferative rate, relatively large tumour burden and a high sensitivity to cytotoxic agents. In AML predisposing factors include high WCC, high LDH and impaired baseline creatinine. It is most commonly witnessed within 12-72 hours of initiation of chemotherapy with symptoms including nausea, vomiting, oedema, overload, congestive cardiac failure, dysrhythmias, seizures, muscle cramps and tetany. Laboratory predictors of onset include hyperkalaemia, hyperuricaemia, hypocalcaemia and hyperphosphataemia, which may progress to acute renal failure.

Recombinant urate oxidase (Rasburicase®) may be chosen in preference to allopurinol in high-risk patients [elevated uric acid, WCC >50x10^9/L, LDH >x2 normal upper limit, aggressive cytoreduction and tumour infiltration of the kidneys][49,50].

6.6 Growth factors

- **Recommended to use GCSF or biosimilars**

Use in induction regimes

The prolonged neutropenia, increased morbidity and early death rates, particularly notable in older individuals following intensive induction chemotherapy has resulted in numerous groups assessing the impact of colony stimulating factors. Various endpoints have been studied, most including survival, CR rates, reduction in period of neutropenia and length of hospital stay. The results have largely been similar with a demonstrated reduction in the period of neutropenia and a shorter duration of hospital stay but no demonstrable effect on CR rates or OS[51-53].

The largest body of prospective data from the MRC AML11 and 12 trials has been reported. In a randomised controlled trial, placebo compared to the GCSF Lenograstim® commencing at day +8 following induction chemotherapy were compared. The time to neutrophil recovery was significantly quicker in the GCSF arm but there was no effect on severity or duration of infective complications and associated antibiotic use. Hospitalisation was however significantly reduced on average by 2 days and individuals proceeded to consolidation chemotherapy on average 3 days earlier. There was no overall effect on CR between the two arms; subgroup analysis however found a significantly lower CR rate in the GCSF arm for patients < 40 years (attributable to excess of induction death and resistant disease). No difference in outcome after remission or relapse rates[54].

Support for the use of growth factors can be found in other international collaborative groups; the NCCN recommend consideration for older individuals based on the ECOG study Group results[55]. However the BCSH guidelines indicate routine use is not recommended[56] and ELN guidelines advocate individual use only[57].

The use of GCSF in induction chemotherapy can be recommended based on of quality of life and health economic decisions; its use is not however routine or widespread and local units should develop their own policy.

Use after consolidation chemotherapy

Two large trials evaluating the use of GCSF after consolidation chemotherapy demonstrated a decrease in the duration of neutropenia and a reduction in antibiotic therapy[58,59].

6.7 Transfusion support

General principles

It is standard practice in the UK that cellular blood products are leukodepleted. In recent years all blood products used routinely are CMV unselected. Individuals receiving fludarabine/clofarabine chemotherapy require blood products to be irradiated.

Platelet transfusion

Three randomised studies have shown no significant difference in bleeding rates for a transfusion threshold of $10x10^9$/L compared to $20x10^9$/L[60-62]. The decision should be revised based on individual patient factors: mucosal bleeding, infection. Severe mucositis and fever when a higher threshold is appropriate. Although alloimmunization

is less likely to occur with the use of leukodepleted products their presence should be investigated in the presence of a platelet refractory status and if confirmed HLA-matched platelets provided.

Red cell transfusion

There is no supportive evidence however 7-8g/dl is generally accepted as the transfusion trigger.

6.8. Neutropenic fever

Recognition and prompt treatment with broad-spectrum antibiotics is essential. Each unit should have a policy document developed with the microbiology department.

6.9. Dietary advice

Individuals receiving chemotherapy are at risk from infection from bacteria and fungus in food products. Patient advice information leaflets are available through Leukaemia Research; Dietary advice for patients with neutropenia.
Contact details; Leukaemia Research; info@lrf.org.uk,
Tel; 020 7405 0101

7. Management of special situations

7.1. Hyperleukocytosis

The condition is generally defined as a WCC >100x10^9/L. It is associated with higher rates of mortality in induction[63]. Leukostasis symptoms such as retinal, cerebral or pulmonary haemorrhage require immediate treatment with chemotherapy. Initial cytoreduction with hydroxycarbamide or daunorubicin should be commenced in all cases with close monitoring for TLS[64]. Leukopheresis can be considered but has not demonstrated any improvement in long-term survival and is logistically challenging. Transfusion of packed red cells can lead to increased blood viscosity and should be avoided until WCC is less than 100[57]. There should be a low threshold for CNS imaging if any neurological symptoms develop as the incidence of intracranial haemorrhage in hyperleukocytosis is high[64].

7.2. Central nervous system involvement

Leptomeningeal involvement is rarely seen in AML (<3%) and therefore a lumbar puncture is not required as part of the routine diagnostic work-up. It should however be performed in certain clinical scenarios where there is concern. Individuals presenting with abnormal focal neurology, headache or confusion a CT/MRI scan should be performed initially to exclude an intracerebral lesion or intracranial haemorrhage with mass effect. If there is no mass effect then lumbar puncture and sampling of the CSF should be performed (microscopy, protein, glucose, cytospin). If the LP demonstrates leptomeningeal involvement, then intrathecal chemotherapy should be administered in conjunction with systemic treatment.

- Cytarabine 50mg IT Initially three times weekly until blast cells are no longer detected on cytospin and then weekly for 4-6 weeks[56].

It is also reasonable to consider a consolidation regime containing HDAC, which will cross the blood brain barrier (FLAG-Ida, high-dose Cytarabine). Palliative radiotherapy can also be considered.

If the initial CT scan identifies a mass lesion biopsy or needle aspiration should be considered. If a leukaemic deposit is confirmed, cranial radiation may be required if systemic and intrathecal chemotherapy is ineffective. Combination chemo-radiotherapy should be avoided due to the high risk of neurotoxicity.

7.3 Management of extramedullary disease/granulocytic sarcoma.

Extramedullary disease in AML ranges from skin and gum infiltrates most frequently seen in AML of monocytic/monoblastic derivation to the rare tumorous masses (also known as granulocytic sarcomas or chloromas). The commonest sites for extramedullary myeloid tumours include skin, lymph nodes, spine, small intestine, orbit, bone, breast, cervix and nasal sinuses, but many other sites have been described Patients presenting de novo with extramedullary leukaemia without evidence of marrow disease have in the past been managed with surgical excision or local radiotherapy as primary treatment, but almost all these patients have gone on to develop marrow disease. It is therefore recommended that patients presenting in this fashion should also receive systemic antileukaemic chemotherapy at diagnosis. Surgical or radiotherapeutic approaches may be reserved for those patients whose extramedullary tumours do not completely resolve with initial treatment. The role for allogeneic SCT still remains unclear.

7.4. Differentiation syndrome with lower-intensity treatments

Differentiation syndrome was historically usually only seen with treatment of APL with ATRA and ATO but is now an important complication of newer targeted therapies. It has been reported in 10-20% of AML treated with IDH inhibitors and can uncommonly be seen with newer FLT3 inhibitors (1-3% in gilteritinib and 5% in quizartinib in the relapsed/refractory setting)[65].

The common signs and symptoms are pulmonary infiltrates, pleuropericardial effusions, fever, weight gain and oedema, leukocytosis, hypotension and renal impairment. Skin manifestations including neutrophilic dermatosis may also occur. The onset of DS can be delayed with these agents, sometimes occurring weeks later, compared to its quick onset in treated APL patients.

Due to the long half-life of these targeted agents, stopping the drug is alone unlikely to be immediately effective, therefore treatment with corticosteroids (dexamethasone 10mg BD) should be initiated at first suspicion[66]. If there is concomitant leukocytosis, hydroxyurea should be considered. The occurrence of differentiation syndrome does not necessarily require permanent discontinuation of the drug. Dose/schedule modifications and cautious reintroduction after clinical improvement should be

considered noting that differentiation syndrome may recur on resumption of therapy weeks after an initial episode.

7.5. Pregnancy

AML in pregnancy should be managed jointly between the haematologist and the obstetrician with full involvement of the mother. Treatment delays may compromise maternal outcome without improving the outcome for the foetus. When the diagnosis of AML is made in the first trimester, a successful pregnancy outcome is unlikely and spontaneous pregnancy loss in this situation carries considerable risks for the mother[67]. Chemotherapy in the first trimester is associated with a high risk of fetal malformation and should be avoided if possible. The opportunity to terminate the pregnancy should be discussed. If termination is refused and the mother's life is at risk, chemotherapy should be started. Chemotherapy in the second and third trimesters is reasonably safe to administer and rarely causes congenital malformation but is associated with an increased risk of abortion, premature delivery and growth restriction[67]. Consideration should be given for early-induced labour between cycles of chemotherapy. The risk-benefit ratio must be carefully considered before using any drugs in pregnancy, including antimicrobials and supportive care medications.

8. Acute Promyelocytic Leukaemia (APML)

In general, the diagnosis is suggested by the presence of the characteristic morphology and there is consensus that the diagnosis should be confirmed at the genetic level. However, this should not delay the initiation of supportive measures or differentiation therapy, which should be initiated immediately on the day of presentation without delay.

8.1 Low/Intermediate-risk patients (WCC ≤10)

- ***Arsenic trioxide plus*** *all-trans-retinoic acid (****ATRA) as per SPC or AML17 trial (if the latter is used,*** *Trust policy regarding unlicensed treatments should be followed)*

8.2 High-risk patients (WCC >10)

- ***AIDA (Chemotherapy + ATRA)***

For patients with high-risk APL the standard therapy is for ATRA and anthracycline based therapy. Such an approach leads to a 95% complete remission rate[68] with primary resistance being an anecdotal occurrence. Comparative trials for the optimal anthracycline have not be done while there appears to be no advantage to adding cytarabine to induction therapy[36].

Course 1
Idarubicin (12mg/m^2, days 2, 4, 6, 8) and ATRA (45mg/m^2/day daily until CR)

Course 2
Idarubicin (7mg/m^2, days 1-4) and ATRA (45mg/m^2/day for 15 days)

Course 3
Mitoxantrone (10mg/m^2, days 1-5) and ATRA (45mg/m^2/day for 15 days)

Course 4
Idarubicin (12mg/m2 1 dose) and ATRA (45mg/m^2/day for 15 days)

Consolidation therapy
Historical comparison suggests that ATRA contributes to the reduction in relapse risk observed in the GIMEMA[69] and PETHEMA[68] group studies. The role of Cytarabine remains controversial and unresolved with numerous studies suggesting a reduction in relapse risk but improved survival has yet to be unequivocally demonstrated. There is no role for stem cell transplantation in first line therapy for patients with APML.

8.3 APL Relapse

- ***Arsenic trioxide plus*** *all-trans-retinoic acid (****ATRA) as per SPC or AML17 trial (if the later is used,*** *hospital Trust policy regarding unlicensed treatments should be followed)*

Repeated molecular relapse should be treated with Arsenic Trioxide (As_2O_3=ATO), 0.30 mg/kg IV over 2 hours daily for 5 days (days 1-5) in week 1, and thereafter 0.25mg/kg IV over 2 hours twice a week for an additional seven weeks. Consolidation of this remission may be in the form of further Arsenic, autologous or allogeneic transplantation. Approximately 10% of APML haematological relapses involve the CNS[70] and should therefore be excluded in all relapsed patients.

Genetic variants of AML e.g. t(11;17)
The nature of the fusion partner of RARA is critical to ATRA sensitivity. Many remain ATRA sensitive and should receive standard therapy. Those that are known to be ATRA resistant are usually treated as AML as sensitivity the ATO is unknown.

8.4 MRD monitoring by RQ-PCR

- ***In low/intermediate-risk APL, MRD assessment for PML-RARA should be performed on bone marrow at completion of consolidation therapy as this is the most important MRD endpoint.***
- ***In high-risk APML, MRD monitoring should be continued for 2 years following completion of consolidation therapy. This can be performed via bone marrow every 3 months or via peripheral blood every 4-6 weeks.***

The aim of treatment in APL is to achieve molecular negativity by RQ-PCR. Persistence or recurrence of molecular disease is invariably associated with haematological relapse. There is strong evidence that intervention at the point of molecular persistence or recurrence is clinically useful as pre-emptive treatment with Arsenic trioxide can result in molecular negativity and prevent re-induction mortality.

8.5 Differentiation Syndrome

- ***Dexamethasone 10mg IV 12-hourly for 5 days if WCC >10x10^9/L***

This is accurately defined by the presence of unexplained fever, weight gain, respiratory distress, pulmonary infiltrates, pleural and pericardial effusion, renal or cardiac failure with or without hyperleukocytosis – this necessitates immediate initiation of Dexamethasone 10mg intravenously 12hrly until disappearance of symptoms. If the syndrome is severe then also discontinuation of the ATRA is recommended.

The standard approach for patients at high risk of differentiation syndrome e.g. white cell count greater than 10 is to receive Dexamethasone 10mgs intravenously 12 hourly for the first 5 days of chemotherapy, this is based on an uncontrolled study demonstrating a low morbidity and mortality[68].

8.6 Coagulopathy

- ***Keep platelets ≥50x10^9/L***
- ***Keep fibrinogen >1.5g/L with cryoprecipitate***
- ***Consider FFP for abnormal DIC screens***

The major cause of treatment failure is induction death due to intracerebral or intra-pulmonary haemorrhage, in up to 5% of presenting patients[71]. APTT, fibrinogen and platelet count should be checked at least twice daily during the initial phase of therapy. Correction should be managed as below until all clinical and laboratory signs of the coagulopathy have disappeared. The role of antifibrinolytic agents and heparin is at best questionable.

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