NATIONAL CLINICAL GUIDELINES

The management of scute myeloid leukaemia

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المبادئ الإرشادية السريرية لدولة قطر
NATIONAL CLINICAL GUIDELINES FOR QATAR

وزارة الصحـــــة العامـــــة
Ministry of Public Health
State of Qatar • دولـــة قطـــر

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Version history

Version	Status	Date	Editor	Description
1.0	Final	19th March 2019	Guidelines Team	Final version for publication.

1 Introduction

1.1 Purpose of the guideline

This guideline is intended to articulate the agreed standards of care for the treatment of acute myeloid leukaemia (AML) within the State of Qatar. The guideline is intended to support clinical staff to provide appropriate care and treatment for patients with AML.

1.2 Scope of the guideline

Aspects of care covered in this guideline:

- Clinical assessment, diagnosis and management of AML in patients aged over 14 years, in primary, secondary and tertiary care.
- Diagnosis and management of patients with acute promyelocytic leukaemia (APL).
- Management of AML and APL in pregnancy.

1.3 End users of the guideline

This guideline is relevant to all healthcare professional (physicians, nurses, allied health professionals, pharmacists and pathologists) who come into contact with patients with AML. It is also expected that this guideline will be of value to those involved in clinical governance in primary, secondary care and private healthcare to help ensure that arrangements are in place to deliver appropriate care to this group of patients.

1.4 Editorial approach

This guideline document has been developed and issued by the Ministry of Public Health of Qatar (MOPH), through a process which aligns with international best practice in guideline development and localisation. The guideline will be reviewed on an annual basis and updated to incorporate comments and feedback from stakeholders across Qatar.

The editorial methodology, used to develop this guideline, has involved the following critical steps:

- Provision of recent reputable guideline documents and published literature by the Qatar Haematology Tumour Board of the MOPH.
- Development of a draft summary guideline.
- Review of the summary guideline with a Guideline Development Group, comprised of subject matter experts nominated by the Haematology Tumour Board and currently practising within provider organisations in Qatar.
- Independent review of the guideline by the Haematology Tumour Board and the National Cancer Committee.

Explicit review of the guideline by patient groups was not undertaken.

Whilst the MOPH has sponsored the development of the guideline, the MOPH has not influenced the specific clinical practice recommendations made within it.

1.5 Evidence grading and recommendations

Recommendations made within this guideline are supported by evidence from the medical literature and where possible the most authoritative sources have been used in the development of this

guideline. In order to provide insight into the evidence basis for each recommendation, the following evidence hierarchy has been used to grade the level of authoritativeness of the evidence used, where recommendations have been made within this guideline.

Where the recommendations of international guidelines have been adopted, the evidence grading is assigned to the underlying evidence used by the international guideline. Where more than one source has been cited, the evidence grading relates to the highest level of evidence cited:

- **Level 1 (L1):**
  - Meta-analyses.
  - Randomised controlled trials with meta-analysis.
  - Randomised controlled trials.
  - Systematic reviews.

- **Level 2 (L2):**
  - Observational studies, examples include:
    - Cohort studies with statistical adjustment for potential confounders.
    - Cohort studies without adjustment.
    - Case series with historical or literature controls.
    - Uncontrolled case series.
  - Statements in published articles or textbooks.

- **Level 3 (L3):**
  - Expert opinion.
  - Unpublished data, examples include:
    - Large database analyses.
    - Written protocols or outcomes reports from large practices.

In order to give additional insight into the reasoning underlying certain recommendations and the strength of recommendation, the following recommendation grading has been used, where recommendations are made:

- **Recommendation Grade A1 (RGA1):** Evidence demonstrates at least moderate certainty of at least moderate net benefit.
- **Recommendation Grade A2 (RGA2):** Evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care.
- **Recommendation Grade B (RGB):** Evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended.
- **Recommendation Grade C1 (RGC1):** Evidence demonstrates a lack of net benefit; additional research is recommended.
- **Recommendation Grade C2 (RGC2):** Evidence demonstrates potential harm that outweighs benefit; additional research is recommended.
- **Recommendation of the GDG (R-GDG):** Recommended best practice on the basis of the clinical experience of the Guideline Development Group members.

1.6 Guideline Development Group members

The following table lists members of the Guideline Development Group (GDG) nominated by their respective organisations and the Clinical Governance Group. The GDG members have reviewed and provided feedback on the draft guideline relating to the topic. Each member has completed a declaration of conflicts of interest, which has been reviewed and retained by the MOPH.

Guideline Development Group members		
Name	**Title**	**Organisation**
Dr Ibrahim Ahmad A H Al-Hijji	Senior Consultant Haematologist & Head of Clinical Haematology, HSCT Unit Director of Haematology Fellowship Program Medical Oncology Dept.	NCCCR, Hamad Medical Corp
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Dr Mohd. Abdel Daem Mohd. Yassin	Consultant Haematologist, Assistant Professor	NCCCR, Hamad Medical Corp

1.7 Responsibilities of healthcare professionals

This guideline has been issued by the MOPH to define how care should be provided in Qatar. It is based upon a comprehensive assessment of the evidence as well as its applicability to the national context of Qatar. Healthcare professionals are expected to take this guidance into account when exercising their clinical judgement in the care of patients presenting to them.

The guidance does not override individual professional responsibility to take decisions which are appropriate to the circumstances of the patient concerned. Such decisions should be made in consultation with the patient, their guardians, or carers and should consider the individual risks and benefits of any intervention that is contemplated in the patient's care.

1.8 Abbreviations used in this guideline

The abbreviations used in this guideline are as follows:

AML	Acute myeloid leukaemia
APL	Acute promyelocytic leukaemia
ATO	Arsenic trioxide
ATRA	All-trans-retinoic acid
CBC	Complete blood count
CBF	Core binding factor
CNS	Central nervous system
CR	Complete remission
CR2	Second complete remission
CRi	Complete remission with incomplete recovery
DIC	Disseminated intravascular coagulation
DS	Differentiation syndrome
ED	Emergency Department
FISH	Fluorescence in situ hybridisation
G-CSF	Granulocyte-colony stimulating factor
GO	Gemtuzumab ozogamicin
HCST	Haematopoietic stem cell transplantation
HiDAC	High-dose cytarabine
MDS	Myelodysplastic syndrome
MDT	Multi-disciplinary team
MOPH	Ministry of Public Health of Qatar
MPAL	Mixed-phenotype acute leukaemia
MPO	Myeloperoxidase
MPN	Myeloproliferative neoplasm
MRD	Minimal residual disease
MS	Myeloid sarcoma
NCCCR	National Centre for Cancer Care and Research
NGS	Next generation sequencing
NSE	Nonspecific esterase
PCR	Polymerase chain reaction
PHC	Primary healthcare centres
PICC	Peripherally inserted central catheter
PR	Partial remission
QNCR	Qatar National Cancer Registry
RIC	Reduced-intensity conditioning
RT-PCR	Reverse transcriptase-polymerase chain reaction
SBB	Sudan Black B
TAM	Transient abnormal myelopoiesis
t-AML	Therapy-related AML
USC	Urgent suspected cancer
WBC	White blood cell count
WHO	World Health Organisation

1.9 Background

Acute myeloid leukaemia (AML) - also known as *acute myelogenous leukaemia* consists of a group of haematopoietic neoplasms involving clonal proliferation of myeloid precursor cells with a reduced capacity for differentiation into more mature cellular elements [1,2]. AML typically accounts for 80-90% of acute leukaemia in adults [3,4].

Systemic symptoms of AML include fever, fatigue, and weight loss [1], which may result from haematopoietic failure and result in anaemia, thrombocytopenia and/or neutropenia [5]. In adults, bone pain is less common and hepatosplenomegaly and lymphadenopathy are rare [1]. Complete blood count (CBC) may show leukocytosis or cytopenia and a peripheral blood smear may demonstrate blast cells [1]. Treatment options typically include chemotherapy, radiation, monoclonal antibodies, or haematopoietic stem cell transplantation (HSCT) [1].

Acute promyelocytic leukaemia (APL) is a biologically and clinically distinct subtype of AML accounting for 5-10% of cases [6]. APL is distinguished from other subtypes of acute myeloid leukaemia by a characteristic morphology (FAB-M3 and M3-variant) and a classic pathognomonic cytogenetic abnormality involving chromosomal t(15;17)(q24;q21). At the molecular level this cytogenetic abnormality corresponds to the formation of the fusion gene *PML-RARA* [7,6]. Consequently, APL is treated differently to other subtypes of AML.

1.10 Epidemiology

The 2014 data from the Qatar National Cancer Registry (QNCR) suggests that AML accounts for 58% of all adult acute leukaemia cases in Qatar. The median age of presentation with AML was shown to be 42 years with a male to female ratio of 3.4:1, however most of the patients were non-Qatari (90.9%).

Information from the National Centre for Cancer Care and Research (NCCCR) states that AML in Qatar has a lower median age, with a higher incidence of the AML-M3 (acute promyelocytic) subtype [3].

APL represents a high proportion of AML cases in Qatar at 18.2% of cases reported at QNCR. with a predominance of APL variants with unfavorable presenting features and high morphological heterogeneity [8]. Disseminated intravascular coagulation (DIC) is a presenting feature of approximately 91% of these APL cases, severe thrombocytopenia in 73%, leukocytosis in 55%, and severe anaemia in 45% [8].

1.11 5-year survival

Data on cancer survival rates in Qatar are presently being collected through the QNCR and in due course it is expected that 5-year survival rates will be published and benchmarked against other international health economies.

In the USA, the 5-year relative survival rate is 55% in patients less than 50 years old, and 14% in patients aged 50 years and older [1].

2 General principles of care

The general principles of patient care in relation to AML are [**R-GDG**]:

- All patients should be managed by a specialist haematology multi-disciplinary team (MDT).
- All patients should be informed of the different treatment options (including no treatment) and should be involved in the decision making process to the extent that they wish.
  Written consent should be obtained before starting treatment.
- All patients should be offered access to a clinical nurse specialist to support them through their cancer experience.
- Patients should be offered prompt access to specialist psychological and social services and, if appropriate, psychiatric services.
- Patients should be made aware of, and have the choice to enter into appropriate clinical trials where possible.
- Following the MDT discussion, the decision is validated and 'signed-off' by members present. The MDT outcome proforma is then uploaded into the patient's records. This ensures that those involved in the patient's care can access the decisions taken. This includes the patient's primary health care physician. The recommended decision for any patients seen originally in the private sector, is fed back to the referring clinician.

3 The Leukaemia Multi-Disciplinary Team

3.1 The purpose of the Leukaemia Multi-Disciplinary Team

All patients with leukaemia should be managed within the context of a leukaemia MDT. An MDT presently meets regularly at the NCCCR to discuss cases of AML.

The Leukaemia MDT is a team of healthcare professionals from different disciplines that meet together regularly to discuss an agreed cohort of patients. The MDT provides an expert consensus and systematic specialist review of the diagnostic and treatment decisions about patients with AML. The required (core) membership of the Leukaemia MDT is described in the *National Peer Review Measures for the Leukaemia MDT* published by the Ministry of Public Health (MOPH).

3.2 Criteria for discussion at the Leukaemia MDT

Patients who meet the following criteria should be referred for discussion to the Leukaemia MDT:

- Patients with a new diagnosis of AML.
- Review of cases after induction therapy and at the end of treatment.
- Patients who have relapsed after treatment.
- Patients that have initiated or completed their management abroad and require further management or follow-up recommendations from the MDT.

3.3 Individual patient management plan

During the MDT meeting, a record is made of the case discussion. The MDT individualised management plan includes the following information:

- The patient identity (patient name and medical number).
- Summary of clinical presentation.
- Summary of investigations completed and summary of results.
- The MDT agreed management planning decision including further investigations or referrals, if required.
- Summary of plans for follow-up.

3.4 Arrangements for decision making outside the regular MDT

Management decisions should be made by the Leukaemia MDT wherever possible. However, in the event that an urgent decision is required [**R-GDG**]:

- Discussion should occur between at least two clinical haematologists or one clinical haematologist and one haematopathologist from the MDT, or their delegated representatives.
- The patient should be listed for discussion at the next available MDT meeting.
- Such discussions and resulting recommendations should be adequately documented in the patient's file.

3.5 The relationship of the Leukaemia MDT with the Haematology Tumour Board

The lead clinician of the Leukaemia MDT must be a member of the Qatar Haematology Tumour Board at the MOPH. The lead clinician must attend the meetings of these forums or must nominate another core member of the MDT to attend. The attendance at the Tumour Board will be recorded and demonstrated in the team's annual report [**R-GDG**].

3.6 Patient information and support

Trained staff should discuss the following points with the patient in the event that a diagnosis of AML is made [9]:

- Information about the diagnosis.
- The individual patient's prognosis:
    - Based on bone marrow cytogenetics, and patient's comorbidities.
- Treatment options, including any current, available clinical trials or research studies.

All patients should have access to a key worker (usually the clinical nurse specialist) [9]:

- The key worker should be present at the time of any significant discussion, e.g.:
    - At the time of diagnosis.
    - When treatment changes and outcomes are discussed.
- A senior nurse may take the place of the clinical nurse specialist where they are not able to attend [**R-GDG**]:
    - All conversations should be documented.
    - When neither a clinical nurse specialist or a senior nurse can attend, the patient should be given the contact number of the clinical nurse specialist.

All patients should be offered a needs assessment at key points in their treatment [9]:

- Within 31 days of diagnosis.
- At the end of each treatment regimen.
- Whenever the patient requests one.
- After a needs assessment has taken place, the patient should be given a written care plan:
    - This will have been developed with the patient and communicated to all appropriate healthcare professionals.

All patients should be given access to supportive care information and rehabilitation at all times during their treatment [9].

4 Referral guidelines and patient pathway

Patients are referred to the haematology cancer specialist team through ay of the following routes:

- Primary healthcare centres (PHC) referral using the *Urgent Suspected Cancer* (USC) form or through routine referral.
- Internal HMC referrals from other consultants or the Emergency Department (ED).
- Referral from other cancer MDTs.
- Referrals from private providers.
- Referrals from clinicians whose patients are returning to Qatar, following treatment overseas.
- Patients referred to the Haematology Cancer Service should be seen by a specialist clinician who has been designated as privileged for this specialty.

4.1 Referral timelines

Refer the following patients to the ED for urgent review by a haematologist [**R-GDG**]:

- Patients with a clinical presentation suspicious of acute leukaemia.
- Patients with a blood count or blood smear showing blast cells or cytopenia.

The development of an Acute Haematology Oncology Outpatient Service is presently in development and this guideline will be updated once the service is available.

5 Clinical presentation

5.1 History and examination

In all cases:

- A full history and examination should be performed [9].
- All co-morbidities should be assessed and documented in order to inform treatment selection and management planning [9].
- Assessment of demographics and medical history should include [10]:
    - Race or ethnicity.
    - Family history.
    - Prior exposure to toxic agents.
    - Prior malignancy.
    - Therapy for prior malignancy.
    - History of smoking.

5.2 Signs and symptoms

Signs and symptoms of AML:

- Symptoms related to complications of cytopenia [1,9]:
    - Anaemia:
        - Shortness of breath.
        - Chest pain.
        - Weakness.
        - Easy fatigability.
    - Neutropenia:
        - Fever.
        - Infections
    - Thrombocytopenia and/or DIC:
        - Haemorrhagic findings, such as:
            - Gingival bleeding.
            - Excessive bruising or ecchymoses.
            - Epistaxis.
            - Menorrhagia.
            - Bleeding secondary to DIC is a common presentation of APL.
- Bone pain (less common in adults).
- Lymphadenopathy and hepatosplenomegaly (although rare in adults with AML).
- Chloroma (e.g. skin and other organ involvement by leukaemic infiltrate).
- Leucostasis manifestations include:
    - Respiratory distress.
    - Neurological symptoms e.g.
        - Confusion.
        - Convulsions.
        - Coma and
        - Focal neurological deficit.

6 Investigation and diagnosis

The diagnosis of AML is typically made using a peripheral blood smear, bone marrow aspirate and/or biopsy and requires multi-disciplinary laboratory investigations.

The World Health Organisation (WHO) sub-classify AML based on morphology, immunophenotyping, cytogenetics and molecular studies. Therefore, if AML is suspected, request the following investigations [1,10][**L1, RGA1**]:

- CBC with differential count.
- Peripheral blood film.
- Bone marrow aspirate and/or biopsy (may include immunohistochemistry).
- Immunophenotyping with flow cytometry (from peripheral blood or bone marrow) or Immunohistochemistry:
    - To establish a leukaemia-associated phenotype.
- Genetic testing:
    - Karyotyping.
    - Fluorescence in situ hybridisation (FISH).
    - Targeted molecular analysis.

6.1 Morphology

Bone marrow and/or blood morphological examination should be performed. The defining criterion for AML is 20% or more myeloblasts in peripheral blood or bone marrow; the promonocytes in AML with monocytic differentiation are considered blast equivalents [11].

The classification of acute erythroid leukaemia is unique and is based on percentage of abnormal erythroblasts for pure erythroid leuakemia and percentage of myeloblasts among non-erythroid cells for erythroid/myeloid type.[11].

The categories of AML with t(15;17), t(8;21), inv(16) or t(16;16) are considered as acute leukaemias without regard to blast count [11].

6.2 Cytochemistry

If immunophenotyping via flow cytometry and immunohistochemistry are unavailable, cytochemistry including myeloperoxidase (MPO) or Sudan Black B (SBB) and nonspecific esterase (NSE) stains, may be used as an alternative (rarely used in practice) [9][**L1, RGA2**].

6.3 Immunophenotyping

A multiparameter flow cytometry test in acute leukaemia is used for [10][**L1, RGA1**]:

- Lineage assignment (myeloid, lymphoid, mixed).
- Diagnosis of mixed-phenotype acute leukaemia (MPAL).
- Detection of aberrant immunophenotypes (to measure the minimal residual disease (MRD)).
- Subclassification of some AML.

Immunohistochemistry panels on the trephine biopsy or clot section, can be done to complement aspirate immunophenotyping and morphology [9][**L1, RGA1**].

6.4 Genetic testing

6.4.1 Karyotyping

Conventional cytogenetic analysis must be used when diagnosing acute leukaemia [10][**L1, RGA1**]:

- Recurrent balanced translocations and inversions, and their variants, are recognised in the WHO category: *AML with recurrent genetic abnormalities*.
- A minimum of 20 metaphase cells analysed from bone marrow is needed to establish the diagnosis of a normal karyotype, and recommended to define an abnormal karyotype.
- Analysis of bone marrow is recommended however abnormal karyotypes can be diagnosed from blood specimens.

6.4.2 Molecular cytogenetics: FISH

Gene rearrangements can be detected using FISH [10][**L1, RGA1**]:

- Usually done using a bone marrow aspirate sample [9]; can be done on peripheral blood if bone marrow is not available [9].
- The FISH panel normally includes the following recurring genetic abnormalities associated with AML [9,10]:
    - *RUNX1-RUNX1T1* for t(8;21).
    - *CBFB-MYH11* for inv16 and t(16;16).
    - *PML-RARA* for t(15;17).
    - *KMT2A* (*MLL* fusion partners in 11q23 translocations).
    - *EVI1* gene fusions.
- Extended testing includes [9]:
    - FISH for chromosome 5 or 7 abnormalities or other gene fusions according to clinical findings, morphology or immunophenotyping.
- Methanol/acetic acid-fixed cell pellets should be stored for further analysis [10].

6.4.3 Molecular genetics

Marrow and blood specimens can also undergo molecular diagnostics [10][**L1, RGA1**] for:

- Diagnostic confirmation of cytogenetics.
- Baseline assessment of fusion transcripts for MRD monitoring.
- Look for additional markers with potential prognostic relevance in AML. FL3-itd & NPM1 mutation analysis are recommended as part of the routine diagnostic workup.

DNA and RNA should be extracted and viable cells should be stored, where possible. If cell numbers are limited, RNA extraction should take priority [10][**L2, RGA1**].

Molecular genetic testing can be done by polymerase chain reaction (PCR) or targeted next generation sequencing (NGS), if available [10][**L1, RGA2**]:

- Are options to detect cytogenetically cryptic gene fusions and mutations; or if there is poor quality chromosome morphology.
- Genomic analysis in Qatar is currently under development and further updates will be provided in the future [**R-GDG**].

7 Classification, risk stratification and prognostic factors

7.1 Classification

The 2008 WHO classification of myeloid neoplasms and acute leukaemia, classifies AML and related neoplasms, as show in *Table 7.1(1)* below [11]:

WHO 2008 classification of acute myeloid leukaemia and related neoplasms
AML with recurrent genetic abnormalities: • AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*. • AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11.* • APL with t(15;17)(q22;q12); *PML-RARA.* • AML with t(9;11)(p22;q23); *MLLT3-MLL*. • AML with t(6;9)(p23;q34); *DEK-NUP214*. • AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1.* • AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1.* • *Provisional entity:* AML with mutated *NPM1.* • *Provisional entity:* AML with mutated *CEBPA*.
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms

AML, not otherwise specified:
• AML with minimal differentiation.
• AML without maturation.
• AML with maturation.
• Acute myelomonocytic leukaemia.
• Acute monoblastic/monocytic leukaemia.
• Acute erythroid leukaemia:
  ○ Pure erythroid leukaemia.
  ○ Erythroleukaemia, erythroid/myeloid.
• Acute megakaryoblastic leukaemia.
• Acute basophilic leukaemia.
• Acute panmyelosis with myelofibrosis.

Myeloid sarcoma:
• Myeloid proliferations related to Down syndrome:
  ○ Transient abnormal myelopoiesis.
  ○ Myeloid leukaemia associated with Down syndrome.
• Blastic plasmacytoid dendritic cell neoplasm.

Table 7.1(1): WHO 2008 classification of AML and related neoplasms [11].

A new WHO classification of AML and related neoplasms has been published in 2016 and is outlined in Table 7.1(2) below [12].

WHO 2016 classification of acute myeloid leukaemia and related neoplasms
AML with recurrent genetic abnormalities: • AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1.* • AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*. • APL with *PML-RARA*. • AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*. • AML with t(6;9)(p23;q34.1); *DEK-NUP214.* • AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM.* • AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); *RBM15-MKL1.* • *Provisional entity:* AML with *BCR-ABL1*. • AML with mutated *NPM1*. • AML with biallelic mutations of *CEBPA*. • Provisional entity: AML with mutated *RUNX1*.
AML with myelodysplasia-related changes.
Therapy-related myeloid neoplasms.
AML, not otherwise specified: • AML with minimal differentiation. • AML without maturation. • AML with maturation. • Acute myelomonocytic leukaemia. • Acute monoblastic/monocytic leukaemia. • Pure erythroid leukaemia. • Acute megakaryoblastic leukaemia. • Acute basophilic leukaemia. • Acute panmyelosis with myelofibrosis.
Myeloid sarcoma
Myeloid proliferations related to Down syndrome: • Transient abnormal myelopoiesis (TAM). • Myeloid leukaemia associated with Down syndrome.

Table 7.1(2): WHO 2016 classification of AML and related neoplasms [12].

7.2 Risk stratification in AML

Patients are classified into groups showing differences in disease-free survival and overall survival [10]. The correlation of cytogenetic and molecular genetic data in AML with clinical data is shown in *Table 7.2* below [10]:

Genetic group	Subsets
Favourable	• t(8;21)(q22;q22)*; *RUNX1-RUNX1T1*. • inv(16)(p13.1q22)* or t(16;16)(p13.1;q22); *CBFB-MYH11*. • Mutated *NPM1* without *FLT3*-ITD (normal karyotype). • Mutated *CEBPA* (normal karyotype).
Intermediate-I	• Mutated *NPM1* and *FLT3*-ITD (normal karyotype). • Wild-type *NPM1* and *FLT3*-ITD (normal karyotype). • Wild-type *NPM1* without *FLT3*-ITD (normal karyotype).
Intermediate-II	• t(9;11)(p22;q23); *MLLT3-MLL.* • Cytogenetic abnormalities not classified as favourable or adverse.
Adverse	• inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*. • t(6;9)(p23;q34); *DEK-NUP214*. • t(v;11)(v;q23); *MLL* rearranged. • -5 or del(5q); -7; abnl(17p); complex karyotype.

*Additional molecular analysis (*KIT* or *CEPBA* testing etc.) can be performed on these patients to further risk stratify the subset [**R-GDG**].

Table 7.2: Correlation of cytogenetic and molecular genetic data in AML with clinical category [10].

7.3 Prognostic factors in AML

The following factors influence prognosis in patients with AML:

- Age.
  - Increasing age ≥60 years is an adverse prognostic factor [10].
- Performance status/comorbidities.
- Cytogenetic and molecular genetic findings.
  - Younger adult patients should be categorised as stated in *Section 7.2.*
- History of prior exposure to chemotherapy and/or radiotherapy.
- History of myeloproliferative neoplasm (MPN) or myelodysplastic syndrome (MDS).
- Response to treatment.

Post-treatment monitoring of MRD may be useful when assessing the patient's early response to treatment and prognosis and guides development of a post-treatment strategy, including early assessment of relapse risk [10][**L1, RGA2**].

8 Management of acute myeloid leukaemia

Management includes [**R-GDG**]:

- Supportive measures.
- Specific measures for AML:
    - Chemotherapy.
    - Differentiating agents.
    - HSCT.
- Other possible measures include:
    - Monoclonal antibodies.
    - Targeted therapies.
    - Radiation.
- Palliative care where appropriate.

The type of treatment will depend on:

- Leukaemia subtype.
- Risk stratification.
- Patient's age.
- Comorbid conditions.

8.1 Management of patients aged 14-18 years

Adolescent patients should be treated in accordance with paediatric protocols [**R-GDG**]:

- A paediatric haematologist should be present at the MDT meetings to discuss the patient.
- A clear plan of follow-up should be articulated to the MDT and the patient.

NB: At present refer all patients to adult haematology services at NCCCR and send patients to the ED, until adolescent services are fully established [**R-GDG**].

8.2 Management of adults age 18-60 years

8.2.1 Induction therapy

Induction chemotherapy should be started after the diagnostic work-up has been completed with minimal delay [10][**L1, RGA2**].

The "3+7" approach is the current standard and comprises of [10]:

- 3 days of an anthracycline e.g.:
    - Daunorubicin, 45-60mg/m^2; or
    - Idarubicin, 10-12 mg/m^2; or
    - Mitoxantrone, 10-12 mg/m^2;
- 7 days of cytarabine (100-200mg/m^2 continuous IV infusion).

NB: Two cycles of induction should be used.

8.2.2 Post-remission therapy

High-dose cytarabine (HiDAC) [10][**L1, RGA2**]:

- 2-3 cycles of HiDAC (3 g/m^2 every 12h on days 1, 3 and 5).
- HiDAC is beneficial in patients with core binding factor (CBF)-AML.

Allogeneic HSCT [10]:

- The main indications are:
  - AML with *Adverse* risk stratification.
  - AML with *Intermediate* risk stratification.
  - Refractory AML.
  - Relapsed AML.
- The benefit of the reduced relapse rate must be weighed against the increased risk of treatment-related mortality.

Autologous HSCT [10]:

- Is controversial but may be used as an alternative to post-remission therapy in patients with favourable- and intermediate-risk cytogenetics [10] [**L2, RGA2**].

8.2.3 Primary refractory disease

A lack of response to induction therapy is a major predictor of poor outcome [10][**L1, RGA1**]:

- 1-2 cycles of FLAG-Ida should be used as salvage therapy (as outlined below), to induce remission followed by allogeneic HSCT:
  - Fludarabine 30 mg/m^2 on days 2-6.
  - Cytarabine 2 grams/m^2 on days 2-6.
  - Granulocyte-colony stimulating factor (G-CSF) on days 1-7.
  - Idarubicin 8mg/m^2 daily on days 4-6.
- A suitable matched donor must be found as soon as possible.
- Patients with induction failure who are not eligible for allogeneic HSCT should be considered for clinical trials evaluating novel agents, if available [**R-GDG**].

8.3 Management of adults aged 60-74 years

Patients aged 60-74 years are more likely to suffer treatment-related early death and to exhibit resistance to therapy [10][**L1, RGA2**]:

- Age should not be a reason to withhold intensive therapy:
  - Remission induction chemotherapy provides better quality of life and longer survival than supportive care alone.

8.3.1 Induction therapy

Trial data does not provide sufficient information for clear recommendations [10]. Treatment should be individualised to the patient and may include the following [**R-GDG**]:

- High-intensity therapy:
  - Patients with performance status of 0-1, no comorbidities and favourable cytogenetic results, can be offered high-intensity induction therapy [10]:
  - 3+7 regimen:
    - 3 days of an anthracycline e.g.:
      - Daunorubicin, 45-60 mg/m^2; or
      - Idarubicin, 10-12 mg/m^2; or
      - Mitoxantrone, 10-12 mg/m^2.

        - 7 days of cytarabine (100-200 mg/m^2, continuous IV).
- Intermediate intensity therapy:
    - Hypomethylating agents e.g. azacitidine.
- Low-intensity therapy:
    - Low-dose cytarabine.
- Supportive therapy, including:
    - Blood transfusions
    - Antimicrobial therapy.

8.3.2 Post-remission therapy after high-intensity induction therapy

Use the following regimen for patients who have achieved remission after high-intensity induction therapy [10][**L1, RGA2**]:

- 2-3 cycles of cytarabine 1.5g/m2 q12h on days 1, 3, 5.

8.3.3 Allogeneic HSCT using reduced-intensity conditioning

Allogeneic HSCT is standard care for medically-fit patients aged 60-74 years using a reduced-intensity conditioning (RIC) regimen [10][**L1, RGA1**].

8.4 Management of adults age over 75 years

Consider supportive therapy in patients aged ≥75 years [**R-GDG**].

8.5 Therapy-related AML

Therapy-related AML (t-AML) may occur as a complication after cytotoxic and/or radiation therapy [10]:

- Previous therapies should be meticulously documented and reported.
- t-AML is associated with a higher frequency of unfavourable cytogenetics.
- Survival of t-AML patients is poor compared to patients with *de novo* AML:
- Survival is also poorer in patients with therapy-related CBF-AML compared with *de novo* CBF-AML.
- Treatment considerations in t-AML, include [**R-GDG**]:
    - Status of the primary cancer.
    - Patient's performance status.
    - Presence of complications from primary therapy.
    - Leukaemic karyotype.
- The treatment most likely to cure t-AML is allogeneic HSCT [10]:
    - Patients who have an HLA-matched donor should be considered for allogeneic HSCT.
    - Overall survival rate is approximately 20-30%.
- t-AML patients should be encouraged to take part in prospective trials that are designed for other AML patients with similar genetic changes [**R-GDG**].

8.6 Response criteria and survival outcomes in AML

Response assessment [10]:

- After completion of induction therapy, response assessment should be carried out between days 21-28 (i.e. day 28 and day 35 from day 1 of chemotherapy induction).

Response assessment during follow-up period [10]:

- Repeat marrow aspirates should be performed if blood counts become abnormal.
- Blood counts should be carried out every 1 to 3 months for the first 2 years, then every 3 to 6 months for up to 5 years.

Complete remission (CR) [10][**L1, RGA1**]:

- All criteria must be fulfilled:
  - Bone marrow blasts <5%.
  - Absence of blasts with Auer rods.
  - Absence of extramedullary disease.
  - Absolute neutrophil count ≥1.0 x 10^9/L (1,000/µL).
  - Platelet count ≥100 x 10^9/L (1,000/µL).
  - Independence of red cell transfusions.
- Marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with particles:
  - If inconclusive, consider repeating examination after 5-7 days.
  - Flow cytometric evaluation may help to distinguish between persistent leukaemia and regenerating normal marrow.
  - Genetic analysis may be considered as appropriate.
- A marrow biopsy should be carried out in cases of dry tap, or if no particles are obtained.
- No minimum duration of response is required.

CR with incomplete recovery (CRi) is defined by [10]:

- All CR criteria except for:
  - Residual neutropenia: <1.0x10^9/L (1,000/µL) or
  - Thrombocytopenia: <100x10^9/L (100,000/µL).

Morphologic leukaemia-free state is defined by [10]:

- Bone marrow blasts <5% in cellular marrow.
- Absence of blasts with Auer rods.
- Absence of extramedullary disease.
- No haematological recovery is required.

Partial remission is defined by [10]:

- All haematological criteria of CR with:
  - Decrease of bone marrow blast percentage to 5-25%; and
  - Decrease of pre-treatment bone marrow blast percentage by at least 50%.

Cytogenetic CR [10]:

- Is defined as a complete reversion to a normal karyotype at time of morphologic CR (or CR with incomplete recovery) in patients with an abnormal karyotype at diagnosis.
- Is based on the examination of a total of 20 metaphase cells taken from bone marrow.

Molecular CR [10]:

- There is no standard definition.
- Depends on molecular target.

Treatment failure is defined by [10][**L1, RGA1**]:

- Resistant disease:
    - CR, Cri, or PR have not been achieved.
    - Is present if the patient has survived ≥7 days after completion of initial treatment, with indicators of persistent leukaemia demonstrated using blood and/or bone marrow examination.
- Death in aplasia:
    - Death occurring ≥7 days after the completion of initial treatment while the patient is cytopenic.
    - Evidence of persistent leukaemia cannot be found in an aplastic or hypoplastic bone marrow that has been collected within 7 days of death.
- Deaths from indeterminate cause include:
    - Deaths occurring prior to treatment completion , or <7 days after its completion.
    - Deaths occurring ≥7 days after the completion of initial therapy with no blasts present in the blood, but bone marrow examination is not available.

Relapse [10]:

- Bone marrow blasts ≥5%, or
- Reappearance of blasts in the blood, or
- Development of extramedullary disease.
- In cases with low blast percentages (5-10%), a repeat marrow should be performed to confirm relapse.
- Appearance of new dysplastic changes should be closely monitored for emerging relapse.
- In patients who have been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of haematopoiesis.
- Cytogenetics should be tested to distinguish true relapse from therapy-related MDS/AML.

8.7 Relapsed AML

Relapsed AML is defined as recurrence of the disease after achievement of CR for ≥6 months [10]. The majority of patients who have achieved CR will have a relapse of the leukaemia within 3 years of initial diagnosis [10]. Prognosis after relapse is poor, and treatment options prove to be unsatisfactory [10].

8.7.1 Prognostic factors for relapse

Assessment of each patient on an individual basis can help to determine whether treatment with curative intent is a realistic possibility [10]:

- Long-term survival is dependent on the ability to achieve remission and the probability to consolidate with HSCT.
- The prognostic index for younger adults with AML relapse is used to categorise patients in to three groups depending on their score:
    - Favourable: 0-6 points (46% five-year survival).
    - Intermediate: 7-9 points (18% five-year survival).
    - Unfavourable: 10-14 points (4% five-year survival).
- Prognostic relapse score is estimated as follows:
    - Duration of remission prior to relapse:

        - ≥18 months (0 points).
        - 7 to 18 months (3 points)
        - ≤6 months or less (5 points).
    - Cytogenetics at initial diagnosis: inv(16) or t(16;16) (0 points), t(8;21) (3 points), other (5 points).
    - Age at time of relapse: 35 years or less (0 points), 36 to 45 years (1 point), more than 45 years (2 points).
    - Prior HSCT: no (0 points), yes (2 points).

8.7.2 Re-induction of remission

There is no generally established treatment standard due to lack of prospective controlled studies [10].

A common approach is to select treatment with the aim of attaining new remission and leading to HSCT [10][**L2**]:

- 1-2 cycles of FLAG-Ida should be used as salvage therapy, to induce remission followed by allogeneic HSCT:
    - Fludarabine 30 mg/m^2 on days 2-6.
    - Cytarabine 2 grams/m^2 on days 2-6.
    - G-CSF on days 1-7.
    - Idarubicin 8 mg/m^2 daily on days 4-6.

8.8 Molecular-targeted therapy

Molecular-targeted therapies include [10][**L2, RGA2**]:

- Demethylating agents (e.g. azacitadine).
- Gemtuzumab ozogamicin (GO) (non-formulary in Qatar).
- FLT3-selective tyrosine kinase inhibitors (non-formulary in Qatar).

8.9 Special situations

8.9.1 Hyperleucocytosis

Initial white blood cell count (WBC) >100 x 10^9/L is associated with a high risk of haemorrhage (mainly within the central nervous system), leucostasis and tumour lysis syndrome [10]. Emergency strategies should therefore be initiated to reduce the risk of fatal haemorrhage, leucocytosis and tumour lysis syndrome.

Leukapheresis is an option for the initial management of hyperleucocytosis; however, no impact on long-term outcomes has been demonstrated and the procedure is associated with early complications [10][**L2, RGC2**]. Initiation of chemotherapy should not be delayed [10].

8.9.2 Central nervous system involvement

Routine evaluation of central nervous system (CNS) involvement is not recommended in asymptomatic patients, as involvement of the CNS at the time of diagnosis, or during treatment is rare [13].

Risk factors for CNS involvement in AML patients are listed below, however it remains unclear whether they are applicable to patients treated with modern induction regimens [13]:

- A prominent monocytic component.

- APL in systemic relapse.
- AML with inv(16) or chromosome 11 abnormality.
- Hyperleucocytosis.
- An elevated lactate dehydrogenase.

Central nervous system treatment consists of intrathecal treatment with cytarabine or cytarabine-methotrexate-hydrocortisone 3 times per week, until clearance of blasts is achieved. This is followed by administration of 3 further injections of the same dosage [10].

The optimal number of intrathecal treatments remains unknown but ranges from 4-12 treatments [10]. In patients with a central nervous system recurrence, cranio-spinal irradiation with or without intrathecal chemotherapy has also been shown to be effective.

Central nervous system prophylaxis with intrathecal therapy for cases of AML with hyperleucocytosis and monocytic leukaemia may be considered [10].

8.9.3 Extramedullary AML

Acute leukaemia may present in a variety of extramedullary tissues with or without bone marrow disease [10]. Myeloid sarcoma (MS) and leukaemia cutis represent two well-known extramedullary manifestations of AML [10,14].

MS is a rare extramedullary tumour of immature myeloid cells. It is also called granulocytic sarcoma or chloroma. The tumour mass consists of myeloid blasts in which the tissue architecture is effaced. It occurs at anatomical sites other than the bone marrow, most commonly in skin, lymph nodes, gastrointestinal tract, bone, soft tissue and testis [10].

MS has been associated with hyperleucocytosis, t(8:21) and CD56 positivity. It can also develop at relapse with or without marrow involvement. The median time to the development of AML in this setting ranges from 5-12 months. Myeloid sarcoma requires systemic treatment similar to that given for de novo AML [10,14]. After chemotherapy, radiotherapy maybe considered as a consolidation treatment for isolated myeloid sarcoma. Radiotherapy can also be considered if there is an inadequate response to chemotherapy, recurrence after HSCT, and in circumstances that require rapid symptom relief because of compression of vital structures (see *Table 8.9.3* below) [10,14].

Leukaemia cutis is the infiltration of the epidermis, dermis, or sub-cutis by neoplastic leukaemia cells resulting in clinically identifiable cutaneous lesions [14]. It commonly results in subcutaneous nodules and can be confusingly referred to as *cutaneous granulocytic sarcoma*. It is treated similarly to isolate MS using intensive chemotherapy (see *Table 8.9.3* below) [14].

MS development	Extent of involvement	Strategies
Initial	• Isolated • Concurrent MS and marrow	• Intensive AML chemotherapy with consideration of RT as consolidation. • Intensive AML chemotherapy with consideration of HCT; RT if MS persists after induction chemotherapy.
Relapse	• **Isolated:** ○ After chemotherapy ○ After transplant • **MS and marrow:** ○ After chemotherapy	• Reinduction AML chemotherapy with consideration of HCT • Donor lymphocyte infusion, tapering of immunosuppression; RT and/or clinical trial. • Reinduction AML chemotherapy with consideration of HSCT, RT and/or clinical trial.

MS development	Extent of involvement	Strategies
Leukaemia cutis	• **Marrow status:** ○ Negative ○ AML	• Intensive AML chemotherapy. • Intensive AML chemotherapy with consideration of HSCT; TSEB after chemotherapy for persistent leukaemia cutis, if marrow is negative.

RT: Radiotherapy; TSEB: total skin electron beam therapy.

Table 8.9.3: Treatment strategies for extramedullary manifestations of AML [14].

8.10 Supportive care

8.10.1 Prophylactic anti-infectious treatment

Fungal prophylaxis [10]:

- Invasive fungal infections represent a significant cause of morbidity and mortality in patients with prolonged neutropenia.
- All patients should receive fungal prophylaxis [10][**L2, RGA2**].

Antibiotic prophylaxis [10]:

- Consider the use of fluoroquinolones given as prophylaxis against both *Streptococcus viridans* and gram-negative sepsis [10][**L2, RGA2**].
- Should follow the results of local antibiogram data.

8.10.2 Transfusion support

Platelet transfusions [10]:

- The induction of platelet transfusions has dramatically reduced mortality from haemorrhage in AML.
- A threshold of 10 x10^9/L should be used for prophylactic platelet transfusion [10][**L1, RGA2**].
- In addition to the platelet count, mucosal bleeding, infection, severe mucositis, and fever should also be considered in the assessment of bleeding risk and appropriateness for platelet transfusion.

Red blood cell transfusions [10]:

- It is generally accepted that the minimum haemoglobin level should be 8 g/dL, but robust evidence for this is lacking [10][**L2, RGB**].
- Packed RBC transfusions should be avoided if WBC > 100 x 10^9/L.

Granulocyte transfusions [10]:

- There is presently insufficient evidence to recommend granulocyte transfusions in the treatment of AML.

8.10.3 Growth factors

G-CSF and other human growth should not be given as part of routine care [10].

9 Management of acute promyelocytic leukaemia

9.1 Introduction

APL is a highly curable malignancy [6,15], it is a subtype of AML accounting for 5-10% of cases [6]. APL is distinguished from other forms of acute leukemia by a characteristic morphology (FAB-M3 and M3 variant) and a pathognomonic cytogenetic abnormality involving chromosomal t(15,17) which at the molecular level corresponds to the formation of the fusion gene *PML-RARA* [6].

APL has a striking age-associated incidence. The incidence increases to a constant level among young adults after the age of 10 years and declines after the age of 60 years [6]. The mean age lies between 40 and 50 years. This is in marked contrast to other subtypes of AML, where there is a steady rise in incidence to the age of 55 years, after which there is an exponential increase with increasing age [15].

The introduction of all-trans-retinoic acid (ATRA) into the therapy of APL has completely revolutionised the management and outcome of this disease. It has led to disease-free survival in up to 80% of patients aged <60 years [6,15]. The introduction of arsenic trioxide (ATO) has also provided a valuable addition and may have contributed to further improvements in the clinical outcome of this disease with survival rates exceeding 70%, when these agents are combined with chemotherapy [6].

Coagulopathy is the most notorious manifestation of APL and is associated with a high mortality at diagnosis, therefore the diagnostic suspicion of APL alone is sufficient to be considered as a medical emergency that requires several simultaneous actions. These include immediate commencement of ATRA therapy, prompt genetic diagnosis, and measures to counteract the coagulopathy [6].

9.2 Investigation and diagnosis of APL

The 2008 and 2016 WHO classifications of *AML and related neoplasms* (see *Section 7.1*) characterise APL under the category of *Acute myeloid leukemia with recurrent genetic abnormalities*. No blast count cut-off is required for diagnosis, once the cytogenetic abnormality is confirmed (see *Section 10.2.2*). Complex cryptic translocations producing the *PML-RARA* gene product are possible but rare and account for <5% of APL cases (see *Section 10.2.4*) [6]. Other *RARA* translocations are:

- *NPM1*, t(5;17).
- *NUMA1*, t(11;17).
- *ZBTB16/PLZF*, t(11;17).
- *STAT5B*, t(17;17).
- *PRKAR1A*, t(17;17).
- *FIP1L1*, t(4;17).
- *IRF2BP2*, t(1;17)(6-8).

The *FLT3*-ITD molecular abnormality, is seen in approximately 12-40% of APL cases, and is associated with: leucocytosis, the short *PML-RARA* (BCR3) isoform, and microgranular morphology [6].

A prominent presenting feature of APL is DIC leading to haemorrhagic symptoms and occasionally thrombosis. However unlike other forms of AML, the total white cell count is typically low or normal [6]. The hypogranular (microgranular) variant of APL is however associated with significant leucocytosis with a rapid doubling time. Hypogranular APL blasts usually express CD34, CD2 and myeloid markers

NB [6,15]:

- Rapid confirmation of the *PML-RARA* genetic diagnosis is mandatory [15] and should ideally be performed within 24 hours [**R-GDG**].
- Morphological diagnosis of hypergranular (typical) APL is highly predictive of an underlying *PML-RARA* rearrangement, and immunophenotyping by multiparameter flow cytometry can improve the accuracy of diagnosis. The APL cells are :CD34-, CD117+, HLADR, CD33 bright, CD13 heterogeneous, CD15-
- Differentiation therapy (ATRA and ATO) and supportive therapy, should both be started immediately, as soon as APL is suspected [6].

9.3 Risk stratification

Risk stratification should be carried out at diagnosis [9]:

- Score depends on the initial white blood cell and platelet counts (*Sanz Score*) [16]:
  - High risk: WBC ≥10,000/µl.
  - Intermediate risk: WBC <10,000/µl and platelets <40,000/µl.
  - Low risk: WBC <10,000/µl and platelets >40,000/µl.

9.4 Prognostic factors

Poor prognostic factors in APL include [15]:

- Absence of molecular remission by PCR at end of consolidation therapy.
- Therapy-related APL (t-APL).

MRD monitoring [9]:

- Is performed using a bone marrow aspirate or peripheral blood sample and should take place at least every three months after the end of consolidation therapy for the first 2 years [9].
- Salvage therapy should be initiated if MRD is found to be positive.

9.5 Treatment of APL

The current approach to treatment of APL at NCCCR is the simultaneous administration of ATRA and anthracycline-based chemotherapy (as per the PETHEMA LPA 2005 / HOVON 79 APL study protocol in Appendix A)[17]. The more-novel approach to treatment of APL is as follows and will be adopted by NCCCR in due course [**R-GDG**].

Once the diagnosis of APL is suspected, treatment should begin as soon as possible with [6][**L1, RGA2**]:

- ATRA 45 mg/m^2/day (rounded to the nearest 10 mg) divided into twice daily dosing.
  - Initiates differentiation of leukaemic promyelocytes
  - Reduces the risk of coagulopathy haemorrhage.

Appropriate counselling around ATRA's teratogenicity is recommended, including pregnancy testing in women of reproductive age, as appropriate [15].

9.5.1 Updates in APL Treatment regimens

The use of ATRA and ATO now forms the mainstay of treatment for APL [6]. ATO is given to induce apoptosis and differentiation of APL cells. ATO binds to the *PML* moiety of the *PML-PARA* fusion protein (and ATRA binds to the *RARA moiety*) which together induce degradation of the *PML-RARA* fusion protein via independent pathways [18-20].

Improved clinical outcomes have been demonstrated with the combination of ATRA and ATO in the treatment of APL [21-28]. The use of ATRA and ATO is also considered cost-effective in comparison to ATRA and chemotherapy [29]. Risks of ATO however include differentiation syndrome, neurological side effects, liver enzyme elevation and arrhythmias [6].

Treatment of low-intermediate risk patients:

- The Lo-Coco protocol [22] (see *Appendix B*) is recommended and comprises of:
    - ATRA and ATO for induction and consolidation therapy.
    - ATRA and ATO should be continued in induction until haematological CR, or a maximum of 60 days.
    - Followed by 4 consolidation cycles of ATRA and ATO.

Treatment of high-risk patients (initial WBC >10 $x10^9$/L):

- The addition of an anthracycline to ATRA and ATO during induction is recommended, using the APML4 protocol [21,23] (see *Appendix C*):
    - Induction with idarubicin and ATRA and ATO.
    - Followed by two consolidation cycles of ATRA and ATO.
    - Followed by 2 years of maintenance therapy with ATRA, 6-mercaptopurine and methotrexate.

NB: In both of the above clinical scenarios [21,22]:

- CNS prophylaxis is not routinely recommended and neurological investigations such as LP or MRI should only be performed if there are clinical signs of neurological disease.
- Patients should be monitored for:
    - Rash.
    - Differentiation syndrome.
    - Coagulopathy.
    - Prolonged QT-interval.
    - Arrhythmias.
    - Elevated liver enzymes.

9.5.2 Treatment of elderly patients

Low-intermediate risk elderly patients [6]:

- ATRA and ATO is recommended.

High-risk elderly patients [6,21]:

- The APML4 protocol is recommended, unless an anthracycline is contraindicated.

9.5.3 Supportive Treatment

Supportive treatments are discussed below and include consideration of the following [6] [R-GDG]:

- Avoidance of procedures that may increase the risk of haemorrhage or thrombosis.
- Coagulopathy.
- Differentiation syndrome.
- Use of cytoreductive therapy.

- Arrhythmias associated with ATO use.
- Antimicrobial prophylaxis.
- Tumour lysis syndrome.
- Nutritional support.

Procedures [6]:

- Consider the use of a peripherally inserted central catheter (PICC) with multiple lumens instead of a central line to avoid haemorrhage or thrombosis.
- Avoid lumbar puncture.
- In the event of leucocytosis, avoid the use of leukapheresis to prevent exacerbation of a coagulopathy.

Coagulopathy [6]:

- In the event of a coagulopathy, monitor frequently (up to maximum of 6 hourly) and provide blood product support as needed [**R-GDG**].
- Transfusions are recommended to maintain the following levels:
    - Platelet count >30 $x10^9$/L.
    - Fibrinogen level >1.5 g/L.
    - Normal INR/PT.
- Heparin is not recommended as part of routine clinical care unless patients have evidence of venous thromboembolism.
- When all evidence of coagulopathy has dissipated, standard transfusion recommendations should be followed.

Differentiation syndrome (DS):

- May result from the use of ATRA or ATO [6].
- Suspect DS in the presence of one of the following [15,30]:
    - Unexplained fever.
    - Weight gain of >5 kg.
    - Peripheral oedema.
    - Dyspnoea with pulmonary infiltrates on chest radiograph.
    - Unexplained hypotension.
    - Acute renal failure.
    - Pleural or pericardial effusion.
- Moderate DS is defined as 2-3 of the above signs or symptoms [31].
- Severe DS is defined as 4 or more of the above signs or symptoms [31].

There is at present insufficient evidence to guide the use of prophylactic steroids in DS and its use remains controversial [32]. Steroids are however part of the protocol using ATO therapy, at a dose of prednisone of 0.5-1.0 mg/kg per day starting on Day 1 for part or all of induction therapy [21,22].

If suspected, increase the dose of steroid to therapeutic levels (e.g. dexamethasone 10 mg IV Q12H) [6]. Consider delaying ATRA and ATO administration in cases of severe DS. Other supportive measures which may be considered include furosemide and in some cases, haemodialysis or mechanical ventilation [6].

Use of cytoreductive therapy:

- The use of the Lo-Coco protocol [22] is frequently associated with hyperleucocytosis during induction, which may increase the risk of DS [6].

- Use hydroxyurea to ensure the WBC is managed appropriately [6]:
    - Hydroxyurea 500 mg QID (if WBC 10-50 x 10^9/L; or
    - Hydroxyurea 1 g QID (if WBC >50 x 109/L).

Arrhythmias associated with ATO [6]:

- Obtain a baseline ECG and at least twice weekly ECGs during the use of ATO therapy to monitor the QT interval [**R-GDG**].
- Other medications which may prolong the QT-interval should be avoided.
- Replace potassium and magnesium to maintain electrolyte levels in the upper half of the normal range.
    - Serum magnesium should be maintained above 1.8mg/dL, serum potassium should be maintained above 4 mmol/L during treatment [9].
- Temporarily postpone ATO therapy if there is evidence of an arrhythmia, or until low electrolytes are replaced and the QT interval has normalised.

Antimicrobial prophylaxis:

- Anti-viral prophylaxis is advisable to prevent reactivation of herpes simplex and varicella zoster viral infections [6][**L1, RGA2**].
- Consider the use of anti-fungal prophylaxis [6]:
    - Avoid the use of azole antifungals due to associated QT prolongation and potential drug-drug interaction with ATO.
    - Co-trimoxazole may also be considered in patients taking prolonged courses of steroids to prevent *Pneumocystis jirovecii* pneumonia.

Tumour lysis syndrome [6]:

- Monitor patients for tumour lysis syndrome [6][**L1, RGA2**].
- Consider the use of allopurinol for patients at high risk of tumour lysis syndrome.

Nutritional support:

- Thiamine deficiency has been reported in patients with APL receiving ATO therapy [22].
- Consider the use of multivitamins to prevent thiamine deficiency, particularly if patients are at risk of malnutrition [6].

9.6 Follow-up

The timing of a follow-up bone marrow aspirate differs based on the protocol used:

- The Lo-Coco protocol [22]:
    - A bone marrow aspirate is recommended after completion of induction treatment to document haematological remission.
- The APML4 protocol [21]:
    - A bone marrow aspirate is recommended after the first cycle of consolidation to document haematological remission, as the response may be delayed.
    - The median time to haematological CR in the APML4 protocol was 53 days.

NB: Molecular remission by PCR must be documented by the end of the final cycle of consolidation therapy, irrespective of the protocol used [6].

9.6.1 Sequential monitoring of MRD

Sequential monitoring for MRD is recommended in patients are deemed to be high risk, in order to predict relapse and guide pre-emptive therapy [33,34].

In high risk patients:

- Following consolidation therapy, MRD testing should be carried out every 3 months for a period of 36 months using the best available PCR test [6].
- The use of peripheral blood specimen to monitor MRD is recommended to reduce the risk of bone marrow procedures and aid adherence.
- MRD monitoring using peripheral blood has reduced sensitivity along with a delay in MRD positivity, when compared to a bone marrow specimen, by a median of 29 days and a difference in 1.5 log reduction [33].

Low-intermediate risk patients:

- Post-consolidation molecular monitoring is not recommended, due to the very low risk of relapse using initial ATRA and ATO therapy.

NB: If relapse is confirmed, pre-emptive therapy should begin as soon as possible in order to prevent frank relapse [6].

9.7 Management of relapse

9.7.1 Molecular and haematological relapse

ATO-naïve patients:

- Use ATO therapy in the treatment of relapse in patients who have not previously been treated with ATO [35][**L1, RGA2**].

Relapse after ATO-induced remission [6]:

- There is limited evidence available to definitively guide treatment in this scenario.
- Arsenic-resistance has been reported, with presence of mutations in the *PML-RARA* B2 binding domain.
- For early relapses, options include the following, prior to HCST:
    - At least two cycles of ATO.
        - Using ATO, a second molecular CR is achieved in nearly 80% of cases [15].
    - "3+7" regimen.
    - Other AML salvage regimens (e.g. anthracycline and HiDAC).
- For late relapses, re-induction with ATRA and ATO, should be used.

Transplant-eligible patients [6]:

- Transplant is recommended to consolidate a remission following ATO therapy [6][**L1, RGA2**].
- Autologous HSCT is associated with a lower transplantation-related mortality than allogeneic HSCT.
- Autologous transplantation should be considered in patients without high risk features who achieve a molecular remission with ATO therapy [35-37].
- Allogeneic HSCT involves a greater risk of transplantation-related mortality, but offers a greater anti-leukaemic activity.
- Allogeneic transplant, should be considered in all patients who do not achieve a molecular remission in second complete remission (CR2) [35-37].

For patients unfit to proceed to HSCT, the available options include [15]:

- Repeated cycles of ATO with or without ATRA or standard chemotherapy.
- The anti-CD33 monoclonal antibody *Gemtuzumab ozogamicin*, appears to induce a high rate of molecular responses even as a single agent in advanced disease.

9.7.2 CNS and other extramedullary relapses

At least 10% of all relapses in APL have CNS involvement and therefore involvement of extramedullary sites (CBS in particular) should be considered in cases of haematological relapse [15]. Induction treatment of CNS relapse involves [15]:

- Weekly intrathecal treatment with methotrexate, hydrocortisone, and cytarabine until there is a complete clearance of blasts in the CSF.
- This is followed by 6-10 further cycles of triple therapy as well as systemic treatment.

An alternative regimen involves ATO and ATRA sequentially in conjunction with triple intrathecal therapy as a non-myeloablative treatment approach . Chemotherapy regimens that offer high CNS penetration have been used in this instance, e.g. high-dose cytarabine) [15].

Further management with craniospinal irradiation and allogenic or autologous transplants should also be considered as the preferential consolidation therapy in patients who are responding to treatment [15].

10 Management of AML and APL in pregnancy

10.1 The multidisciplinary team

All pregnant women with leukaemia should be managed within a MDT comprising of the following specialists [10,38][**R-GDG**]:

- Haematologist.
- Obstetrician.
- Clinical Pharmacist.
- Neonatologist.

The patient should be kept fully informed about the diagnosis, and treatment of the disease Consideration must be given to the health of both the mother and foetus [38].

10.2 Investigation and diagnosis of AML and APL in pregnancy

All investigations and diagnostic criteria for AML and APL are identical to those described in *Section 6* and *Section 10.2* above.

10.3 Treatment of AML in pregnancy

Leukaemia in pregnancy increases the risk of complications, such as [38]:

- Abortion.
- Intrauterine growth restriction.
- Perinatal mortality.

Treatment delays put the maternal outcome at risk, without improving the foetus's risk. Causes of foetal death include [10,38]:

- Maternal anaemia.
- DIC and leukaemic cells hindering blood flow, oxygen delivery, and nutrient exchange within the placenta.

In the first trimester, administration of chemotherapy is associated with increased risks of early fetal loss, congenital malformation, and low birth weight [10]. In the second and third trimesters, consideration should be given to early induced labour between cycles of chemotherapy [10,38]. Daunorubicin is considered the safest anthracycline in pregnancy [10].

10.4 Treatment of APL in pregnancy

APL diagnosis in pregnancy is a challenging situation that nevertheless carries a high chance of successful outcome for mother and baby after a decision-making process that should be individualised to the patient and requires the involvement of the mother and the MDT [38]. Management may be addressed differently according to gestational age [38].

10.4.1 Treatment in the first trimester

ATRA and ATO are highly teratogenic [6,15] and as a result, they should be avoided during the first trimester. Administration of chemotherapy during the first trimester, although frequently safe for the mother carries a 10-20% risk of congenital malformations, increased risk of abortion, and low birth weight [38].

A crucial decision in that must be made during the first trimester in APL patients is whether to continue with the pregnancy and receive anthracycline chemotherapy alone, or commit to termination of the pregnancy once the patient is hemodynamically stable [10,38]. If the pregnancy is terminated, the patient may receive conventional treatment with ATRA, and chemotherapy may be started immediately. Daunorubicin is a safer anthracycline when used during early pregnancy than idarubicin [10].

10.4.2 Treatment in the second and third trimesters

Treatment with ATRA and anthracycline-based chemotherapy appear to be reasonably safe in the second and third trimester [15]. Chemotherapy is associated with a low risk of malformation to the fetus in the second and third trimesters, but increases the risk of abortion, prematurity, low birth weight, neonatal neutropenia, and sepsis [38].

Strict fetal monitoring is recommended for patients receiving ATRA alone or in combination with chemotherapy due to the potential for reversible foetal arrhythmias and other cardiac complications to present at birth [15].

Following delivery, breastfeeding is contraindicated if chemotherapy, ATRA or ATO is necessary [15].

11 Follow up and surveillance

Leukaemia survivors should be monitored closely for signs of [1]:

- Relapse.
- Secondary malignancies.
- Cardiac complications.
- Endocrine disturbances such as:
    - Metabolic syndrome.
    - Hypothyroidism.
    - Hypogonadism.

Surveillance of AML survivors [**R-GDG**]:

- For patients treated with chemotherapy and radiation only:
    - CBC:
        - In the first 3 years, CBC every 1-3 months
        - 3-5 years: CBC every 3-6 months.
        - After 5 years: once or twice per year.
    - ECG and echocardiogram, every two years with cardiology follow-up, if an abnormality is noted.
    - Further investigations, as directed by the haematologist.

Appendix A

The diagram below outlines the PETHEMA/HOVON LPA 2005 protocol, which is used in the management of APL at NCCCR at present [17].

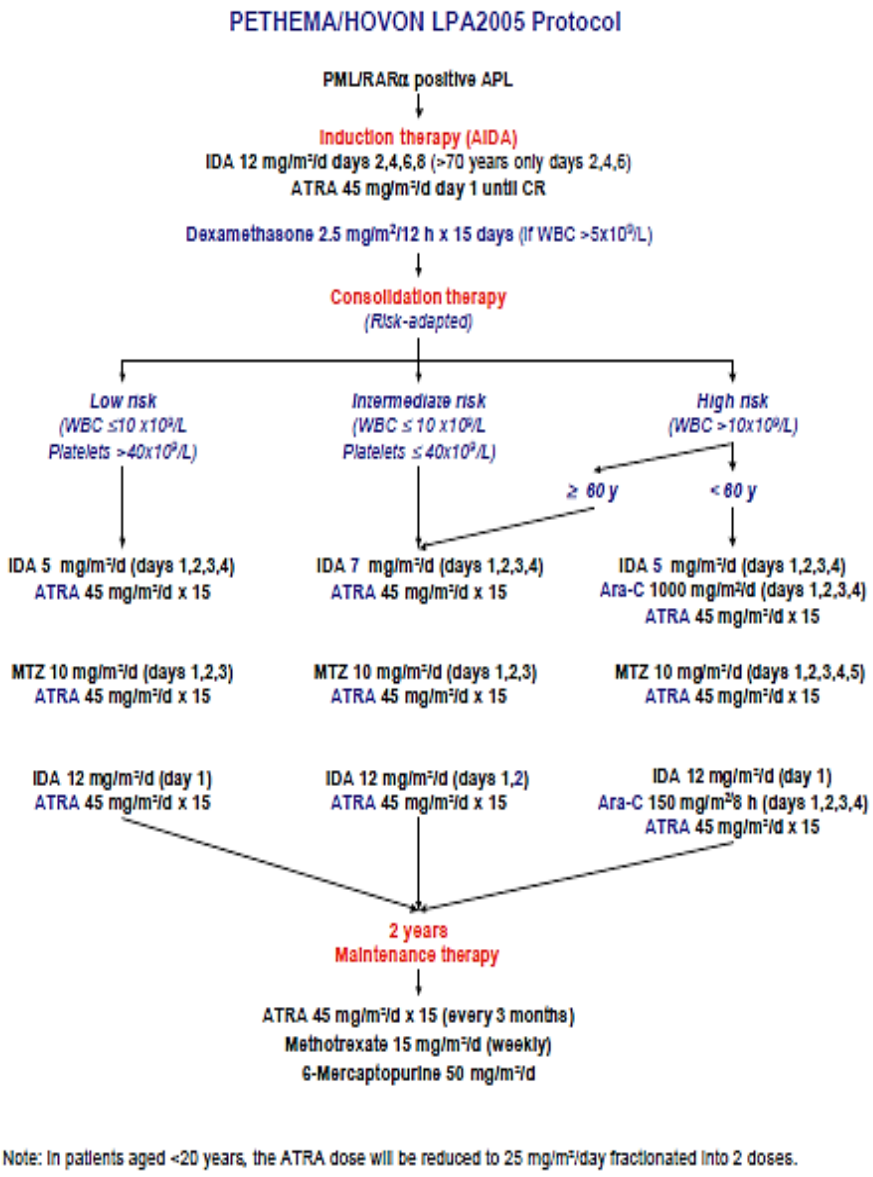

Fig A1: PETHEMA protocol [17].

Appendix B

The Lo-Coco protocol is outlined below [22]:

Induction:

- ATO (Arsenic trioxide) (IV over 2 hours) 0.15 mg/kg/day:
    - Starting on day 1, continued until haematological CR or maximum 60 days, see above guidelines for supportive measures.

- ATRA (All-trans retinoic acid) (orally) 45 mg/m2/day:
    - Starting on day 1, administered in two equally divided doses and rounded to the nearest 10mg increment, continued until haematological CR or maximum 60 days.

- Prednisone 0.5 mg/kg per day:
    - Starting on day 1 until the end of induction therapy.

Consolidation:

- ATO (IV over 2 hours) 0.15 mg/kg daily for 5 days every week:
    - Treatment should be continued for 4 weeks on and 4 weeks off, for a total of 4 cycles (last cycle administered on weeks 25-28).

- ATRA (orally) 45 mg/m^2/day:
    - Administered in two equally divided doses and rounded to the nearest 10 mg increment.
    - Treatment should be administered for 2 weeks on and 2 weeks off for a total of 7 cycles (last cycle administered on weeks 25-26).

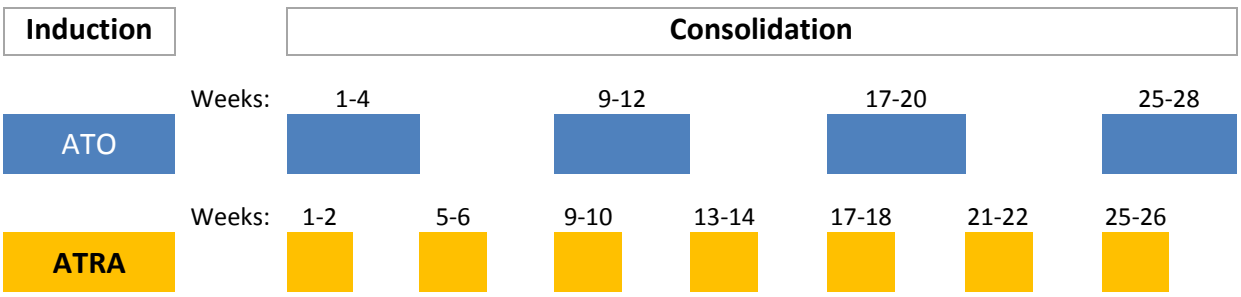

Fig B1: Diagrammatic representation of Induction and consolidation under the Lo-Coco protocol [21].

Appendix C

The APML4 protocol outlined below [21]:

Induction:

- ATRA (orally) 45 mg/m2/day:
    - Administered in two equally divided doses and rounded to the nearest 10 mg increment, on days 1-36.
- ATO (IV) 0.15 mg/m2/day:
    - Administered on days 9-36, see above guidelines for supportive measures.
- Idarubicin (IV) 12 or 9 or 6 mg/m^2/day. This dose is based on the patient's age (i.e 12 mg/m^2/day for 18-60 years, or 9 mg/m^2/day 61-70 years, or 6 mg/m^2/day >70 years):
    - Idarubicin is given on days 2, 4, 6, and 8
- Prednisone 1 mg/kg/day:
    - This is given either on days 1-10 , until the total WBC falls below 1 x 109/L or until there is a resolution of differentiation syndrome.
    - When ATRA or ATO has been omitted for 3 or more days, the duration of prednisone treatment should be extended to beyond day 36 to compensate for any missed doses.

Consolidation
Should begin 3-4 weeks after the end of induction.

First Consolidation cycle:

- ATRA (orally) 45 mg/m^2/day: Days 1-28.
- ATO (IV over 2 hours) 0.15 mg/kg/day: Days 1-28.

Second Consolidation cycle:

- ATRA (orally) 45 mg/m^2/day: Days 1-7, 15-21, and 29-35.
- ATO (IV over 2 hours) 0.15 mg/kg/day: Days 1-5, 8-12, 15-19, 22-26, and 29-33.

Maintenance: Eight 3-monthly cycles of:

- ATRA (orally) 45 mg/m^2/day: Days 1-14.
- 6-Mercaptopurine (6-MP) (orally) 50-90 mg/m^2/day: Days 15-90.
- Methotrexate (orally) 5-15 mg/m^2/weekly: Days 15-90.

A summary table of the APML4 protocol is included on the next page.

Induction		
ATRA	45 mg/m2/d PO	Days 1-36 in divided doses
Idarubicin	12 mg/m2/d IV (ages 1-60) 9 mg/m2/d IV (ages 61-70) 6 mg/m2/d IV (ages >70)	Days 2, 4, 6 and 8
ATO	0.15 mg/kg/d IV	Days 9-36 as a 2-hour IV infusion Supplemental potassium and magnesium as required to maintain serum levels in the upper half of the respective normal ranges
Prednisolone	1 mg/kg/d PO	Days 1-10 or until WBC falls below 1 x109/L or until resolution of differentiation syndrome (whichever occurs last)
Haemostatic support	Products administered once or twice daily as required to achieve specified targets	Platelets >30 x109/L Normal prothrombin time Normal activated partial thromboplastin time Fibrinogen >1.5 g/L
Consolidation cycle 1 (3-4 weeks after the end of induction)		
ATRA	45 mg/m2/d PO	Days 1-28
ATO	0.15 mg/kg/d IV	Days 1-28
Consolidation cycle 2 (3-4 weeks after the end of consolidation cycle 1)		
ATRA	45 mg/m2/d PO	Days 1-7, 15-21, 29-35
ATO	0.15 mg/kg/d IV	Days 1-5, 8-12, 15-19, 22-26, 29-33
Maintenance: 8 cycles (3-4 weeks after the end of consolidation cycle 2)		
ATRA	45 mg/m2/d PO	Days 1-14
Methotrexate	5-15 mg/m2/wk PO	Days 15-90
6-Mercaptopurine	50-90 mg/m2/d PO	Days 15-90

Table C1: Summary of the APML4 protocol for treatment of APL [6].

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