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The World Health Organisation (WHO) system for the diagnosis and classification of AML (Jaffe et al 2001) superseded the modified FAB classification (Bennett et al 1985) and its use was proposed in the 2006 BCSH guidelines (Milligan et al 2006) The WHO system has subsequently been revised and updated (Vardiman et al 2009, Arber et al 2016). The revised WHO classifications reflect the fact that an increasing number of acute leukaemias can be categorised based upon their underlying cytogenetic or molecular genetic abnormalities and that these genetic changes form clinico-pathologic entities. In the WHO classification 2016 a new category ‘myeloid neoplasms with germ line predisposition’ was added.

Table 1:Revised WHO classification of myeloid neoplasms and acute leukaemia, includes leukaemias with ambiguous lineage (WHO 2016)

AML with recurrent genetic abnormalities	**Acute myeloid leukaemia, not otherwise specified**
AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*	AML with minimal differentiation
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*	AML without maturation
Acute promyelocytic leukemia with *PML-RARA* *****	AML with maturation
AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* **†**	Acute myelomonocytic leukemia
AML with t(6;9)(p23;q34.1); *DEK-NUP214*	Acute monoblastic/monocytic leukemia
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*	Pure erythroid leukemia #
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); *RBM15-MKL1*	Acute megakaryoblastic leukemia **‡**
Provisional entity: AML with *BCR-ABL1*	Acute basophilic leukemia
AML with mutated *NPM1* **§**	Acute panmyelosis with myelofibrosis
AML with biallelic mutations of *CEBPA* **§**	**Acute leukaemias of ambiguous lineage**
Provisional entity: AML with mutated *RUNX1*	Acute undifferentiated leukaemia
Myeloid leukaemia with germline predisposition (see table 2)	Mixed phenotype acute leukaemia (MPAL)with t(9;22)(q34;q11.2); BCR-ABL1 ******
AML with myelodysplasia related changes ‖	MPAL with t(v;11q23); MLL rearranged
Therapy related myeloid neoplasms ¶	MPAL, B/myeloid, NOS
Myeloid sarcoma (syn: extramedullary myeloid tumor; granulocytic sarcoma; chloroma)	MPAL, T/myeloid, NOS
Myeloid proliferations related to Down syndrome	**Blastic plasmacytoid dendritic cell neoplasm**
Transient abnormal myelopoiesis (syn: transient myeloproliferative disorder)	
Myeloid leukaemia associated with Down syndrome	

Notes on WHO clinical classification

	For a diagnosis of AML, a marrow blast count of ≥20% is required, except for AML with the recurrent genetic abnormalities t(15;17), t(8;21), inv(16), or t(16;16). Adapted from Arber et al
*	Other recurring translocations involving *RARA* should be reported accordingly: for example, AML with t(11;17)(q23;q12); *ZBTB16-RARA*; AML with t(11;17)(q13;q12); *NUMA1-RARA*; AML with t(5;17)(q35;q12); *NPM1-RARA*; or AML with *STAT5B-RARA* (the latter having a normal chromosome 17 on conventional cytogenetic analysis).
†	Other translocations involving *KMT2A* (*MLL*) should be reported accordingly: for example, AML with t(6;11)(q27;q23.3); *MLLT4-KMT2A*; AML with t(11;19)(q23.3;p13.3); *KMT2A-MLLT1*; AML with t(11;19)(q23.3;p13.1); *KMT2A-ELL*; AML with t(10;11)(p12;q23.3); *MLLT10-KMT2A*
‡	Rare leukemia most commonly occurring in infants.
§	Diagnosis is made irrespective of the presence or absence of multilineage dysplasia.
ǁ	At least 20% (≥20%) blood or marrow blasts AND any of the following: previous history of MDS or MDS/MPN; myelodysplasia-related cytogenetic abnormality (see list below); multilineage dysplasia; AND absence of both prior cytotoxic therapy for unrelated disease and aforementioned recurring genetic abnormalities. Cytogenetic abnormalities sufficient to diagnose AML with myelodysplasia-related changes are: **Complex karyotype** (defined as 3 or more chromosomal 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*); **Unbalanced abnormalities**: −7 or del(7q); −5 or del(5q); i(17q) or t(17p); −13 or del(13q); del(11q); del(12p) or t(12p); idic(X)(q13); **Balanced abnormalities**: t(11;16)(q23.3;p13.3); t(3;21)(q26.2;q22.1); t(1;3)(p36.3;q21.2); t(2;11)(p21;q23.3); t(5;12)(q32;p13.2); t(5;7)(q32;q11.2); t(5;17)(q32;p13.2); t(5;10)(q32;q21.2); t(3;5)(q25.3;q35.1).
¶	Cases should be classified with the related genetic abnormality given in the diagnosis.
#	The former subgroup of acute erythroid leukemia, erythroid/myeloid type (≥50% bone marrow erythroid precursors and ≥20% myeloblasts among nonerythroid cells) was removed; myeloblasts are now always counted as percentage of total marrow cells. The remaining subcategory AML, NOS, pure erythroid leukemia requires the presence of >80% immature erythroid precursors with ≥30% proerythroblasts
**	*BCR-ABL1*+ leukemia may present as MPAL; treatment should include a tyrosine kinase inhibitor.

Table 2: Myeloid neoplasms with germ line predisposition and guide for molecular genetic diagnostics

Myeloid neoplasms with germ line predisposition without a preexisting disorder or organ dysfunction
AML with germ line *CEBPA* mutation
Myeloid neoplasms with line *DDX41* mutation†
Myeloid neoplasms with germ line predisposition and preexisting platelet disorders
Myeloid neoplasms with germ line *RUNX1* mutation†
Myeloid neoplasms with germ line *ANKRD26* mutation†
Myeloid neoplasms with germ line *ETV6* mutation†
Myeloid neoplasms with germ line predisposition and other organ dysfunction
Myeloid neoplasms with germ line *GATA2* mutation
Myeloid neoplasms associated with bone marrow failure syndromes
Myeloid myelomonocytic leukaemia associated with neurofibromatosis, Noonan syndrome, or Noonan syndrome-like disorders
Myeloid neoplasms associated with Noonan syndrome
Myeloid neoplasms associated with Down syndrome†
Guide for molecular genetic diagnostics‡
Myelodysplastic predisposition/acute leukaemia predisposition syndromes *CEBPA*, *DDX41*, *RUNX1*, *ANKRD26*, *ETV6*, *GATA2*, *SRP72*, 14q32.2 genomic duplication *(ATG2B/GSKIP)*
Cancer predisposition syndromes§ Li Fraumeni syndrome (*TP53*) Germ line *BRCA1/BRCA2* mutations
Bone marrow failure syndromes Dyskeratosis congenital (*TERC, TERT*) Fanconi anaemia

†Lymphoid neoplasms also reported.

‡Molecular genetic diagnostics are guided by a detailed patient and family history; diagnostics should be performed in close collaboration with a genetic counselor; patients with a suspected heritable myeloid neoplasm, who tested negative for known predisposition genes, should ideally be entered on a research study to facilitate new syndrome discovery.

§Mutations in genes associated with cancer predisposition genes such as *TP53* and *BRCA1/2* appear to be frequent in therapy-related myeloid neoplasms.

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	Marrow aspirate (morphology)	Immunophenotyping (peripheral blood and marrow)	Cytogenetics/ FISH
Molecular/ genomics sample (DNA/ RNA extraction) (May also require a peripheral blood sample)	Trephine (immunohistochemistry)	Trial samples	Whole genome sequencing sample and germ line sample (skin punch biopsy or saliva)

The HCDP website has a wealth of information and discusses in detail each test available and their interpretation. Please refer to https://live.gmhcdp.nhs.uk and click on the 'Help' tab.

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.

For a diagnosis of AML a blast count of 20% or more is required, except for AML with t(15;17), t(8;21), inv(16) or t(16;16) and some cases of erythroid leukaemia. Multilineage dysplasia is defined as ≥50% dysplastic cells in two lineages.

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. Acute panmyelosis is a trephine diagnosis, requiring antibodies that identify CD34, MPO, glycophorin and megakaryocyte antigens.

2.2.2 Immunophenotyping

Is performed to confirm cell lineage but also to identify acute leukaemias of ambiguous lineage (Bennett et al 1985). 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. If APML is suspected, please state this in the clinical request and HLA DR will be performed.

2.2.3 Cytogenetics/ FISH

Conventional cytogenetics/ FISH still play a key role in the investigation of acute leukaemia today and are combined with molecular genetics to maximise their prognostic potential.

Recurrent cytogenetic abnormalities are recognized in the WHO category “AML with recurrent genetic abnormalities” and certain abnormalities are sufficient to establish a diagnosis of “AML with myelodysplasia related features” if the blast count is over 20%.

Furthermore, risk stratification of patients into favourable, intermediate or adverse prognosis groups (ELN Classification) is an important factor in determining survival (Grimwade et al 2001, Grimwade et al 2010).

2.2.4 Molecular & Genomics

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.

Next generation sequencing is used to screen for mutations in 39 significant genes associated with myeloid neoplasms. Details of the genes involved and information regarding prognostic significance can be found here:
http://haematologyetc.co.uk/Myeloid_Panel_(NGS)

NPM1 mutations can be used to monitor minimal residual disease. The presence of FLT-3 ITD mutations can be used to guide treatment. The presence or absence of specific molecular mutations is also important to risk stratify patients (ELN 2017).

Repeat myeloid panels after diagnosis are not routinely indicated.

A diagnosis of AML also confirms eligibility for whole genome sequencing (WGS) as per the current National Genomic Test Directory. 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) must also be sent for WGS to proceed. Normal standard of care molecular testing for this diagnosis proceeds in parallel.

2.2.4.1 Trial patients

Patients in NCRI AML trials (AML18 and AML19) will have molecular screening of presentation BM and PB carried out routinely.

2.2.4.2 Non-trial patients

All patients should routinely have a myeloid gene panel and be screened for FLT3 and NPM1 mutations as this may influence their management. MRD should be monitored on BM & PB for NPM1. It is recommended that patients with APL and CBF positive AML* should have molecular screening of diagnostic BM & PB, including cKIT mutations in CBF AML. The identification of a specific gene transcript would allow subsequent MRD monitoring.

* 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.

2.2.5 Risk Stratification

Table 3: Risk stratification (ELN 2017)

Standardised reporting for correlation of cytogenetic / molecular data in AML with clinical outcome was proposed by the European Leukaemia Net (ELN) and includes mutation analyses of the NPM1, CEBPA, FLT3 genes.

Favourable	Intermediate	Adverse
t(8;21)(q22;q22); *RUNX1-RUNX1T1*	Mutated *NPM1* and *FLT3*-ITD^{high} (normal karyotype)	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*	Wild-type *NPM1* without *FLT3*-ITD or with FLT3-ITD ^{low}(without adverse risk genetic lesions)	t(6;9)(p23;q34); *DEK-NUP214*
Mutated *NPM1* without *FLT3*-ITD or with FLT3-ITD ^{low}(normal karyotype)	t(9;11)(p22;q23); *MLLT3-MLL*	Wild-type *NPM1* and mutated FLT3-ITD^{high} (normal karyotype)
Biallelic mutated *CEBPA* (normal karyotype)	Cytogenetic abnormalities not classified as favorable or adverse†	Mutated RUNX1, ASXL1 or TP53
		t(v;11)(v;q23); *KMT2A* rearranged
		–5 or del(5q); –7; abnl(17p)
		Complex karyotype‡, monosomal karyotype
		t(9;22)(q34.1;q11.2); BCR-ABL1

†For most abnormalities, adequate numbers have not been studied to draw firm conclusions regarding their prognostic significance.

‡Three or more chromosome abnormalities in the absence of one of the WHO designated recurring translocations or inversions, that is, t(15;17), t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23), t(6;9), inv(3) or t(3;3);

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 (Juliusson et al 2009), even after accounting for disease specific prognostic factors, and performance status. Despite this, age in itself is not the most important factor in determining treatment related mortality, and so a careful evaluation of co-morbidities should be undertaken, so that patients suitable for intensive treatment may receive it.

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 into 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.

3.1.1 AML19

Patients aged 16-60 years should be considered for the AML19 trial. Please note that patients older than 60 years, if considered fit for intensive therapy can also be entered into this study.

3.1.2 AML18

Patients aged 60-80, should be considered for entry into the AML18 trial if they are fit for intensive chemotherapy.

3.1.3 Other trials

Other trials can be accessed via http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/clinical-trialssearch?f[0]=field_trial_status%253A4222&populate=Acute%20myeloid%20leukaemia%20%28AML%29

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, Mylotarg or substitution with CPX351 as per NICE guidance (3.2.3 - 3.2.5)***
- ***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 (Vogler et al 92) and Mitoxantrone (Arlin leuk 90) at comparable doses with no improvement in overall survival. High doses of Cytarabine with Daunorubicin have also been studied, including by the SWOG group (Weick Blood 1996), with no increase in CR but a demonstrable increase in toxicity. Priming with growth factors at induction should only be undertaken as part of a clinical trial as no studies have convincingly influenced OS (Thomas leuk 2007). Recent data is available suggesting improved CR and survival rates with higher doses of Daunorubicin (Fernandez et al 2009), however the survival is comparable to MRC outcomes.

3.2.2 Post-Remission / Consolidation

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

Historically most units have the greatest experience in using the MRC standard consolidation: 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) followed by MiDAC (Mitoxantrone 10mg/m^2 1-hour infusion days 1-5, Cytarabine 1g/m^2 12-hourly 2-hour infusion days 1-3). 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 (Mayer et al 1994). The AML15 study has yet to demonstrate a significant difference between the varying doses of high-dose Cytarabine. Variable availability of Amsacrine and trial evolution has now 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 >60yrs.

The optimal number of cycles of therapy continues to be investigated within clinical trials; current published evidence suggests this consists of 4 cycles in total. Patients with poor risk disease have a dismal outcome with conventional consolidation (Bloomfield et al 1998) and should be considered for allogeneic transplantation.

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 Ratify study was the basis for NICE recommendations and demonstrated an 8% gain 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 (Stone et al NEJM 2017).

3.2.4 Mylotarg (Gemtuzumab Ozogamicin)

- **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 (Burnett et al JCO 2011 and 2013). There are now at least 5 randomised studies published. Mylotarg was NICE approved using the ALFA 0701 schedule: Mylotarg at 3mg/m^2/dose (max one 5mg vial) infused over 2-hours on days 1, 4, 7 in combination with DA 3+7 induction. For patients in complete remission, up to 2 consolidation courses of Mylotarg (3mg/m^2/dose - max one 5mg vial - on days 1) with Daunorubicin (60mg/m^2 for 1 day [first course] or 2 days [second course]) and Cytarabine (1,000mg/m^2 12-hourly on days 1 & 4) are recommended.
In cases where gemtuzumab is started prior to knowing cytogenetic results, is should be stopped if subsequent results indicate poor prognostic karyotype.

3.2.5 Vyxeos (CPX351)

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

Liposomal Cytarabine and Daunorubicin 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; hazard ratio, 0.69; 95% CI, 0.52 to 0.90; one-sided P = 0.003).

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 (Appelbaum et al 2006). Several studies however confirm a better quality of life and survival advantage for low intensity induction therapy compared to supportive care only (Juliusson et al 2009).

3.3.1 Up to 80 years

- ***Consider intensive chemotherapy if good performance status in absence of both significant comorbidities and poor risk/complex cytogenetics.***
- ***Consider venetoclax and azacytidine if patient unsuitable for an intensive chemotherapy approach. Give a minimum of six cycles if responding. Stop after two cycles if no response.***
- ***Consider Azacitidine for those with poor performance status and/or comorbidities with poor risk/complex cytogenetics and <30% blasts***
- ***Consider low-dose Cytarabine for those not suitable or eligible for Azacitidine or intensive chemotherapy***

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% (Appelbaum et al 2006). 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 (Goldstone et al 2001) 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 Over 80 years

- ***Consider low-dose Cytarabine or Azacitidine in the over 80s or those younger with poor performance status and/or comorbidities***

Patients 'over 80' or younger with comorbidity also includes those over 65 years old with a performance status >2 and significant comorbidity can be considered for low-dose Cytarabine or Azacitidine.

3.3.3 Venetoclax in combination with azacytidine

Patient must have one of following 3 types of AML and patient characteristics:

- Patient does not have core binding factor AML [i.e. t(8;21) or inv(16)] and is aged >60 years.
- Patient with NPM1 or IDH1/2 AML aged >50 years or with comorbidities.
- Patient with NPM1mut FLT3 ITD^{neg} genotype AML of any age.

This guidance was approved by NHS England during the COVID-19 pandemic and NICE are due to report their recommendations in November 2021. The data for the use of venetoclax and azacitidine is from DiNardo et al, where venetoclax/ azacitidine was compared to venetoclax/ placebo. The median overall survival was 14.7 months in the treatment arm Vs 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 for at least 5 days of cycle one is recommended. Dosing is as follows:

Cycle 1
AZACITIDINE 75 mg/m2 SC once daily Days 1 to 5 (Monday to Friday), weekend rest, then: AZACITIDINE 75 mg/m2 SC once daily Days 8 to 9 (Monday to Tuesday), of 28 day cycle 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.
Cycle 2 onwards
AZACITIDINE 75 mg/m2 SC once daily Days 1 to 5 (Monday to Friday), weekend rest, then AZACITIDINE 75 mg/m2 SC once daily Days 8 to 9 (Monday to Tuesday), of 28 day cycle VENETOCLAX 100 mg PO once daily on Days 1-28 continuously.

Note venetoclax dose is adjusted due to interaction with azole antifungal prophylaxis.

Treatment should be for a minimum of 6 cycles, with no maximum number of cycles. Treatment can continue for as long as the patient derives benefit, or until disease progression or unacceptable drug toxicity.

3.3.4 Azacitidine

- ***Consider Azacitidine (75mg/m^2 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 (Fenaux et al 2009) has demonstrated a survival advantage for patient with int-2 and high risk MDS. 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.

3.3.5 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 (Burnett et al 2007) study has demonstrated a survival advantage for low-dose Cytarabine 20mg BD SC for 10 days, repeated every 28 days, when compared to hydroxycarbamide. 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 (Schlenk et al 2003) 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.

4. Allogeneic Stem Cell Transplantation (SCT)

4.1 Trial patients

- ***Patients on AML19 identified to have high-risk disease should be offered allogeneic SCT either from a sibling or unrelated donor.***
- ***Older patients treated in AML18 who have a suitable donor (sibling or unrelated) should be considered for a non-myeloablative (reduced intensity conditioning, RIC) allogeneic SCT.***

4.2 Non-Trial Patients suitable for transplant

Intermediate risk AML	Poor risk AML	Relapsed/ refractory
FLT3-ITD+/ NPM1-	As per ELN criteria	In 2nd or higher remission
FLT3-ITD +/ NPM1- & MRD +ve on PB after 1st consolidation		
FLT3-ITD-/ NPM1- (no MRD marker)		
≥40years old & HLA-identical sibling		

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. Although single prospective trials have not shown a significant benefit in overall survival (OS) of patients undergoing allogeneic SCT in first complete remission 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 (Cornelissen et al 2007). 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.

SCT is not indicated in good risk AML with t(15;17), t(8;21) and inv (16) in 1st remission.

4.3 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 Cheryl Fitzgerald at 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. Other agents including clofarabine (Kantarjian et al 2003) and mylotarg (Sievers et al 2001) have demonstrable activity in the relapse setting although further investigation is required to outline if they offer an advantage over more established salvage regimens and are currently not NICE approved. Consideration to clinical trial

Please note 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.

An investigational approach for those with refractory disease that has demonstrated limited efficacy in multi centre studies includes- intensive chemotherapy with sequential RIC allograft (Schmid et al 2006) however such an approach requires validation and should ideally be undertaken as part of a clinical trial protocol.

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 ration 0.68; 95% CI 0.53% to 0.88, p=0.0013)

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. BSCH guidelines (Milligan et al, 2006) conclude that empirical use is not recommended due to lack of evidence of a survival benefit (level IIb). 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 (Gafter-Gvilli et al, 2005). This effect is most marked in individuals receiving quinolone antibiotics (Leibovici L et al, 2006). Recently published guidance by the European Leukamia Net recommends their use (Döhner et al, 2010).

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 (Robenshtok et al, 2007). Prophylaxis with a drug active against Aspergillus species is to be preferred given the epidemiology of IFI in this patient group. Recent studies suggest that posaconazole may be superior (Cornely et al, 2007).

For prophylaxis an agent with activity against Aspergillus/mould species should be selected, many units use posaconazole tablets but if itraconazole is used the liquid formulation is preferred due to absorption issues. 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 Anti viral 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] (Cairo et al 2004).

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 (Dombret et al 1995; Rowe et al 1995; Godwin et al 1998).

Most recently 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 (Wheatley et al 2009).

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 (Larson et al 2002). However the BCSH guidelines indicate routine use is not recommended (Milligan et al 2006) and ELN guidelines advocate individual use only (Dohner et al 2010).

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 (Heil et al 1997; Harousseau et al 2000).

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 (Heckman et al 2007); (Rebulla et al1997);(Zumberg et al 2002). 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. Antifungal therapy

The following recommendations for the treatment of suspected and confirmed invasive fungal infection are based on the Guidelines form the First European Conference on Infections in Leukaemia (Herbrecht et al 2007).

Invasive candidiasis
The shift in epidemiology towards infection with non-albicans Candida such as C.glabrata and C.krusei result in infections with reduced susceptibility or resistance to azole drugs. C.glabrata is sensitive to amphoteracin and the echinocandins. C.krusei is sensitive to amphoteracin, the echinocandins and voriconazole. For

invasive candida infections, Ambisome (3mg/kg) or Caspofungin is suggested until species identification and sensitivity data are available.

Invasive aspergillosis
Voriconazole and Ambisome are the recommended agents for use based on data from clinical studies.

6.10. 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 (Powles et al 2003). Leukostasis symptoms such as retinal, cerebral or pulmonary haemorrhage require immediate treatment with chemotherapy. 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 (Döhner et al 2010).

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.

Drugs: CYTARABINE- 50mg IT

Regime: Initially three times weekly until blast cells are no longer detected on cytospin and then weekly for 4-6 weeks (Milligan et al 2006).

It is also reasonable to consider a consolidation regime containing HDAC, which will cross the blood brain barrier (FLAG-I, 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. Pregnancy

AML in pregnancy should be managed jointly between the haematologist and the obstetrician with full involvement of the mother. 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 associated with an increased risk of abortion and premature delivery as well as small for dates babies. Consideration should be given for early-induced labour between cycles of chemotherapy.

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 later 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 (Sanz et al 2004) with primary resistance being an anecdotal occurance. Comparative trials for the optimal anthracycline have not be done while there appears to be no advantage to adding cytarabine to induction therapy (Burnett blood 2007).

<u>Course 1</u>

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 (Lococo et al 2004) and PETHEMA (Sanz et al 2004) 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 (Evans et al 1999) and should therefore be excluded in all relapsed patients.

Genetic variants of AML eg 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

- ***Monitor MRD after each cycle of treatment***
- ***MRD monitoring after completion of chemotherapy is not routinely recommended in low or intermediate risk APL (not financially viable) but should be considered 3-monthly for 2 years after completion of chemotherapy***

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 now 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 iv 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 eg 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 (Sanz et al 2004).

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 (Tallman leuk res 2005). 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.

References

Appelbaum FR, Gundacker H, Head DR, et al. Age and acute myeloid leukemia. Blood. 2006;107(9):3481-3485.

Bennett JM, Catowski D, Daniel M-T, Flandrin G, Galton DAG & Sultan C. Proposed revised criteria for the classification of acute myeloid leukaemia. Annals of Internal Medicine. 1985;103:626-629.

Bennett JM, Catowski D, Daniel M-T, Flandrin G, Galton DAG & Sultan C. Proposals for the recognition of minimally differentiated acute myeloid leukaemia (AML M0) British Journal of Haematology. 1985;78:325-329.

Bow EJ. Considerations in the approach to invasive fungal infection in patients with haematological malignancies. British Journal of Haematology. 2008;140:133-152.

Bloomfield CD, Lawrence D, Byrd JC, et al. Frequency of prolonged remission duration after high-dose cytarabine intensification in acute myeloid leukemia varies by cytogenetic subtype. Cancer Research. 1998;58(18):4173-4179.

Burnett AK, Milligan D, Prentice AG, et al. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. Cancer. 2007;109(6):1114-1124.

Burnett AK, Hills RK, Milligan D, et al. Identifi cation of patients with acute myeloblastic leukemia who benefi t from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial. Journal of Clinical Oncology 2011;29:369-377.

Burnett AK, Russell NH, Hills RK, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy improves survival in older patients with acute myeloid leukemia. Journal of Clinical Oncology 2012;30:3924-3931.

Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled, phase 3 trial.Burnett AK, Russell NH, Hills RK, Bowen D, Kell J, Knapper S, Morgan YG, Lok J, Grech A, Jones G, Khwaja A, Friis L, McMullin MF, Hunter A, Clark RE, Grimwade D; UK National Cancer Research Institute Acute Myeloid Leukaemia Working Group. Lancet Oncology. 2015;16(13):1295-1305.

Cairo MS & Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. British Journal of Haematology. 2004;127:3-11.

Cornelissen JJ, van Putten WLJ, Verdonck LF, et al. Results of a HOVON/SAKK donor versus no-donor analysis of myeloablative HLA-identical sibling stem cell transplantation in first remission acute myeloid leukemia in young and middle-aged adults: benefits for whom? Blood. 2007;109(9):3658-3666.

Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs fluconazole or itraconazole prophylaxis in patients with neutropenia. New England Journal of Medicine. 2007;356:348-359.

DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. New England Journal of Medicine. 2020;383(7):617-29.

Döhner K, Schlenk RF, Habdank M, et al. Mutant nucleophosmin (NPM1) predicts favorable prognosis in younger adults with acute myeloid leukemia and normal cytogenetics: interaction with other gene mutations. Blood. 2005;106(12):3740-3746.

Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international panel. Blood. 2017; 129(4):424-447.

Döhner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukaemia in adults: recommendations from an international expert panel, on behalf of the European LeukaemiaNet. Blood. 2010;115:453-474.

Dombret H, Chastang C, Fenaux P, et al. A controlled study of recombinant human granulocyte colony stimulating factor in elderly patients after treatment for acute myeloid leukaemia. New England Journal of Medicine. 1995;332: 1678-1683.

Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH, Kumar R,Cavenagh J, Schuh AC, Candoni A, Récher C, Sandhu I, Bernal Del Castillo T,Al-Ali HK, Martinelli G, Falantes J, Noppeney R, Stone RM, Minden MD, McIntyre H,Songer S, Lucy LM, Beach CL, Döhner H. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with>30% blasts. Blood. 2015;126(3):291-299.

Evans GD, Grimwade DJ. Extramedullary disease in acute promyelocytic leukemia.Leuk Lymphoma. 1999;33(3-4):219-229.

Fernandez HF, Sun Z, Yao X, Litzow MR, Luger SM, Paietta EM, Racevskis J,Dewald GW, Ketterling RP, Bennett JM, Rowe JM, Lazarus HM, Tallman MS.Anthracycline dose intensification in acute myeloid leukemia. N Engl J Med. 2009;361(13):1249-1259.

Fenaux P, Chastang C, Chevret S, Sanz M, Dombret H, Archimbaud E, Fey M, Rayon C, Huguet F, Sotto JJ, Gardin C, Makhoul PC, Travade P, Solary E, Fegueux N, Bordessoule D, Miguel JS, Link H, Desablens B, Stamatoullas A, Deconinck E, Maloisel F, Castaigne S, Preudhomme C, Degos L. A randomized comparison of alltransretinoic acid (ATRA) followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia.
The European APL Group. Blood. 1999;94(4):1192-1200.

Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk

myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol. 2009;10(3):223-232.

Fröhling S, Schlenk RF, Breitruck J, et al. Prognostic significance of activating FLT3 mutations in younger adults (16 to 60 years) with acute myeloid leukemia and normal cytogenetics: a study of the AML Study Group Ulm. Blood. 2002;100(13):4372-4380.

Fröhling S, Schlenk RF, Stolze I, et al. CEBPA mutations in younger adults with acute myeloid leukemia and normal cytogenetics: prognostic relevance and analysis of cooperating mutations. Journal of Clinical Oncology. 2004; 22(4):624-633.

Gafter-Gvili A, Fraser V, Paul M, et al. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. Annals of Internal Medicine. 2005; 142:979-995.

Gale RE, Green C, Allen C, et al. The impact of FLT3 internal tandem duplication mutant level, number, size and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukemia. Blood. 2008;111(5):2776-2784.

Godwin JE, Kopecky KJ, Head DR, et al. A double-blind placebo-controlled trial of granulocyte colony-stimulating factor in elderly patients with previously untreated acute myeloid leukaemia: a Southwest Oncology Group Study (9031). Blood. 1998;91:3607-3615.

Goldstone AH, Burnett AK, Wheatley K, Smith AG, Hutchinson RM, Clark RE. Attempts to improve treatment outcomes in acute myeloid leukemia (AML) in older patients: the results of the United Kingdom Medical Research Council AML11 trial. Blood. 2001;98(5):1302-1311.

Grimwade D. The clinical significance of cytogenetic abnormalities in acute myeloid leukaemia. Best Practice Research of Clinical Haematology. 2001;14(3):497-529.

Grimwade D, Walker H, Oliver F, Wheatley K, Harrison C, Harrison G, Rees J, Hann I, Stevens R, Burnett A, Goldstone A. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. Blood. 1998;92:2322-2333.

Grimwade D Screening for core binding factor gene rearrangements in acute myeloid leukaemia. Leukaemia. 2002;16(5):964-969.

Grimwade D, Hills RK, Moorman AV, Walker H, Chatters S, Goldstone AH, Wheatley K, Harrison CJ, Burnett AK; National Cancer Research Institute Adult Leukaemia Working Group. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. Blood. 2010; 116(3):354-65.

Harousseau JL, et al. Journal of Clinical Oncology. 2000;18:780-787.

Heckman KD, WeinerGJ, Davis CS, et al. Randomised study of prophylactic platelet transfusion threshold during induction therapy for adult leukaemia: 10,000/µL versus 20,000/µL. Journal of Clinical Oncology. 1997;15:1143-1149.

Heil G, Hoelzer D, Sanz MA, et al. A randomised, double blind, placebo controlled, phase III study of filgrastim in remission induction and consolidation therapy for adults with de nove acute myeloid leukaemia. Blood. 1997;90:4710-4718.

Herbrecht R, Flückiger U, Gachot B, et al. Treatment of invasice candida and invasive aspergillus infections in adult haematological patients. European Journal of Cancer. 2007;5:49-59.

Jaffe ES, Harris NL, Stein H & Vardiman J. Tumours of Haemopoietic and Lymphoid Tissues. World Health Organisation Classification of Tumours. IARC Press, Lyon 2001.

Juliusson G, Antunovic P, Derolf Å, et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. Blood. 2009;113(18):4179-4187.

Kottaridis PD, Gale RE, Frew ME, et al. The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. Blood. 2001;98(6):1752-1759.

Krakoff IH & Meyer RL. Prevention of hyperuricaemia in leukaemia and lymphoma: use of allopurinol, a xanthine oxidase inhibitor. Journal of the American Medical Association. 1965;193:89-94.

Lancet JE, Uy GL, Cortes JE, Newell LF, Lin TL, Ritchie EK, Stuart RK, Strickland SA, Hogge D, Solomon SR, Stone RM, Bixby DL, Kolitz JE, Schiller GJ, Wieduwilt MJ, Ryan DH, Hoering A, Banerjee K, Chiarella M, Louie AC, Medeiros BC.CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia Journal of Clinical Oncology. 2018 Sep 10;36(26):2684-2692.

Larson RA, Boogaerts M, Estey E, et al. Antibody targeted chemotherapy of older patients with acute myeloid leukaemia in first relapse using Myelotarg (gemtuzumab ozogamicin). Leukaemia. 2002;16:1027-1636.

Leibovici L, Paul M, Cullen M, et al. Antibiotic prophylaxis in neutropenic patients. New evidence, practical decisions. Cancer. 2006;107:1743-1751.

Lo Coco F, Avvisati G, Vignetti M, Fioritoni G, Liso V, Ferrara F. Frontline treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation: results of the AIDA-2000 trial of the Italian GIMEMA group. Blood 2004;104:392a.

Milligan DW, Grimwade D, Cullis JO, et al. Guidelines on the management of acute myeloid leukaemia in adults. British Journal of Hamatology. 2006; 135:450-474.

Mrozek K. Cytogenetic, molecular genetic, and clinical charecteristics of acute myeloid leukaemia with a complex karyotype. Seminals of Oncology. 2008; 358(4):365-377.

Mrozek K, Prior TW, Edwards C, et al. Comparison of cytogenetic and molecular genetic detection of of t(8;21) and inv(16) in a prospective series of adulats with de novo acute myeloid leukemia:a Cancer and Leukemia Group B Study. Journal of Clinical Oncology. 2001;19(9);2482-2492.

National Institute for Clinial Excellence (NICE Guidelines): https://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers/leukaemia#path=view%3A/pathways/blood-and-bone-marrow-cancers/myeloid-leukaemia.xml&content=view-node%3Anodes-acute-myeloid-leukaemia Accessed 21/9/21

Pagano L, Caira M, Candoni A, et al. The epidemiology of fungal infection in patients with haematological malignancies: the SEIFEM-2004 study. Haematologica. 2006;91:1068-1075.

Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory *FLT3*-mutated AML. N Engl J Med 2019;381:1728-1740

Powles R, Sirohi B & Kulkarni S (2003). Investigation and management of hyperleukostasis in adults. The effective prevention and management of common complications of induction chemotherapy in haematological malignancy. Eds Pinketon R, Rohatiner A and Miles A. Chapter 3, 33-50 Aesculapius Medical Press Published 2003.

Pui CH, Mahmoud HH, Wiley JM, et al. Recombinant urate oxidase for the prophylaxis or treatment of hyperuricaemia in patients with leukaemia or lymphoma. Journal of Clinical Oncology. 2001;19:697-704.

Rebulla P, Finazzi G, Maramgoni F, et al. The threshold for prophylactic platelet transfusions in adults with acute myeloid leukaemia. New England Journal of Medicine. 1997;337:1870-1875.

Robenshtok E, Gafter-Gvili A, Goldberg E, et al. Antifungal prophylaxis in cancer patients after chemotherapy or haematopoietic stem cell transplantation: systemic review and meta-anlaysis. Journal of Clinical Oncology. 2007;25:5471-5489.

Rowe JM, Anderson JW, Mazza, et al. A randomised placebo–controlled phase III study of granulocyte-macrophage colony stimulating factor in adults (>55-70 years of age) with acute myelogenous leukaemia: a study of the Eastern European Oncology Group (E1490). Blood. 1995;86:457-462.

Sanz MA, Martín G, González M, León A, Rayón C, Rivas C, Colomer D, Amutio E, Capote FJ, Milone GA, De La Serna J, Román J, Barragán E, Bergua J, Escoda L,

Parody R, Negri S, Calasanz MJ, Bolufer P; Programa de Estudio y Traitmiento de las Hemopatías Malignas. Risk-adapted treatment of acute promyelocytic leukemia with all-trans-retinoic acid and anthracycline monochemotherapy: a multicenter study by the PETHEMA group. Blood. 2004;103(4):1237-1243.

Schlenk RF, Benner A, Hartmann F, et al. Risk adapted post-remission therapy in acute myeloid leukemia: results of the German Multicenter AML HD93 treatment trial. Leukemia. 2003;17(8):1521-1528.

Schlenk RF, Döhner K, Krauter J, et al. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. New England Journal of Medicine 2008;358(18):1909-1918.

Schmid C, Schleuning M, Schwerdtfeger R, et al. Long-term survival in refractory acute myeloid leukemia after sequential treatment with chemotherapy and reduced-intensity conditioning for allogeneic stem cell transplantation. Blood. 2006;108(3):1092-1099.

Sievers EL, Larson RA, Stadtmauer EA, et al. Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse. Journal of Clinical Oncology. 2001;19(13):3244-3254.

Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD, Thiede C, Prior TW, Döhner K, Marcucci G, Lo-Coco F, Klisovic RB, Wei A1, Sierra J, Sanz MA, Brandwein JM, de Witte T, Niederwieser D, Appelbaum FR, Medeiros BC, Tallman MS, Krauter J, Schlenk RF, Ganser A, Serve H, Ehninger G, Amadori S, Larson RA, Döhner H. N Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. New England Journal of Medicine. 2017;377(5):454-464.

Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haemopoietic and Lymphoid Tissues. IARC Press, Lyon 2008.

Tallman MS, Andersen JW, Schiffer CA, Appelbaum FR, Feusner JH, Ogden A, Shepherd L, Willman C, Bloomfield CD, Rowe JM, Wiernik PH. All-trans-retinoic acid in acute promyelocytic leukemia. New England Journal of Medicine. 1997;337(15):1021-1028.

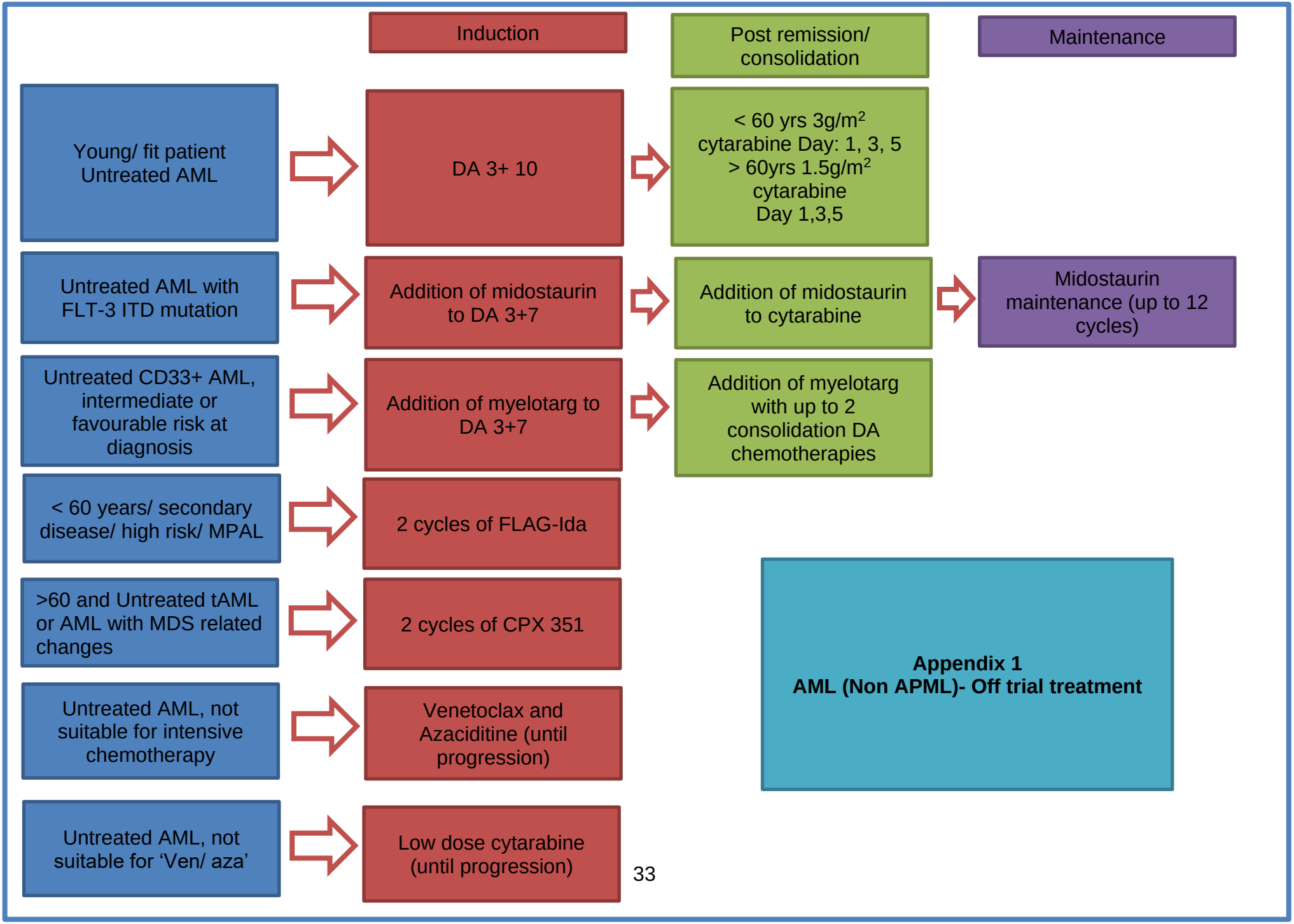
Thiede C, Koch S, Creutzig E, et al. Prevalence and prognostic impact of NPM1 mutations in 1485 adult patients with acute myeloid leukemia (AML). Blood. 2006;107(10):4011-4020.

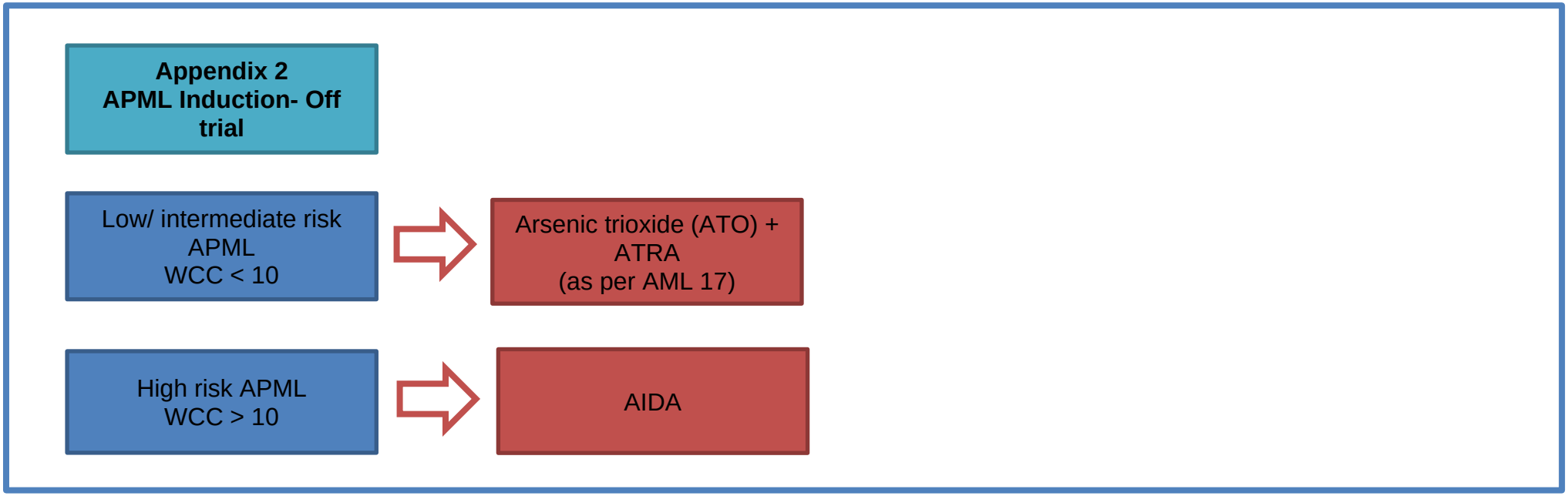
Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, Harris NL, Le Beau MM, Hellström-Lindberg E, Tefferi A, Bloomfield CD. The 2008 revision of the WHO classification of Myeloid Neoplasms and Acute Leukaemia; rationale and important changes. Blood. 2009;114(5):937-951.

Wheatley K, Goldstone AH, Littlewood T, et al. Randomised placebo-controlled trial of granulocyte colony stimulating factor (G-CSF) as supportive care after induction chemotherapy in adult patients with acute myeloid leukaemia: a study of the United

Kingdom Medical Research Council Adult Leukaemia Working Party. British Journal of Haematology. 2009;146:54-63.

Zumberg MS, del Roasario MLU, Nejane CF, et al. A prospective randomised trial of prophylactic platelet transfusion and bleeding incidence in haematopoietic stem cell transplant recipients: 10,000/µL versus 20,000/µL trigger. Biology of Blood and Bone Marrow Transplantation. 2002;8:569-576.


Induction
Post remission/ consolidation
Maintenance
Young/ fit patient Untreated AML
DA 3+ 10
< 60 yrs 3g/m2 cytarabine Day: 1, 3, 5
> 60yrs 1.5g/m2 cytarabine Day 1,3,5
Untreated AML with FLT-3 ITD mutation
Addition of midostaurin to DA 3+7
Addition of midostaurin to cytarabine
Midostaurin maintenance (up to 12 cycles)
Untreated CD33+ AML, intermediate or favourable risk at diagnosis
Addition of myelotarg to DA 3+7
Addition of myelotarg with up to 2 consolidation DA chemotherapies
< 60 years/ secondary disease/ high risk/ MPAL
2 cycles of FLAG-Ida
>60 and Untreated tAML or AML with MDS related changes
2 cycles of CPX 351
Untreated AML, not suitable for intensive chemotherapy
Venetoclax and Azaciditine (until progression)
Untreated AML, not suitable for 'Ven/ aza'
Low dose cytarabine (until progression)
Appendix 1
AML (Non APML)- Off trial treatment


Appendix 2
APML Induction- Off trial
Low/ intermediate risk APML
WCC < 10
Arsenic trioxide (ATO) + ATRA
(as per AML 17)
High risk APML
WCC > 10
AIDA