CONTENTS

1. Diagnosis, investigations and general management ...................................................3

2. Acute myeloid leukaemia (non-APL) ........................................................................3
   2.1 Patients under the age of 60 years .....................................................................3
   2.2 Patients over the age of 60 years and good performance status .........................4
   2.3 Patients with poor performance status ................................................................5
   2.4 Primary induction failure ....................................................................................5
   2.5 Relapsed acute myeloid leukaemia (non-APL) .....................................................6

3. Acute promyelocytic leukaemia (APL) .....................................................................7
   3.1 de novo APL .........................................................................................................7
   3.2 Relapsed acute promyelocytic leukaemia ..............................................................8
1. Diagnosis, investigations and general management


<table>
<thead>
<tr>
<th>Genetic group</th>
<th>Subsets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>t(8;21)(q22;q22); <em>RUNX1</em>-RUNX1T1</td>
</tr>
<tr>
<td></td>
<td>inv(16)(p13.1q22) or t(16;16)(p13.1;q22); <em>CBFB</em>-MYH11</td>
</tr>
<tr>
<td>Mutated NPM1</td>
<td><em>FLT3</em>-ITD (normal karyotype)</td>
</tr>
<tr>
<td>Mutated CEBPA</td>
<td>(normal karyotype)</td>
</tr>
<tr>
<td>Mutated NPM1</td>
<td><em>FLT3</em>-ITD (normal karyotype)</td>
</tr>
<tr>
<td>Intermediate-I</td>
<td>Wild-type NPM1 and <em>FLT3</em>-ITD (normal karyotype)</td>
</tr>
<tr>
<td>Intermediate-II</td>
<td>Wild-type NPM1 and <em>FLT3</em>-ITD (normal karyotype)</td>
</tr>
<tr>
<td></td>
<td>t(9;11)(p22;q23); <em>MLLT3</em>-MLL</td>
</tr>
<tr>
<td>Adverse</td>
<td>Cytogenetic abnormalities not classified as favorable or adverse</td>
</tr>
<tr>
<td></td>
<td>inv(3)(q21q26.2) or t(3;3)(q21;q26.2); <em>RPN1</em>-EVI1</td>
</tr>
<tr>
<td></td>
<td>t(6;9)(p23;q34); <em>DEK</em>-NUP214</td>
</tr>
<tr>
<td></td>
<td><em>MLL</em> rearranged</td>
</tr>
<tr>
<td></td>
<td>−5 or del(5q); −7; abnl(17p); complex karyotype</td>
</tr>
</tbody>
</table>

For all patients document HCT-CI and, for patients over 60, consider recording frailty assessments.

Low threshold for CNS examination in presence of neurological signs/symptoms. Consider one off CSF examination with IT Ara-C 50mg in those patient with presenting WBC >100, skin involvement or M4/M5 phenotype. Those patients with confirmed CNS disease require intrathecal cytarabine 50mg twice weekly until CSF clear and then weekly for 4 weeks. Consider Depocyte as alternative.

Consider baseline CT/PET in those patients presenting with a chloroma.

2. Acute myeloid leukaemia (non-APL)

2.1 Patients under the age of 60 years
Enter on to current NCRN protocol where possible, currently AML17.

Off study
DA 3+10, DA 3+8, ARA-C 1.5g/m², ARA-C 1.5g/m²
Alternatively give MACE/MIDAC as blocks 3 and 4 (problems of amsacrine availability and cost).
**Future considerations**

- HIDAC 3g/m² in selected favourable risk patients.

**Transplant**

Good risk patients defined by cytogenetic analysis should be treated with chemotherapy alone. Mylotarg should be added, if available, to induction chemotherapy for core binding factor (CBF) leukaemias - inv(16) and t(8;21).

Patients with molecularly defined good risk disease including biallelic CEBPA mutated cases and those who are FLT3-ITD negative/NPM1 mutated should be treated with chemotherapy alone. The latter group may be refined in the future using IDH mutational status.

Standard risk patients should be considered for a myeloablative or reduced intensity allogeneic transplant if a matched sibling is available.

Poor risk patients are recommended to proceed to myeloablative or reduced intensity sibling, VUD, haploidentical or cord blood allogeneic transplantation. Defining ‘poor risk’ is becoming increasingly complicated and may be defined clinically (using the AML17 risk score), molecularly (ITD⁺ and FLT3wt/NPMwt/CEBPAwt vs LeukemiaNet vs. Patel _et al._, 2013) or karyotypically (Revised MRC criteria with concept of monosomal karyotype). Those with residual and persistent MRD positivity should also be assessed for potential allogeneic transplant, especially in the face of a rising MRD level. For this reason transplant decisions regarding these patients should be discussed by the relevant AML MDT.

Myeloablative transplantation should occur after 2 cycles of chemotherapy. Reduced intensity transplantation should occur after 3 cycles of chemotherapy.

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**2.2 Patients over the age of 60 years and good performance status**

Enter onto current intensive therapy NCRN protocol where possible, currently AML18. Patients can also enter AML17 at their clinician’s discretion. Other clinical trial options may be open to this group at certain times.

Consideration should be given to the patient’s diagnostic karyotype, if available, and those patients with adverse cytogenetics may not be best served by standard intensive therapy (due to the high refractory disease rate and very low long term LFS) unless as a bridge to allograft.

**Off study**

DA 3+10, DA 3+8 and HiDAC 1.5g/m². MidAC with reduced Ara-C dose (as per AML 14) can be used as an alternative 3rd course.
Consider 4\textsuperscript{th} cycle of HIDAC 1.5g/m\textsuperscript{2} in fit, older patients with t(8;21) or inv(16) AML. Consider 5-azacitidine (NICE approved) for non-proliferative cases with 20-30% bone marrow blasts and adverse cytogenetics.

**Transplant**
Consider sibling or 10/10 VUD RIC transplant in CR1 for appropriate low HCT-CI, good ECOG, 60-70 year old, standard/poor risk patients with an available donor. Alternative donor transplants and 1 antigen mismatched VUD donors should be considered on a case by case basis and may not be appropriate in the 65-70 age group.

### 2.3 Patients with poor performance status
Enter onto current non-intensive therapy NCRN protocol where possible, **currently LI1**. Other clinical trial options may be open to this group at certain times.

**Off study**
Options include low-dose cytarabine, hydroxycarbamide, low dose etoposide, 6MP or 6TG and supportive care. LDAC is unlikely to be effective in the presence of adverse cytogenetics. Treat to 4 cycles and reassess. If CR achieved, treat to a total of 12 cycles. Consider 5-azacitidine (NICE approved) for cases with 20-30% bone marrow blasts.

### 2.4 Primary induction failure
MDT discussion is crucial. Ablative allogeneic transplant if fit enough for the procedure and Craddock score is 0 or 1: more than two induction courses (1 point), pre-transplant blasts in the bone marrow > the median 38.5% (1 point) and patients with seronegative CMV serology (1 point).

![Graph](image)


Consider FLAMSA-RIC or sequential chemo-RIC approaches as part of a clinical trial.
Consider clofarabine containing regimen (Clofarabine/etoposide/cyclophosphamide or D-Clo or Clo+high-dose Ara-C) for those with an identified allogeneic donor and transplant-eligible.

Consider other clinical trial options and palliative approaches

2.5 Relapsed acute myeloid leukaemia (non-APL)


<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse-free interval from first complete remission, months</td>
<td></td>
</tr>
<tr>
<td>➢ &gt; 18</td>
<td>0</td>
</tr>
<tr>
<td>➢ 7-18</td>
<td>3</td>
</tr>
<tr>
<td>➢ ≤ 6</td>
<td>5</td>
</tr>
<tr>
<td>Cytogenetics at diagnosis</td>
<td></td>
</tr>
<tr>
<td>➢ t(16;16) or inv(16)</td>
<td>0</td>
</tr>
<tr>
<td>➢ t(8;21)</td>
<td>3</td>
</tr>
<tr>
<td>➢ Other</td>
<td>5</td>
</tr>
<tr>
<td>Age at first relapse, years</td>
<td></td>
</tr>
<tr>
<td>➢ ≤ 35</td>
<td>0</td>
</tr>
<tr>
<td>➢ 36-45</td>
<td>1</td>
</tr>
<tr>
<td>➢ &gt; 45</td>
<td>2</td>
</tr>
<tr>
<td>SCT before first relapse</td>
<td></td>
</tr>
<tr>
<td>➢ No SCT</td>
<td>0</td>
</tr>
<tr>
<td>➢ Previous SCT (autologous or allogeneic)</td>
<td>2</td>
</tr>
</tbody>
</table>

A – 1-6 points; B – 7-9 points; C 10-14 points
Enter onto NCRN trial where possible (currently only for those relapsing after initial treatment on AML17). Other clinical trial options may be open to this group at certain times

MDT discussion is crucial for this group of patients. Total anthracycline dose and future cardiac risk needs to be assessed on a case by case basis.

**Off study**
Relapse less than 2 years CR: FLA-Iida +/- Mylotarg, ADE +/- Mylotarg or ‘Vancouver DA’.
CR more than 2 years: Consider using initial induction regimen or ‘Vancouver DA’.
If not in CR2 after above, consider clofarabine containing regimen (Clofarabine/etoposide/cyclophosphamide or D-Clo or Clo/high-dose Ara-C) for those with an identified allogeneic donor and transplant-eligible.
Consider sorafenib or alternative FLT3i for those FLT3-ITD patients with an identified donor as both initial therapy and post-allograft maintenance until GvL established.
Consider FLAMSA-RIC or sequential chemo-RIC approaches as part of clinical trial in those with an identified donor ready to go.

CNS relapse: HIDAC regimen +/- anthracycline e.g FLA-Iida or ‘Vancouver DA’ plus intrathecal cytarabine 50mg twice weekly until CSF clear and then weekly for 4 weeks. Consider Depocyte as alternative.

Palliative options include hydroxycarbamide, low dose etoposide, 6MP or 6TG and supportive care.

**Transplant**
Patients entering 2nd CR should, if possible, receive an allogeneic stem cell transplant (related, 10/10 or 9/10 unrelated, cord blood, haploidentical)
Myeloablative or RIC conditioning should be tailored to the patient’s age and HCT-CI.
Consider autologous stem cell transplant for CBF patients who are MRD negative in both marrow and PBSCH or those intermediate-risk cytogenetic patients without an allogeneic donor.

3. **Acute promyelocytic leukaemia (APL)**


3.1 **de novo APL**
Enter onto NCRN trial where possible, currently AML17.
For non-trial patients, use AIDA protocol as per AML17 with MRD monitoring in CR
For patients in whom anthracyclines are precluded, use ATO+ATRA as per AML17 with MRD monitoring in CR

### 3.2 Relapsed acute promyelocytic leukaemia

Arsenic trioxide plus ATRA (as per AML17) followed by autologous transplant if MRD negative in marrow and PBSCH or allogeneic transplant if MRD positive

For those relapsing after ATO+ATRA treatment, options include palliative chemotherapy +/- ATRA, AIDA, ADE+ATRA, Mylotarg+ATRA or repeat ATO+ATRA if initial CR>1year.

Consider one off CSF examination with IT Ara-C 50mg for patients with relapsed disease. Those patients with confirmed CNS disease require intrathecal cytarabine 50mg twice weekly until CSF clear and then weekly for 4 weeks. Consider Depocyte as alternative.