Haematology Cancer Clinical Guidelines

Haematology Expert Advisory Group (EAG)
on behalf of Northern Cancer Alliance

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SECTION 4

GUIDELINES FOR MANAGEMENT OF ACUTE MYELOID LEUKAEMIA (AML)

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

Diagnostic Criteria

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

Essential Investigations

Blood

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

Marrow

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

Principles of Management

Intensive vs Non-intensive Therapy

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

treating physician who will discuss this issue with individual patients and with the MDT.

Non-intensive therapy is given with palliative intent.

Risk Stratification

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

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

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

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

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

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

Risk Stratification in Normal Karyotype AML

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

The following subgroups can be demonstrated:

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

CKIT mutation

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

CEBPA Mutations

Biallelic mutations of CEBPA are associated with a relatively favourable prognosis and as a result we would not recommend allogeneic bone marrow transplant in CR1 for these patients.

The Role of Haematopoietic Stem Cell Transplantation (HSCT)

As for any haematological malignancy, the potential benefits of transplantation must be balanced against the morbidity and mortality associated with the procedure.

The following patients should be considered for allografts in the absence of significant co-morbidities:

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

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

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

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

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

Newly diagnosed patients treated with DA induction followed by high dose cytarabine consolidation are eligible for midostaurin if they are FLT3+ and midostaurin can be continued for up to 12 x 28 day cycles as a single agent maintenance therapy in patients who reach CR

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

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

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

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

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

Once again such patients who are FLT3 mutated are eligible for midostaurin treatment +/- maintenance if following a DA induction and high dose cytarabine consolidation strategy

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

Management of Fitter Patients with Refractory or Relapsed Disease

- Refractory disease or relapse should be treated with FLAG-Ida.
- All suitable patients should be discussed with a transplant specialist to consider HSCT.

Potential Palliative Options as First Line Treatment or For Refractory/Relapsed Disease

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

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

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

Idarubicin/Etoposide
This is a more myelosuppressive regimen than those outlined above but has been shown to induce temporary remissions
Idarubicin 20mg/m^2days 1-3 PO
Etoposide 80mg/m^2days 1-3 PO

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

Riverside Schedule
Idarubicin 12mg/m^2 IV days 1-3
Cytarabine 100mg/m^2 over 12 hours IV, once daily days 1-7

Azacitidine

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

The recommended starting dose for the first treatment cycle, for all patients regardless of baseline haematology laboratory values, is 75 mg/m^2 of body surface area, injected subcutaneously, daily for 7 days. Each 7-day treatment is followed by a rest period of 21 days (28-day treatment cycle). It is recommended that patients be treated for a minimum of 6 cycles. Treatment should be continued as long as the patient continues to benefit or until disease progression.

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

Appendix of Regimens

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

Daunorubicin+Ara-C (DA: 3+10)
Daunorubicin 50 mg/m^2 IV days 1, 3, 5 (3 doses)
Ara-C 100 mg/m^2 IV 12-hourly on days 1-10 inclusive (20 doses)

Daunorubicin+Ara-C (DA: 3+8)
Daunorubicin 50 mg/ m^2 IV days 1, 3, 5 (3 doses)
Ara-C 100 mg/m^2 IV 12-hourly on days 1-8 inclusive (16 doses)

Daunorubicin+Ara-C infusion (DA: 3+7)
Daunorubicin 50 mg/m^2 IV days 1, 3, 5 (3 doses)
Ara-C 100 mg/m^2 IV over 24 h daily for 7 days
[This may be used for non-trial patients and approved by BCSH. It may be given as day case chemotherapy if the patient is well.]

High-dose cytarabine
Ara-C 3 g/m^2 IV over 4 h 12-hourly days 1,3,5

Cytarabine 1.5g/ m^2
Ara-C 1.5 g/m^2 IV over 4 h 12-hourly days 1,3,5

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

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

Midostaurin
50mg BD on days 8-21 of DA induction or high dose ara-c consolidation
50mg BD 12x28 days cycles in single agent maintenance

Management of Patients with Acute Promyelocytic Leukaemia (APL)

Patients with newly diagnosed t(15:17) APL can be offered treatment with ATRA in combination with arsenic trioxide (ATO) if the disease is classified as low/intermediate risk (WCC < $10x10^9$/l). Of note we would strongly support the ATO/ATRA schedule as tested in AML 17 clinical trial (Burnett et al (2015) Lancet Oncology 16(13): 1295-1305).

The AIDA regimen commencing with idarubicin and ATRA should be offered to those with WCC >$10x10^9$/l and can clearly be discussed with those with lower risk disease

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

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

AIDA (ATRA + idarubicin based treatment for APML)

Induction

- All-transretinoic acid (ATRA), 45 mg/m²/day orally in two equally divided doses and rounded to the nearest 10 mg increment, starting on day 1. ATRA treatment will be continued until haematologic CR and for a maximum of 60 days. If haematological CR is not achieved by day 60, consider the “High Risk” APL protocols of AML 17.
- Idarubicin, 12 mg/m² on days 2, 4, 6 and 8 by short (20 minute) intravenous infusion. Idarubicin doses should be brought forward by one day in patients presenting with WBC>$10x10^9$/L, with first dose given within a few hours of starting ATRA.

First consolidation cycle

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

Second consolidation cycle

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

Third consolidation cycle

- Idarubicin, 12 mg/m^2/d as short (20 minute) intravenous infusion only on day 1.
- ATRA, 45 mg/m^2/d will be administered orally in two equally divided doses from day 1 to day 15.

Relapsed APL

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