Guidelines on the management of acute myeloid leukaemia in adults


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Keywords: acute myeloid leukaemia, guidelines, transplantation, pregnancy, acute promyelocytic leukaemia.

Key recommendations

Diagnosis

1 Bone marrow aspirate and trephine biopsy unless the peripheral blast count is high.
2 Immunophenotyping [CD3, CD7, CD13, CD14, CD33, CD34, CD64, CD117 and cytoplasmic myeloperoxidase (MPO)].
3 Cytochemistry (MPO or Sudan Black, combined esterase). Can be omitted if four-colour flow cytometry is available.
4 Cytogenetics [with reverse-transcription polymerase chain reaction (RT-PCR) for AML 1-ETO and CBFB-MYH11 in non-acute promyelocytic leukaemia (APL) and promyelocytic leukaemia (PML) and retinoic acid receptor-alpha (RARA) in suspected APL; fluorescent in situ hybridisation (FISH) in selected cases].

Treatment

1 Patients should be treated by a multidisciplinary team that is experienced in the management of acute myeloid leukaemia (AML), serving a population base of 0.5 m and intensively treating five or more patients per annum (recommendation grade C; evidence level IV).
2 All eligible patients up to age 60 years (or older than 60 years but able to receive intensive treatment) with de novo or secondary AML should be asked to participate in the current National Cancer Research Institute (NCRI) study, at present AML 15 (http://www.aml15.bham.ac.uk/trial/index.htm) (recommendation grade C; evidence level IV).
3 Patients over 60 years old who are unable to tolerate remission induction chemotherapy, but are suitable for non-intensive therapy, should be asked to participate in the current NCRI study, at present AML 16 (http://www.aml16.bham.ac.uk) (recommendation grade C; evidence level IV).
4 Patients opting for non-intensive chemotherapy who are not entered into clinical trials should be offered treatment with low-dose cytarabine (grade A; evidence level Ib). Patients not able to tolerate chemotherapy should be given best supportive care: transfusion support and hydroxycarbamide to control the white cell count (recommendation grade A; evidence level Ib).

Acute promyelocytic leukaemia

1 All trans-retinoic acid (ATRA) should be started as soon as the diagnosis is suspected (grade A; evidence level Ib).
2 Leucopheresis should be avoided in patients a high white cell count (grade B; evidence level III).
3 The platelet count should be maintained at >50 x 10^9/l, together with fresh frozen plasma (FFP) and cryoprecipitate to normalise the activated partial thromboplastin time and fibrinogen levels (grade B; evidence level IIb).
4 Differentiation syndrome should be treated promptly with dexamethasone 10 mg twice daily iv, and ATRA stopped temporarily until the symptoms resolve (grade C; evidence level IV).
5 Diagnostic work-up should include documentation of underlying PML-RARA fusion (grade B; evidence level IIA).
6 Patients with PML-RARA-positive APL, deemed suitable for intensive therapy, should be treated with concurrent ATRA and anthracycline-based chemotherapy for induction, followed by anthracycline-based consolidation therapy (grade A; evidence level Iib).
7 Patients should undergo molecular monitoring after treatment to guide further therapy (grade B; evidence level IIA).

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For relapsed disease, ATRA should not be used as single agent therapy due to the significant possibility of acquired secondary resistance and arsenic trioxide (ATO) should only be used in patients with confirmed PML–RARA-positive APL. Treatment of relapse, with respect to use of autologous or allogeneic transplantation as consolidation should be guided by minimal residual disease (MRD) assessment (grade B; evidence level IIa).

### Pregnancy
1. AML in pregnancy should be managed jointly between the haematologist and the obstetrician with full involvement of the mother (grade B; evidence level III).
2. Chemotherapy in the first trimester is associated with a high risk of fetal malformation and should be avoided if possible. The opportunity to terminate the pregnancy should be discussed with the mother. If termination is refused and the mother’s life is at risk, chemotherapy should be started (grade B; evidence level III).
3. Chemotherapy in the second and third trimesters is associated with an increased risk of abortion and premature delivery as well as low birth weight babies. Consideration should be given to early induction of labour between cycles of chemotherapy (grade B; evidence level III).

### Transplantation
1. Allogeneic transplantation should be offered to patients with high-risk AML in first remission who have a human leucocyte antigen (HLA) identical donor, although it is accepted that only a minority of patients will benefit (recommendation grade B; evidence level III). Standard risk patients may be offered allo-transplantation as part of a clinical trial (recommendation grade B; evidence level III).
2. HLA-matched sibling allogeneic transplantation may be the treatment of choice for younger patients who are in second remission (recommendation grade B; evidence level III).
3. Older patients with high-risk disease or beyond first remission may be offered a reduced-intensity conditioned transplant but this should be in the context of a clinical trial (recommendation grade C; evidence level IV).
4. Younger high-risk patients or those beyond first remission may be considered for a haplo-identical transplant but this should be in the context of a clinical trial (recommendation grade C; evidence level IV).
5. The role of autografting in the management of AML is contentious. Autografting should only be carried out in a clinical trial (recommendation grade A; evidence level Ia).

Acute myeloid leukaemia has an overall incidence of 3.4 per 100,000. The disease is more common in the elderly and two-thirds of all cases occur in those aged over 60 years. The management of AML represents a significant clinical challenge. These guidelines give an up-to-date overview of evidence-based and expert opinion-based optimum management of AML in the UK. These guidelines are abbreviated from the full version that is available on http://www.bcsh-guidelines.com.

### 1. Methods

The PubMed, Cochrane and Medline databases in the English language were searched using the key words ‘acute myeloid leukaemia/leukemia’, ‘acute promyelocytic leukaemia/leukemia’, ‘stem cell transplantation’ with subheadings ‘anthracycline’, ‘pregnancy’, ‘disseminated intravascular coagulation’ (DIC), ‘growth factors’ and ‘quinolones’ from 1983 to 2005. The authors have substantial experience in their field. Stakeholder involvement was secured through patient representation from the Leukaemia Research Fund and the Leukaemia Care Society. The recommendations were agreed using the Agree instrument (http://www.agreecollaboration.org) and were further reviewed by a Sounding Board of 100 haematologists representing adult practice in both teaching and district hospitals. The levels of evidence used were those of the US Agency for Health Care Policy and Research (Appendix 1).

### 2. Classification of AML

The World Health Organisation (WHO) system for the diagnosis and classification of AML (Jaffe et al, 2001) (Table I) supersedes the modified French–American–British (FAB) classification (Bennett et al, 1985a,b, 1991). This guideline proposes that the WHO system is adopted for the diagnosis and classification of AML. It differs significantly from the FAB system as follows.

- Reducing the marrow blast percentage separating myelodysplastic syndrome (MDS) from AML from 30% to 20%.
- Taking account of preceding MDS or myeloproliferative disorders.
- Creating categories defined by certain non-random cytogenetic abnormalities or the equivalent molecular genetic abnormality \((t(8;21), t(15;17), \text{inv}(16)/t(16;16)\) and \(t(\gamma11q23)\).
- Taking account of multilineage dysplasia with or without a preceding marrow disorder.
- Recognising previous cytotoxic therapy as part of the classification.
- Introducing new morphological subtypes.

The laboratory diagnosis of AML has been recently reviewed (Swirsky & Richards, 2001).

Practical issues regarding the diagnosis of AML include the following.
Immunophenotyping is essential to identify AML cases that require morphological categorisation. All patients should have a marrow aspirate and trephine biopsy unless the aspirate is inadequate. Acute panmyelosis with multilineage dysplasia is defined as ≥250% dysplastic cells in two of the erythroid, megakaryocytic and granulocytic/monocytic lineages. Cytochemistry is not essential if four-colour flow cytometry and estimation of cytoplasmic MPO is available.

Immunophenotyping is essential to identify AML cases that are negative for cytochemical MPO, e.g. AML minimally differentiated (FAB M0) and megakaryocytic leukaemia (FAB M7). Both surface and intracellular antigens should be studied. The absence of the lymphoid-specific antigens cCD3 and cCD79a should be confirmed. Immunophenotyping of whole lysed marrow samples gives an objective quantification of the blast percentage based on CD45/side scatter (ssc), CD34/ssc or CD117/ssc characteristics. Complex multicolour phenotyping patterns also correlate with the common balanced translocations (Orfao et al, 1999; Ferrara & Del Vecchio, 2002). Immunophenotyping should utilise a minimum of two-colour flow cytometry. Multicolour flow cytometry correlates well with morphological blast characterisation.

All patients should have conventional cytogenetics performed to identify favourable and unfavourable prognostic abnormalities (Grimwade et al, 1998). All patients who are suitable for intensive chemotherapy should be tested for the favourable translocations by RT-PCR as a few of these patients have normal cytogenetics (Langabeer et al, 1997a,b). Cases testing positive in the absence of the associated cytogenetic lesion should be subject to confirmation by FISH or RT-PCR performed independently. Patients suitable for intensive chemotherapy should be tested for FLT3 internal tandem duplication (ITD), predictive for poor outcome (Kottaridis et al, 2001), although it remains uncertain whether alteration of the treatment strategy in the light of this knowledge would improve the outlook.

If FISH is not immediately available, patients with suspected APL should have the diagnosis rapidly confirmed by a slide immunofluorescence test for the characteristic microparticulate nuclear promyelocytic leukaemia (PML) protein pattern of an underlying PML–RARA fusion (Falini et al, 1997; O’Connor et al, 1997). In doubtful cases, ATRA should be commenced until a definitive result is available.

Patients with suspected acute basophilic leukaemia should have this lineage confirmed by a toluidine blue stain.

Minimum laboratory requirements for the diagnosis of AML

- Bone marrow aspirate and trephine biopsy unless the peripheral blast count is high.
- Immunophenotyping (CD3, CD7, CD13, CD14, CD33, CD64, CD117 and cytoplasmic MPO) and HLA-DR.
- Cytochemistry (MPO or Sudan Black, combined esterase). Can be omitted if four-colour flow cytometry is available.
- Cytogenetics (with RT-PCR for AML 1-ETO and CBFB-MYH11 in non-APL and PML–RARA in suspected APL; FISH in selected cases).

3. Prognostic factors

Significant progress has been made in predicting the outcome of patients with AML. A number of factors readily identifiable after presentation can be used to predict the risk of disease recurrence. The most important are age, karyotype, FMS-like receptor tyrosine kinase (FLT3) status and response to induction chemotherapy. Cytogenetic examination at diagnosis allows patients to be stratified into three groups with relapse risks varying from 35% to 76% (Table II). Recent data demonstrate that length mutations leading to constitutive
with overexpression of a number of genes including WT1, BAALC, et al. Indeed in APL, quantification of ERG, EVI1, and RARA could provide risk stratification in the context of clinical trials.

Moreover, there is increasing evidence that monitoring for overexpression of the MDR1 gene encoding the drug efflux pump p-glycoprotein (Leith et al., 1999), presenting white blood cell count, and a history of antecedent myelodysplasia (Wheatley et al., 1999).

4. Appropriate setting for the management of AML

The British Committee for Standards in Haematology (BCSH) has produced guidelines for the minimum standards for the treatment of patients with haematological malignancy (Whittaker et al., 1995; Table III). Recent guidance from the National Institute for Clinical Excellence has made recommendations for the clinical facilities that should be available for the management of patients with haematological malignancy (http://www.nice.org). The recommendations are that patients should be managed by a multidisciplinary team (Table IV) serving a population of 500 000 and induction therapy should only be carried out in centres treating at least five patients per annum with induction chemotherapy with curative intent.

Table II. Use of risk stratification to determine consolidation therapy.

| Good risk | Any patient with favourable genetic abnormalities – t(8;21), inv(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 or with adverse genetic abnormalities: 5−, 7−, del(5q), -a(3q), t(9;22) or complex (five or more abnormalities) – and without favourable genetic abnormalities |

From the results of the MRC AML 10 and 12 trials, the MRC have defined the following risk groups (Grimwade et al., 1998, 2001).

activation of FLT3, present in 25–30% of all patients with AML, predict an increased risk of relapse across all cytogenetic subgroups (Kottaridis et al., 2001). Over the last few years, a number of other molecular markers have emerged that distinguish subgroups of patients with cytogenetically ‘standard-risk’ AML with differing risk of relapse. In particular, mutations in the gene encoding nucleophosmin (NPM1) occur in approximately a third of AML cases, including over half of those with normal karyotype (Falini et al., 2005); while mutations in the gene encoding the transcription factor CCAAT/enhancer-binding protein-α (CEBPA) are found in approximately 10% of cases (Preudhomme et al., 2002). Recent studies have shown that in the absence of co-existing FLT-ITD, NPM1 and CEBPA mutations predict a relatively favourable outcome in standard risk AML (Preudhomme et al., 2002; Fröhling et al., 2004; Döhner et al., 2005; Schnittger et al., 2005; Verhaak et al., 2005). Whereas, presence of partial tandem duplications of MLL, identified in approximately 3% of AML, is associated with a poorer prognosis (Schnittger et al., 2000; Döhner et al., 2002). Adverse outcome has also been associated with overexpression of a number of genes including WT1, BAALC, EVI1 and ERG (Bergmann et al., 1997; Barjesteh van Waalwijk van Doorn-Khosravani et al., 2003; Marcucci et al., 2005; Baldus et al., 2006). Work is currently in progress to establish which markers are primary and secondary lesions in AML and to determine which provide the most powerful independent prognostic factors, forming the basis for improved risk stratification in the context of clinical trials. Moreover, there is increasing evidence that monitoring for MRD provides an independent prognostic factor in AML; indeed in APL, quantification of PML–RARA transcript numbers by real-time PCR has been shown to reliably identify the subgroup of patients who would relapse in the absence of additional therapy (reviewed in Grimwade & Lo Coco, 2002; Goulden et al., 2006). Age remains one of the strongest adverse prognostic factors in AML, partly reflecting the higher proportion of cases with adverse cytogenetics and/or overexpression of the MDR1 gene encoding the drug efflux pump p-glycoprotein (Leith et al., 1999), presenting white blood cell

Table III. The British Committee for Standards in Haematology Guidance on the provision of facilities for the care of adult patients with haematological malignancies (Whittaker et al., 1995).

| Level 1 | Hospitals providing conventional chemotherapy and other forms of outpatient treatment, using dose levels that would not be expected to produce prolonged neutropenia |
| Level 2 | Facilities for remission induction in patients with acute leukaemia, using standard intensive chemotherapy regimens. This level of facility is also required to treat patients with aggressive lymphoma |
| Level 3 | Facilities for autologous transplantation, not requiring total body irradiation |
| Level 4 | Centres with expertise in both allogeneic and autologous transplantation |

Table IV. Haemat-Oncology Multidisciplinary Team recommended by the National Institute for Clinical Excellence improving outcomes guidance.

<table>
<thead>
<tr>
<th>Core team members</th>
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<tr>
<td>Consultant haematologist(s)</td>
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<tr>
<td>Central nervous system in haematology</td>
</tr>
<tr>
<td>Ward sister</td>
</tr>
<tr>
<td>Consultant haematopathologist</td>
</tr>
<tr>
<td>Palliative care specialist (consultant or nurse)</td>
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<tr>
<td>Consultant microbiologist</td>
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<tr>
<td>Oncology pharmacist</td>
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<tr>
<td>Multidisciplinary team coordinator</td>
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<tr>
<th>Extended team members</th>
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<tr>
<td>Social worker</td>
</tr>
<tr>
<td>Clinical psychologist</td>
</tr>
<tr>
<td>Consultant radiologist</td>
</tr>
<tr>
<td>Data manager</td>
</tr>
<tr>
<td>Clinical oncologist (if a level 4 transplant centre)</td>
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4.1. Patient support

Patients with AML require considerable support. Excellent written information concerning the disease and its management should be readily available, e.g. information provided by CancerBACUP (http://www.cancerbacup.org.uk), the Leukaemia Research Fund (http://www.lrf.org.uk) and the Leukaemia Care Society (http://www.leukaemiacare.org). Translators should be provided when required. Employment/financial issues may be a problem and social worker support should be available. Palliative care input should be provided as part of the multidisciplinary team.

5. Treatment of AML

5.1. General measures and supportive care

There has been a steady improvement in survival for patients entering the UK Medical Research Council (MRC) trials over the last 30 years without a major chemotherapeutic breakthrough, suggesting that these improvements have occurred because of better supportive care and increased treatment intensity (Burnett, 2002). Current studies show that nearly half of all patients aged between 15 and 60 years will survive to 5 years of which many will be cured (Mayer et al, 1994; Hann et al, 1997).

The most important threats to the patient come from complications of the disease at presentation, myelosuppression as a consequence of both the disease process and remission induction chemotherapy and from resistant/relapsing disease.

5.1.1. Hyperleucocytosis. A high white cell count at presentation is a poor prognostic factor (Powles et al, 2003). Hyperleucocytosis is generally defined as an initial white cell count/blast count of more than 100 × 10⁹/l. Around 14% of patients present with hyperleucocytosis and are at a greater risk of early death (15% vs. 5-4%) when compared with patients presenting with a white cell count of <100 (Powles et al, 2003). There are no trials that prove leucopheresis is of benefit in these patients but this procedure is generally safe and should be considered in patients with AML presenting with symptomatic hyperleucocytosis (Powles et al, 2003). However, this procedure is contraindicated in patients with suspected APL, as it can exacerbate the coagulopathy with fatal consequences (Vahdat et al, 1994).

5.1.2. Prevention of tumour lysis syndrome. Acute tumour lysis syndrome (ATLS) may be a consequence of initial therapy and is more likely in patients presenting with hyperleucocytosis. ATLS describes a collection of metabolic abnormalities that include hyperuricaemia, hyperphosphataemia, hyperkalaemia, hypocalcaemia and renal failure.

Preventative measures include hydration and allopurinol. The urea and electrolytes should be monitored together with the urine output. A rising potassium level is the most serious life-threatening consequence of tumour lysis syndrome and may require emergency therapy and dialysis. There is evidence that recombinant urate oxidase (rasburicase) can rapidly reverse hyperuricaemia and it may benefit some patients with hyperleucocytosis at presentation, patients with renal impairment or patients who are developing ATLS (Goldman et al, 2001).

**Recommendation**

Rasburicase should be used with chemotherapy in patients with hyperleucocytosis at risk of ATLS (recommendation grade B; evidence level IIb).

5.1.3. Red cell transfusion support. There is no good evidence to support a particular red cell transfusion policy in AML. All patients in whom allogeneic transplantation may be considered should receive cytomegalovirus (CMV)-negative products until their CMV status is known. Patients treated with fludarabine-based chemo therapeutic regimens should be supported with irradiated blood products (Voak et al, 1996).

Iron overload may occur and it is important to assess iron load in patients who have completed therapy. Some patients with iron overload may benefit from venesection. Where possible, chlorpheniramine should be used to control allergic reactions and treatment with hydrocortisone should be avoided.

5.1.4. Platelet support. Platelet transfusions are given to support thrombocytopenia with a transfusion threshold of 10 × 10⁹/l unless there are additional risk factors. Risk factors include sepsis, concurrent use of antibiotics or other abnormalities of haemostasis (Rebulla et al, 1997; Murphy et al, 2003). The presence of a coagulopathy increases the likelihood of haemorrhage at any platelet count. The platelet count should be kept at >20 × 10⁹/l in patients who are haemorrhagic (British Committee for Standards in Haematology, Blood Transfusion Task Force, 2003) or >50 × 10⁹/l in patients with APL who are bleeding (Falanga & Rickles, 2003). In the UK practice platelet (and blood) transfusions are routinely leucodepleted and this may reduce the risk of alloimmunisation and a poor response to platelet transfusion. Patients who are alloimmunised maybe befit from HLA-matched platelet support. Tranexamic acid may be useful for local bleeding, e.g. oral haemorrhage, but is contraindicated in the presence of haematuria because of the possibility of ureteric clot formation.

5.1.5. Granulocyte transfusions. There is no randomised controlled trial evidence to support the routine use of granulocyte transfusions following AML chemotherapy and they are not recommended. There is anecdotal evidence that pooled buffy coat or apheresed granulocytes may be used to treat localised unresolved infection in neutropenic patients (Kerr et al, 2003).
5.1.6. Antibiotic and anti-infective therapy. Patients with acute leukaemia are prone to bacterial and fungal infections as a result of prolonged neutropenia secondary to marrow infiltration and/or the effects of chemotherapy.

Careful attention to personal hygiene and dental care are important. The BCSH guidelines on facilities for haematological patients recommend that patients with AML are looked after in units with at least level-2 facilities with dedicated haematological beds and with single cubicles with en suite facilities available (Whittaker et al, 1995).

Careful attention to hand washing and decontamination before contact with the patient is mandatory for all healthcare workers and visitors.

Flowers and plants are a potential source of fungal spores and Pseudomonas and should be removed from the unit.

The development of infection may be accompanied by marked clinical signs or by none at all. A temperature of over 38°C may indicate a systemic infection but infection may be associated with hypothermia, declining mental status, myalgia or increasing lethargy.

The patient should be examined regularly, including the mouth/throat for perioral/periodontal infection and to exclude thrush, the skin for focal infections or for septic emboli and intravenous catheter sites including the Hickman catheter. Particular attention should be paid to the perineum for signs of occult infection. Vaginal and rectal examination should only be performed after careful consideration. Chest X-rays should be performed regularly and high-resolution computerised tomography (CT) scans of the chest should be considered to exclude pulmonary aspergillosis and other infections. X-rays or CT scans of the sinuses may help to exclude occult fungal infections.

5.1.7. Bacterial infection. Severe sepsis may occur during therapy and the prompt treatment of severe life-threatening bacterial, fungal and viral infections is critical in patients with AML. Patients should be aware of their susceptibility to infection and the importance of presenting early to hospital. All patients should have emergency contact details. Patients with a central venous catheter are at risk of catheter-related infections. These may be serious and require prompt attention; persistent infection, infection with Gram-negative organisms and infection with Candida should lead to catheter removal.

The use of prophylactic antibiotics remains contentious and there is no evidence that their use improves survival.

Empiric broad-spectrum antibacterial therapy is an absolute necessity for febrile neutropenic patients. The choice of therapy should be decided with local microbiologists. Meta-analysis suggests an advantage for beta-lactam antibiotic monotherapy rather than the combination of a beta-lactam with an aminoglycoside (Paul et al, 2005). There should be clear guidelines agreed for the management of patients admitted as an emergency with neutropenic sepsis and patients should be admitted to a haematology unit.

5.1.8. Fungal infection. The risk of developing fungal infection increases with the severity and duration of neutropenia so patients should be observed for the symptoms and signs of fungal infections. Symptoms are often non-specific. As established fungal infections carry a high mortality, empiric antifungal therapy is indicated in patients with persistent pyrexia despite appropriate empirical antibacterial therapy. Early detection of respiratory fungal infections may be aided by the use of spiral CT scans of the chest.

5.1.9. Growth factors. Several large controlled trials have examined whether growth factors influence the outcome of remission induction therapy in AML. They show a modest reduction in the duration but not the depth of the neutropenia and provide no evidence that growth factors induce the growth of myeloid leukaemia cells (Dombret et al, 1995; Rowe et al, 1995; Stone et al, 1995; Takeshita et al, 1995; Zittoun et al, 1996; Heil et al, 1997; Lowenberg et al, 1997; Godwin et al, 1998; Witz et al, 1998; Usuki et al, 2002). The effects of growth factors on outcome, incidence of severe infection, antibiotic usage, duration of hospitalisation and complete remission (CR) rate are variable and the American Society of Clinical Oncology (ASCO) and BCSH guidelines conclude that there is no evidence to support the routine use of growth factors after remission induction chemotherapy for AML (Ozer et al, 2000; Pagliuca et al, 2003). Granulocyte colony-stimulating factor (G-CSF) is recommended after induction if it is appropriate to reduce hospital stay or antibiotic usage. Two trials, in which G-CSF was given after consolidation chemotherapy in AML showed a marked decrease in the duration of neutropenia compared with placebo, as well as a reduction in the use of antibiotic therapy (Heil et al, 1997; Harousseau et al, 2000).

The BSCH and the ASCO guidelines conclude that G-CSF can be recommended following consolidation chemotherapy.

There is experimental evidence to suggest that G-CSF given prior to or with chemotherapy may enhance the cytotoxicity of chemotherapy. It is not possible to separate a possible priming effect from the impact on granulocyte recovery (Ohno et al, 1994; Zittoun et al, 1996; Lowenberg et al, 1997). A recent European trial of G-CSF in AML (Lowenberg et al, 2003) demonstrated a survival gain for patients with standard-risk AML which appears to be due to a reduction in relapse risk, but this is based on a subgroup analysis within the trial, and has not been supported by other studies.
Guideline

Recommendations

There is no survival benefit from the use of growth factors following AML chemotherapy but growth factor use does reduce the duration of neutropenia, of antibiotic use and of hospital stay. The cost–benefit advantages of routine growth factor use are uncertain. The routine use of growth factor therapy in AML is not recommended (recommendation grade A; evidence level IIa).

5.2. Treatment of younger adult patients

The benefits of chemotherapy are greater in younger patients because they withstand chemotherapy better and because of the biological nature of their disease. The therapy of AML is divided into two phases: induction therapy to achieve CR and consolidation therapy once a CR has been achieved. It is important to assess the response to initial treatment as patients who fail to achieve CR have a poor prognosis. Patients who have resistant disease after course 1 or who have an adverse risk cytogenetic or molecular marker, should be considered for an alternative treatment for high-risk leukaemia within the context of a controlled study.

5.2.1. Induction therapy. The goal of remission induction chemotherapy is the restoration of normal bone marrow function. In MRC studies CR is defined as the recovery of normal bone marrow cellularity with fewer than 5% blast cells and without a detectable cytogenetic abnormality. Elsewhere, the term morphologic remission is reserved for patients who also have recovery of peripheral blood counts with a neutrophil count >1.0 × 10^9/l and platelet count exceeding 100 × 10^9/l (Cheson et al, 2003).

The effectiveness of induction therapy can be measured by the percentage of patients who achieve CR and also by relapse-free or disease-free survival (RFS or DFS) and overall survival (OS).

Initial therapy should comprise an anthracycline/anthracycline-like drug given for 3 d combined with cytarabine given over 7–10 d as a continuous infusion or as a twice daily bolus. The most commonly used regimen is daunorubicin, given for 3 d at a dose of 45–60 mg/m^2, and cytarabine 200 mg/m^2 either given as a bolus in divided doses twice daily or as an infusion over 12 h for 10 d (3 + 10) regimen (Hann et al, 1997). Although 10 d of cytosine has been widely used there is no evidence that this schedule is superior to 7-d treatment and may be associated with greater toxicity (Preisler et al, 1987).

Daunorubicin was the first anthracycline of value against AML. It is less toxic than doxorubicin. An Eastern Cooperative Oncology Group (ECOG) study randomised 363 adults with AML over the age of 55 years to receive daunorubicin (45 mg/m^2), idarubicin (12 mg/m^2) or mitoxantrone (12 mg/m^2) each for 3 d together with cytarabine Ara-C. The CR rates were 40%, 43% and 43%, and the median DFS was 5, 7, 9 and 11 months respectively (Rowe et al, 1995). A further trial from ECOG demonstrated no evidence that either mitoxantrone or idarubicin was superior to daunorubicin if given in equitoxic doses (Rowe et al, 2004).

The inclusion of high-dose cytarabine (2–3 g/m^2) in remission induction regimens has been investigated by the South West Oncology group (SWOG; Weick et al, 1996) and the Australian Leukemia Study Group (ALS; Bishop et al, 1996). There was no increase in the CR rate in patients <60 years of age although there was an improvement in DFS in the ALS study but with increased toxicity.

5.2.2. Addition of other drugs. A study by the ALSG in which etoposide (75 mg/m^2) per day for 7 d was added to a ‘3 + 7’ regimen demonstrated that in younger patients (<55 years) there was no difference in the CR rate, but the addition of etoposide (ADE) resulted in a longer duration of remission but not OS (Bishop et al, 1990). The MRC AML 10 trial found no difference in DFS with the ADE or thioguanine (DAT) to a standard MRC 3 + 10 regimen in a randomised trial of 1857 patients (Hann et al, 1997).

Patients who have not achieved at least a partial remission (<15% blasts) after remission induction treatment may be considered for treatment on experimental protocols as their outlook is poor.

Recommendations

1 All eligible patients up to the age of 60 years (or >60 years but able to receive intensive treatment) with de novo or secondary AML should be asked to participate in the current NCRI study, at present AML 15 (http://www.aml15.bham.ac.uk/trial/index.htm).

2 Patients over 60 years who are able to tolerate remission induction chemotherapy should be asked to participate in the current NCRI study, at present LRF AML 14 (http://www.aml14.bham.ac.uk) or HOVON/SAKK AML 43.

3 Patients not eligible or unwilling to participate in the NCRI studies should be offered standard daunorubicin and cytarabine 3 + 10 or 3 + 7 induction chemotherapy (level 1b).

4 Patients opting for non-intensive chemotherapy who are not entered into clinical trials should be offered treatment with low-dose cytarabine (grade A; evidence level Ib). Patients not able to tolerate chemotherapy should be given best supportive care: transfusion support and hydroxycarbamide to control the white cell count (recommendation grade A; evidence level Ib).

5.2.3. Postremission therapy. Following remission induction therapy it is important that additional treatment is given, as the median DFS for patients who receive no additional therapy is only 4–8 months (Cassileth et al, 1998). The aim of postinduction therapy is to prevent relapse with maximal efficiency and minimal toxicity. Options include consolidation chemotherapy and autologous, allogeneic-related or –unrelated donor transplantation. The same chemotherapy regimen used
for remission induction can be repeated but usually non-cross-resistant drugs are used. When several courses of consolidation chemotherapy are given, survival rates at 2–3 years are 35–50% for young to middle-aged adults who have achieved CR.

The UK MRC approach has been to give two courses of induction chemotherapy followed by a third course of m-amsacrine, cytarabine and etoposide, and a fourth course of mitoxantrone and intermediate-dose cytarabine (Hann et al, 1997). Other groups have studied responses of patients to variable and higher doses of cytarabine. The most important study was the Cancer and Leukaemia Group B (CALGB) trial (Mayer et al, 1994), which compared high-dose cytarabine (3 g/m²) with 400 and 100 mg/m² doses. For patients <60 years old, the 4-year DFS was 44% in the high-dose cytarabine arm compared with 29% and 24% in the intermediate- and low-dose groups respectively (P = 0.002). There were very few late relapses in the high-dose group but this therapy was toxic, with 5% treatment-related mortality and significant neurotoxicity in patients older than 40 years. Only 56% of patients received all four courses at the 3 g dose. In a subgroup analysis there was a benefit from the higher dose in younger patients, particularly those with a favourable cytogenetic abnormality and especially those with core-binding factor leukaemias. However, these patients have chemosensitive disease and there is no evidence that high-dose cytarabine is superior to other intensive regimens and good-risk patients in the MRC AML 10 trial fared just as well (Grimwade et al, 1998). There was no evidence that patients with a normal or an unfavourable karyotype benefited from high-dose cytarabine-based chemotherapy.

The ALSG have treated all patients with high-dose cytarabine and idarubicin induction and then randomised patients to a single similar course of consolidation or two courses of idarubicin with conventional dose of cytarabine. With short follow up there was no difference between these groups with an OS of 60% at 3 years (Bishop et al, 1996). The UK MRC approach does not use high-dose cytarabine and results are very similar to the CALGB and ALSG results (Hann et al, 1997; Burnett et al, 2002a).

Despite the use of more intensive consolidation therapy, it is uncertain which drugs, in what combination and how many courses are needed. As around 50% of patients still relapse, all eligible patients with AML should be offered entry into clinical trials so that important questions about remission induction and consolidation therapy are answered.

5.2.4. Maintenance therapy. There is no evidence that maintenance therapy is of benefit in patients with AML who have undergone intensive consolidation therapy with the possible exception of APL.

5.3. Management of AML in patients who are pregnant

Acute myeloid leukaemia may be diagnosed during pregnancy. Chemotherapy during the first trimester is teratogenic (Artlich et al, 1994) and associated with an increased risk of abortion and should be avoided if possible. The risks of continuing the pregnancy should be carefully discussed and, if appropriate, the pregnancy should be terminated. If termination of pregnancy is unacceptable, this presents a considerable management dilemma as delay in treatment is associated with an adverse outcome (Kawamura et al, 1994) and the risks of delay must be explained. Chemotherapy can proceed but is associated with increased risks of early fetal loss, congenital malformation and low birth weight (Felici et al, 1988; Artlich et al, 1994; Ali et al, 2003). Patients presenting in the second and third trimesters can more confidently be offered chemotherapy without a risk of causing congenital malformation (reviewed in Cardonick & Iacobucci, 2004). A report of 58 cases of acute leukaemia in pregnancy (Reynoso et al, 1987) showed that 49 resulted in the birth of 50 live infants. Half were born prematurely and four had low birth weights for their gestational age. One of the 50 infants had congenital malformations and subsequently developed tumours of the adrenal and thyroid glands. Long-term follow up of a cohort of eight children in this series has shown normal growth and development. Chemotherapy given close to delivery may result in significant fetal pancytopenia requiring intensive support (Reynoso et al, 1987; Murray et al, 1994).

For patients presenting with PML–RARA-positive APL in the second or third trimesters of pregnancy, single-agent ATRA may be the safest treatment approach and has been associated with good outcome. Successful outcomes have also been obtained with ATRA in combination with an anthracycline for patients presenting with APL in second or third trimesters (reviewed in Breccia et al, 2002). However, this approach may confer increased risk to the fetus and therefore might be best employed in patients with a white blood cell count >10 × 10⁹/l who have poorer risk disease, including higher rate of induction death. ATRA should be avoided in the first trimester as it is a teratogen. ATO is teratogenic and there have been no reports of its use for APL in pregnancy. Patients with other forms of AML and with stable disease may defer chemotherapy and be supported with growth factors and blood products until delivery can be safely induced at about 30 weeks. It is critical that the patient is fully informed of her choices and is able to exercise these. Finally, further information is required about the outcome of pregnant patients with cancer and new cases should, with the consent of the patient, be reported to the International Registry of Cancer in Pregnancy (http://www.motherisk.org/cancer/index).

Recommendations

1. AML in pregnancy should be managed jointly between the haematologist and the obstetrician with full involvement of the mother (grade B; evidence level III).

2. Chemotherapy in the first trimester is associated with a high risk of fetal malformation and should be avoided if possible. The opportunity to terminate the pregnancy...
should be discussed with the mother. If termination is refused and the mother’s life is at risk, chemotherapy should be started (grade B; evidence level III).

3 Chemotherapy in the second and third trimesters is associated with an increased risk of abortion and premature delivery as well as low birth weight babies. Consideration should be given to the early induction of labour between cycles of chemotherapy (grade B; evidence level III).

4 ATRA can be used in pregnancy in the second and third trimesters (grade B; evidence level III).

5.4. Management of extramedullary disease

Extramedullary disease in AML includes skin and gum infiltrates, often seen in monocytic/monoblastic AML, and the rare granulocytic sarcomas that may be seen in any organ. Extramedullary tumours can arise:

- *de novo* as a primary manifestation of AML in patients with no medullary evidence of leukaemia;
- simultaneously with marrow disease at presentation;
- as an isolated focus of relapse;
- simultaneously with marrow disease at relapse.

The incidence of extramedullary disease is not well established but predisposing factors are thought to include the t(8;21) translocation (Swirsky et al., 1984; Tallman et al., 1993), inv(16) (Holmes et al., 1985), high presenting white cell count, lack of Auer rods and poor nutrition.

Extramedullary myeloid tumours may present in any site (reviewed in Byrd et al., 1995). Histology reveals a diffuse infiltrative population of mononuclear cells, usually accompanied by granulocytic cells at various stages of maturation. The tumours are frequently misdiagnosed, usually as large cell lymphoma, and immunohistochemistry is essential to make the correct diagnosis.

Patients presenting *de novo* or in relapse with extramedullary leukaemia should receive systemic antileukaemic chemotherapy. Surgical or radiotherapeutic approaches are reserved for patients whose extramedullary tumours do not completely resolve with initial treatment.

The prognostic impact of extramedullary disease is unclear but may be an adverse prognostic factor in patients with t(8;21) AML (Byrd et al., 1997).

**Recommendation**

Patients presenting with extramedullary leukaemia should receive systemic antileukaemic chemotherapy (grade C; evidence level IV).

5.5. Management of central nervous system disease

Leptomeningeal disease at presentation occurs in approximately 0.5% of patients. Risks are greater in patients with a high white cell count or monocytic lineage involvement. A large randomised trial of intrathecal prophylaxis in AML has shown no benefit (Rees et al., 1986). In patients achieving remission approximately 5% of primary relapses involve the central nervous system (CNS), with or without concurrent marrow relapse (Rees et al., 1986).

Extradural deposits can present with neurological symptoms depending on the site of disease, and may be more common in AML with t(8;21). Extremely rarely intracerebral deposits of AML occur, most commonly in patients with inv/t(16) (Holmes et al., 1985).

In suspected CNS disease 50 mg of cytarabine should be given intrathecally at the time of the diagnostic lumbar puncture. If infiltration is confirmed, intrathecal cytarabine 50 mg should be given three times per week until the cerebrospinal fluid is clear, and then fortnightly until consolidation treatment is completed. Platelet support may be required (British Committee for Standards in Haematology, Blood Transfusion Task Force, 2003).

Central nervous system relapse is generally followed by marrow relapse if not already present. Reinduction chemotherapy should be given in addition to intrathecal treatment. Extradural deposits generally respond to systemic chemotherapy.

6. Acute promyelocytic leukaemia

6.1. Diagnosis of APL

For patients with APL, it is important to establish the underlying molecular abnormality. Presence of the PML–RARA fusion gene, even in the absence of the t(15;17), predicts a favourable response to molecularly targeted therapies in the form of ATRA and ATO (Grimwade et al., 2000; reviewed Mistry et al., 2003). Rapid confirmation of the presence of the PML–RARA fusion can be undertaken by PML immunofluorescence test or FISH analysis; but marrow and peripheral blood should also be routinely sent for molecular analysis as a baseline for subsequent MRD monitoring. Approximately 1% of APL cases have an underlying PLZF–RARA fusion, typically as a result of t(11;17)(q23;q21). This subset of APL, which has characteristic features (Sainty et al., 2000) is important to recognise as it is resistant to both ATRA and ATO. This section focuses on the management of PML–RARA-associated APL; the treatment approach for rarer molecular variants has been considered elsewhere (Mistry et al., 2003).

6.2. Clinical management

The presentation of APL is a haematological emergency due to the high risk of death as a result of the associated coagulopathy. Rapid diagnosis and prompt initiation of therapy is essential.

6.2.1. Induction. Anti-leukaemic therapy; a number of studies have reported that ATRA improves the coagulopathy associated with APL (Huang et al., 1988; Chomienne et al,
1990; Fenaux et al, 1993; Tallman et al, 2004; reviewed in Falanga & Rickles, 2003). Hence ATRA should be commenced as soon as the diagnosis of APL is suspected. Treatment should not be delayed until the diagnosis has been confirmed. The optimal timing of starting chemotherapy relative to the first dose of ATRA has not been established. For patients with a lower presenting white cell count (<10 × 10⁹/l), there may be an advantage in giving ATRA for a longer period (i.e. 2–3 d) before commencing chemotherapy to ameliorate the coagulopathy; but chemotherapy should be started before the onset of any ATRA-induced leucocytosis that accompanies the retinoic acid (RA) syndrome (Tallman et al, 2002). For patients with a higher presenting white cell count (>10 × 10⁹/l), risk of developing RA syndrome is higher and chemotherapy should ideally be given on day 1 after the first dose of ATRA. Induction with ATRA in combination with chemotherapy has been shown in randomised clinical trials to reduce relapse rates significantly and to improve OS when compared with chemotherapy alone (Fenaux et al, 1993; Tallman et al, 1997). Best results have been obtained when ATRA is given as a prolonged course (21–60 d) commenced at the same time as induction chemotherapy, when compared with sequential therapy involving short (5 d) or more prolonged courses of ATRA prior to starting chemotherapy (Burnett et al, 1999; Fenaux et al, 1999). APL is very sensitive to anthracyclines (Head et al, 1995), and excellent results have been obtained with protocols based upon ATRA and anthracyclines (Avvisati et al, 1996; Sanz et al, 1999, 2004a), including older patients (Sanz et al, 2004b). However, these protocols are only suitable for patients with PML–RARA APL, not patients with the PLZF–RARA fusion or other forms of AML, which should be treated with more intensive anthracycline and cytarabine protocols. Patients with PML–RARA associated APL should receive concurrent ATRA and chemotherapy for induction, with ATRA being continued at least until documentation of morphological CR (level 1b, grade A).

6.2.2. Supportive care. Coagulopathy: a major cause of treatment failure is induction death due to haemorrhage (reviewed in Falanga & Rickles, 2003). Patients with a higher presenting white cell count (i.e. >10 × 10⁹/l) are at highest risk of haemorrhagic death. They should not undergo leucopheresis as it can precipitate fatal exacerbation of the coagulopathy (Vahdat et al, 1994). Evidence suggests that patients with high presenting white cell counts are best commenced on ATRA and anthracycline-based induction therapy. Haemorrhage may be reduced by monitoring of the coagulation profile and administration of appropriate replacement therapy until CR has been attained. Activated partial thromboplastin time (APTT), prothrombin time, thrombin time, fibrinogen level and platelet count should be checked at least twice daily during the early stages of treatment. Coagulation times should be kept within the normal range using FFP as replacement. Fibrinogen levels may be low due to DIC and cryoprecipitate should be given as replacement aiming for a level of approximately 2 g/l. Elevated levels of fibrinogen should be avoided due to an increased risk of thrombosis, which may be further exacerbated by ATRA. The platelet count should be maintained above 50 × 10⁹/l (Falanga & Rickles, 2003; Sanz et al, 2005) until remission. There is no proven benefit for use of heparin/anti-fibrinolytics to reduce induction death rates and their use is not recommended (reviewed in Tallman & Kwaan, 1992; Falanga & Rickles, 2003; Sanz et al, 2004a). Indeed, anti-fibrinolytic agents when combined with ATRA may increase the risk of thrombosis. Nevertheless, anti-fibrinolytic agents could be contemplated in situations of life-threatening haemorrhage in the presence of normal coagulation assays.

RA syndrome: this life-threatening complication of ATRA therapy is characterised by fluid retention and capillary leak and is most likely related to surface adhesion molecule modulation and cytokine release following differentiation of APL cells. Symptoms and signs include cough, dyspnoea, fever, weight gain, oedema, pleural and pericardial effusions and pulmonary infiltrates (reviewed in Larson & Tallman, 2003). RA syndrome occurs in up to a third of patients receiving ATRA as single-agent induction therapy and was fatal in approximately 30% in early studies (Larson & Tallman, 2003). The syndrome typically develops 10 d after initiation of ATRA, but can occur earlier and is usually associated with a rising white cell count. Lower rates of ATRA syndrome (<10%) have been reported when chemotherapy is commenced with ATRA.

Patients on ATRA should be observed carefully for symptoms, signs or falling oxygen saturation levels. If early RA syndrome develops, ATRA should be discontinued and steroids administered promptly (dexamethasone 10 mg i.v. b.d. until disappearance of symptoms and signs, and for a minimum of 3 d). This may prevent progression to fulminant respiratory failure. ATRA can then be cautiously reintroduced. As RA syndrome is linked to the differentiation of APL blasts, its occurrence during induction is not a contraindication to use of ATRA later in the patient’s treatment. Patients with a high presenting white cell count (>10 × 10⁹/l) are at higher risk of RA syndrome and some use prophylactic steroids with induction therapy. Whether this approach confers any benefit is uncertain (Wiley & Firkin, 1995; Firkin et al, 1999).

6.2.3. Consolidation. Primary resistance of APL to simultaneous ATRA and anthracycline-based chemotherapy is exceptionally rare. However, bone marrow appearances following induction can be difficult to interpret and misconstrued as primary resistance (Stone & Mayer, 1990; Sanz et al, 2005); therefore, marrow assessment at this time has been abandoned in some protocols. The majority of such patients will achieve morphological CR following a further course of chemotherapy in combination with continued ATRA therapy and should not be considered to have an adverse prognosis (Burnett et al, 1999). Induction therapy is followed by two to three further anthracycline-based consolidation
courses. The number of consolidation courses or intensity of consolidation may be reduced in patients experiencing excessive toxicity in earlier courses and in the elderly. In such instances, maintenance therapy provides a therapeutic option and MRD monitoring may guide the need for additional therapy (see below). A number of groups have reported that maintenance therapy, given for 2 years, reduces relapse risk, with the best results being obtained with ATRA in combination with 6-mercaptopurine and methotrexate (Tallman et al, 1997; Fenaux et al, 1999). It is unclear whether maintenance is of any value in patients who have received more intensive first-line therapy or who are in molecular remission at the end of consolidation (Avvisati et al, 2003). Transplantation using autologous or allogeneic stem cells performed in first CR (CR1) confers no OS advantage in patients with PML–RARA-positive APL (Burnett et al, 1998, 2002b) and patients should not routinely undergo transplant in CR1 (grade A; evidence level 1b).

6.3. Management of APL patients at high risk of relapse
For patients with PML–RARA-positive APL, a key goal is achievement of PCR negativity in the bone marrow using assays that detect one leukaemic cell in 10^6 cells. Patients with persistent disease or molecular relapse, confirmed in two consecutive assays after completion of consolidation, will invariably relapse unless additional therapy is given (Diverio et al, 1998). The optimal management for such patients is uncertain although a matched donor stem cell transplantation (SCT) can be curative (Lo Coco et al, 2003). Achievement of PCR negativity is critical to achieving cure; for patients lacking a donor, ATO or gentuzumab ozogamicin (GO) used as single agents or in conjunction with chemotherapy are potential options (Petti et al, 2001; Douer et al, 2003; Lo Coco et al, 2004; Douer & Tallman, 2005). Once PCR negativity has been achieved, stem cells may be harvested and if PCR negative, autologous SCT (auto-SCT) can be undertaken. Poor results are seen in patients with evidence of residual disease prior to auto-SCT who receive a PCR-positive graft (Meloni et al, 1997) and this treatment is not recommended in this setting. Outcome in patients in whom PCR status prior to transplant and PCR status of the graft differ are uncertain (reviewed in Grimwade, 1999).

6.4. Management of relapse
Approximately 10% of relapses involve an extramedullary site (most commonly CNS, particularly in patients initially presenting with elevated white cell count) and this should be considered in the assessment and management of relapsed disease (reviewed in Evans & Grimwade, 1999).

One treatment option for patients with confirmed PML–RARA-positive relapse is ATO, which achieves high CR rates, accompanied by PCR negativity in a significant proportion of cases (reviewed in Douer et al, 2003; Douer & Tallman, 2005). ATO has a number of adverse effects including cardiac toxicity and fatal arrhythmias associated with lengthening of the QT interval. It is critical to maintain serum magnesium and potassium levels within the high normal range and monitor the electrocardiogram regularly (drug data sheet and Sanz et al, 2005). ATO can induce a differentiation syndrome akin to RA syndrome, which should be managed in the same way with steroids (see above). ATO-induced hyperleucocytosis commonly accompanies clinical response but is not an indication for treatment modification (Douer et al, 2003; Sanz et al, 2005). ATO-induced remissions are generally not sustained and hence this agent is typically used as a ‘bridge to transplantation’ (Leoni et al, 2002).

As an alternative to ATO, ATRA combined with chemotherapy or GO may induce a second CR, but ATRA alone should not be used for treatment of relapse due to high rates of secondary resistance (reviewed in Mistry et al, 2003).

The optimum management of relapsed APL remains to be established; however, the key aim is to induce molecular remission, as this is essential to achieve cure (grade B; evidence level 1b). It is standard practice (if feasible) to proceed to transplant as the final consolidation course. For patients failing to achieve PCR negativity who have a donor, allogeneic bone marrow transplantation (allo-BMT) is a potential option. The role of reduced-intensity conditioned transplants has not been established in APL; however, a recent study has provided some evidence supporting a graft-versus-APL effect (Lo Coco et al, 2003). For patients who fail to achieve molecular remission with ATO or ATRA/chemotherapy, GO provides a treatment option that has been reported to achieve molecular CR in advanced APL (Petti et al, 2001; Lo Coco et al, 2004). For patients in molecular CR, transplantation using autologous stem cells can be used as consolidation. This may be the preferred treatment approach, even in patients with a potential donor, in view of the reduced toxicity and favourable results obtained with autologous transplantation in this subset of AML (Meloni et al, 1997; De Botton et al, 2005).

6.5. Role of molecular monitoring
Molecular monitoring using an RT-PCR assay with a sensitivity threshold of 1 in 10^4 should be undertaken for 2 years following completion of therapy. Patients with molecularly persistent disease require additional treatment to prevent relapse. Serial monitoring of bone marrow on a 3-monthly basis following consolidation using conventional end-point RT-PCR has been shown to permit early detection of disease in approximately 70% of patients who ultimately relapse (Diverio et al, 1998). It is likely that improvements in MRD monitoring will be achieved with ‘real-time’ quantitative approaches that afford comparable sensitivity, but are more readily standardised and allow identification of poor quality RNA samples that can give false-negative results with conventional assays (reviewed in Yin & Grimwade, 2002). For patients found to test positive, the bone marrow should be repeated within
2 weeks and positivity confirmed in a second laboratory before further treatment is given (although it is prudent to commence the patient on ATRA whilst the result of the second assay is pending). There is evidence to suggest that pre-emptive treatment at molecular relapse affords superior outcome when compared with treatment at frank relapse (Lo Coco et al, 1999; reviewed in Grimwade & Lo Coco, 2002). Use of peripheral blood for MRD assessment has not been validated as a reliable means of predicting relapse (Sanz et al, 2005).

Recommendations

1. ATRA should be started as soon as the diagnosis is suspected (grade A; evidence level Ib).
2. Leucopheresis should be avoided in high count patients (grade B; evidence level III).
3. The coagulopathy should be treated to keep the platelets $>50 \times 10^9/l$, together with FFP and cryoprecipitate to normalise the APTT and fibrinogen levels (grade B; evidence level IIb).
4. Differentiation syndrome should be treated promptly with dexamethasone 10 mg twice daily i.v., and ATRA stopped temporarily until the symptoms resolve (grade C; evidence level IV).
5. Diagnostic workup should include documentation of underlying PML–RARA fusion (grade B; evidence level IIa).
6. Patients with PML–RARA-positive APL, deemed suitable for intensive therapy, should be treated with concurrent ATRA and anthracylene-based chemotherapy for induction, followed by anthracylene-based consolidation therapy and should be offered entry into the NCRI AML trial (currently AML 15) (grade A; evidence level Ib).
7. Patients should undergo molecular monitoring after treatment to guide further therapy (grade B; evidence level IIa).
8. For relapsed disease, ATRA should not be used as single-agent therapy due to the significant possibility of acquired secondary resistance and ATO should only be used in patients with confirmed PML–RARA-positive APL (grade B; evidence level IIa). Treatment of relapse, with respect to use of autologous or allogeneic transplantation as consolidation should be guided by MRD assessment.

7. Management of relapsed AML

Relapse occurs in over 50% of patients and treatment options for these patients remain limited. Median survival figures vary from 3 to 12 months (reviewed by Leopold & Willemze, 2002). The most important predictors of response to reinduction chemotherapy are age, karyotype, duration of first remission and history of previous SCT (Breems et al, 2005). Up to 90% of patients with favourable karyotypic features who relapse can be successfully reinduced, in contrast to patients with adverse cytogenetics where response rates are <40% (Wheatley et al, 1999; Weltermann et al, 2004). Significantly higher rates of response are also observed if the duration of CR1 is >6 months (Rees et al, 1986; Kern et al, 2000). Patients with relapsed disease should therefore be stratified according to cytogenetics, age and length of CR1 to identify the best salvage approach (Estey et al, 1996). In older patients with adverse cytogenetics who relapse within 6 months of chemotherapy the likelihood of durable response to salvage therapy is extremely low. In those younger, fitter patients who achieve a second remission it is reasonable to aim for SCT as part of the salvage therapy. There is a suggestion from the Netherlands group (Breems et al, 2005) that SCT conferred an improved outcome, however, this data are descriptive and subject to considerable selection bias.

Although there are very few randomised trials comparing salvage treatments, the mainstay of salvage treatment in relapsed AML is cytarabine, which has been used in low (100–200 mg/m²), intermediate (1 g/m²) and high doses (2–3 g/m²) and in combination with other drugs. Laboratory data demonstrates that concurrent use of fludarabine enhances the cytotoxicity of cytarabine (Gandhi et al, 1993) and this combination (combined with G-CSF as the FLAG regimen) has been reported to improve salvage rates in non-randomised studies (Estey et al, 1994; Jackson et al, 2001). However, the recent randomised MRC trial for high risk AML (MRC AML-HR) found no benefit for fludarabine + cytarabine, with or without G-CSF, in comparison with standard ADE (cytarabine, daunorubicin and etoposide) (Milligan et al, 2006). Neither is there evidence that timed sequential therapy is of benefit (Yin et al, 2001). However, regimens incorporating high-dose cytarabine are still widely used in young patients in whom allogeneic SCT (allo-SCT) is planned. Clearly, improved strategies are required and recent data show encouraging results with both clofarabine and GO (Mylotarg) (Bross et al, 2001; Sievers et al, 2001; Kell et al, 2003).

8. Transplantation in AML

High relapse rates in patients with AML have led to enthusiasm for the intensification of treatment by the use of high-dose chemoradiotherapy followed by ‘rescue’ using allogeneic stem cells (Beutler et al, 1982; Gale et al, 1982; Kersey et al, 1982; Forman et al, 1983). The early results were encouraging. Allo-SCT reduces the risk of relapse with a relapse risk post-transplant of about 20% compared with 50% after conventional chemotherapy. However, the transplant-related mortality (TRM) remains high at about 15–25%, eroding the anti-leukaemic advantage. Mortality rates are higher for older patients and those transplanted from non-HLA-identical family members or unrelated donors.

Although large registry studies have suggested that allo-SCT in first remission is better than standard chemotherapy (Gale et al, 1996), caution must be exercised in interpreting results from non-randomised studies (Wheatley, 2002). There are a
number of prospective trials available to inform us. In the US Intergroup Trial (Cassileth et al, 1998) a comparison was made between consolidation with high-dose cytarabine (36 g/m² total dose), allo-SCT from a matched-related donor and autografting using purged bone marrow. The results demonstrated a small overall survival advantage for high-dose cytarabine compared with either auto- or allo-SCT. Allo-SCT was associated with a lower relapse risk in comparison with chemotherapy or auto-transplant (29% vs. 61% and 48%, respectively) but these gains were offset by non-relapse mortality (allo-transplant 25%, chemotherapy 3% and auto-transplant 14%). In the MRC AML 10 trial (Burnett et al, 1998, 2002b), patients with no allogeneic donor received four cycles of chemotherapy and were randomised to no further treatment or a bone marrow autograft. Those with a matched sibling donor were recommended an allograft. Comparing the outcome of patients with and without a donor has shown a significant reduction in the relapse risk and improvement in DFS for the ‘with donor’ group (relative risk: 36% vs. 52%, \[P = 0.001\]; DFS: 50% vs. 42%, \[P = 0.001\]). However, the OS was not different between the groups (56% vs. 50% at 7 years, \[P = 0.1\]) because of the higher TRM in the donor group (19% vs. 9%, \[P = 0.001\]). Some subgroups might benefit from an allo-SCT in CR1 and this study suggested an advantage for patients aged below 35 years with standard risk AML. The MRC AML 12 trial explored whether five cycles of chemotherapy was better than four and whether the final cycle should be a transplant (Burnett et al, 2002a). This trial again found no gain for patients undergoing a transplant on a donor versus no donor analysis.

In the European Organization for Research (EORTC) and Treatment of Cancer-Gruppo Italiano Malattie Ematologiche dell’ Adulto AML 8 trial (Zittoun et al, 1995) patients with AML in CR1 were treated with a consolidation cycle of treatment and underwent allo-SCT if they had a matched family donor or were randomised to either an autograft or additional chemotherapy. The results for OS were similar in all groups at 4 years (allo-SCT 59%; auto-SCT 56%; chemotherapy 46%) but both transplant arms demonstrated an improvement in relapse risk and DFS. A subsequent trial from the same group (Suciu et al, 2003) has confirmed that, on a donor/no donor analysis, allogeneic transplantation is associated with an improved 4-year DFS (52% vs. 42%, \[P = 0.05\]) but no OS gain (58% vs. 51%, \[P = not significant\]). The only group to derive survival benefit in this small study were patients with an abnormal karyotype without favourable cytogenetic changes. In the Group Ouese Est Leucemies Aigues Myeloblastiques trial (Harrouseau et al, 1997), no survival advantage could be discerned for allografting patients aged 40 years or less with AML in CR1 from matched family donors.

In most intention-to-treat studies of allo-SCT there is a significant attrition of patients in the donor arm who fail to receive a SCT and this makes the analysis of the impact of a transplant difficult (Frassoni, 2000). There is little evidence that patients who receive an allogeneic transplant benefit from intensive pretransplant consolidation treatment (Tallman et al, 2000) and transplant-related toxicity might be reduced by earlier transplantation.

If a matched sibling donor is not available closely matched donors can be established through the donor registries (http://www.bmdw.org). The results of unrelated donor SCT (UD-SCT) are inferior to those from matched siblings because of increased graft-versus-host disease and graft failure (Szydlo et al, 1997) although it is hoped that, with high-resolution HLA typing, the results may improve. Unrelated donor allografting should be restricted to those with high-risk disease in first remission and patients in second remission.

**Transplantation in relapsed and refractory disease**

Stem cell transplantation represents a potentially curative strategy in relapsed disease although patients, particularly with ‘good risk’ cytogenetics and a CR1 duration longer than 24 months, can achieve durable second remissions using chemotherapy alone (Gale et al, 1996).

While auto-SCT may produce long-term DFS the majority of autografted patients relapse and allo-SCT using a sibling donor remains the most effective transplant option in eligible patients. There are fewer data to suggest outcome is improved with an UD-SCT as there are no randomised trials and potential biases in non-randomised studies hinder the interpretation of the results (Burnett et al, 2004a).

Long-term DFS rates of 30–40% have been reported in patients with AML in second CR who undergo an allo-SCT from an HLA-identical sibling donor (Gale et al, 1996). While most centres restrict allo-SCT to patients who are in second CR, data from Seattle suggest that equivalent results may be obtained if patients are allografted in early first relapse (Clift et al, 1992). However, arranging a transplant at such short notice in all but indolent relapses limits the usefulness of this approach. Patients who achieve a second CR with chemotherapy should proceed to SCT. There is no evidence that additional cycles of chemotherapy improve outcome. The majority of sibling allografts are performed using mobilised peripheral blood stem cells, which appear to improve outcome and lower TRM in patients with advanced acute leukaemia (Bensinger et al, 2001). Patients under the age of 45 years who lack an HLA-identical sibling are candidates for allografting using an UD-SCT and long-term DFS rates in excess of 30% have been reported (Sierra et al, 2000).

In patients who have failed to respond to two courses of induction chemotherapy, transplantation using a myeloablative conditioning regimen is associated with long-term DFS rates in the region of 20–30% (Fung et al, 2003).

Auto-SCT has the capacity to produce durable second remissions in 25–30% of patients with relapsed AML who achieve a second CR but its low TRM is offset by a high relapse rate (Meloni et al, 1996; Tomas et al, 1996). Autografting is currently restricted to older patients (in whom a myeloablative allograft is precluded), patients with APL in second molecular...
remission and younger AML patients lacking a sibling or matched unrelated donor.

8.1. Reduced-intensity conditioning allografts

There are limited data on reduced-intensity conditioning (RIC) schedules in AML. In general, the follow up has been short and the patients heterogeneous. This procedure has frequently been reserved for older patients (Sayer et al, 2003; Taussig et al, 2003; Wong et al, 2003). In these patients TRM varied from 6% to 53% with 1 year actuarial survival and event-free survival being about 70% and 50% respectively. The role of RIC regimens in the management of AML remains to be established.

8.2. Haplo-identical transplants

The reports (reviewed by Reisner et al, 2003) that massive doses of donor CD34 cells and T-cell depletion could overcome host-versus-graft immunity and generate full-donor chimaeraism have generated interest in haplo-identical transplants. The conditioning schedules employed are profoundly immunosuppressive and patients require detailed surveillance post-transplant. The best results have been reported from Perugia (Aversa et al, 1998, 2002). In a very high-risk group of patients there was 98% engraftment. For patients with AML in CR at the time of transplant, the probability of event-free survival was 60% and was much better (70% vs. 7%) for those demonstrating donor versus recipient natural killer cell allo-reactivity.

8.3. T-cell depletion

T-cell depletion can control graft-versus-host disease and reduce the TRM but the loss of a graft-versus-leukaemia (GVL) effect considerably increases the risk of disease relapse. In AML there is less evidence of a prominent GVL effect and good results with improved quality of life (QoL) have been demonstrated in a number of studies employing T-cell depletion (Papadopoulos et al, 1998; Bunjes, 2001; Kroger et al, 2002).

8.4. Quality of life issues

For most patients in first remission the gains from transplantation are likely to be small. BMT is associated with increased treatment-related mortality and co-morbidity and a high cost for remedial treatments for side effects.

Two cross-sectional QoL studies (Zittoun et al, 1997; Watson et al, 1999, 2004), undertaken within randomised controlled trials, have confirmed that there is higher risk of long-lasting impairment of QoL after BMT. In these studies there was a consistent ranking of the treatment effect on QoL. Both BMT groups had greater impairment than patients treated with chemotherapy alone, and those receiving allo-BMT had worse QoL than those with autologous BMT.

Areas of QoL affected were physical, social functioning, global health, fatigue and infection. There was a severe adverse impact on sexual functioning and fertility in the BMT group.

Recommendations

1 Patients should be fully informed of both the advantages and disadvantages of the available treatments, and of the strategies that can be used to treat long-term side effects, particularly in the area of sexual function and infertility.

2 Intensive consolidation chemotherapy treatment during CR1 should be offered as the preferred treatment to patients with favourable cytogenetics and to those unwilling to accept the risk of permanent damage to their sexual health and fertility, with BMT remaining as the choice for salvage treatment in the event of relapse.

3 All patients of childbearing years undergoing BMT should be offered the opportunity of preserving their fertility (where possible) prior to treatment.

4 Allogeneic transplantation should be offered to patients with high-risk AML (risk groups are defined in Table II) in first remission who have an HLA-identical donor, although it is accepted that only a minority of patients will benefit (recommendation grade B; evidence level III).

5 Standard-risk patients may be offered allo-transplantation as part of a clinical trial (recommendation grade B; evidence level III).

6 Older patients with high-risk disease or beyond first remission may be offered a reduced-intensity conditioned transplant but this should be in the context of a clinical trial (recommendation grade C; evidence level IV).

7 Younger high-risk patients or those beyond first remission may be considered for a haplo-identical transplant but this should be in the context of a clinical trial (recommendation grade C; evidence level IV).

8 The role of autografting in the management of AML is contentious. Autografting should only be carried out in a clinical trial (recommendation grade A; evidence level Ib).

9. Acute myeloid leukaemia in the elderly

The median age at diagnosis of patients with AML is approximately 65 years; in the UK around 70% of patients presenting with AML are over the age of 60 years (Cartwright et al, 1990). The reclassification by the WHO of refractory anaemia with excess blasts in transformation as AML means that the incidence of AML will be even higher. These older patients have a poorer prognosis, more unfavourable cytogenetic abnormalities, higher incidence of secondary leukaemia...
and increased frequency of overexpression of multidrug resistance (MDR) phenotypes (Leith et al, 1997; Grimwade et al, 2001). There is an increased resistance to chemotherapy, increased treatment-related complications and an inferior outcome. As a result, older patients require different treatment approaches that take into account the features of the disease, the performance status and co-morbidities of the patient, as well as patient preference.

For the purposes of this guideline, we will define elderly as over the age of 60–65 years. However, it is important to consider the physiological age of the patient and the existence of co-morbidities that permit some flexibility over the age cutoffs. Options for management of these patients are:

- standard chemotherapy (e.g. daunorubicin + cytosine arabinoside 3 + 7);
- non-intensive (palliative) treatment;
- investigational treatments.

9.1. Standard chemotherapy

Overall, the results of standard chemotherapy in elderly patients are poor and such patients are progressively under-represented in clinical trials. CR rates are about 60%, but remissions are short with median survival being 5–10 months, and the probability of remaining in remission 3 years after diagnosis is <10% (Baudard et al, 1994; Stone et al, 1995; Goldstone et al, 2001).

Standard remission induction therapy should be considered for those with the following features: relatively young age (60–70 years), good performance status (WHO grade 0–2), white cell count <100 x 10⁹/l (Goldstone et al, 2001), normal organ function, de novo presentation, lack of unfavourable cytogenetic abnormalities and lack of MDR gene expression (Leith et al, 1997).

There have been few randomised studies comparing intensive with non-intensive chemotherapy. An EORTC randomised trial (Lowenberg et al, 1989) showed that elderly patients with good performance status and preserved organ function had improved survival following intensive therapy and also required less hospitalisation than those receiving supportive care. A trend towards improved survival was also seen in another study (Tilly et al, 1990) in which patients aged 65 years and over were randomised to receive intensive therapy or low-dose cytarabine.

Attempts have been made to improve induction chemotherapy by either reducing its intensity or substituting mitoxantrone or idarubicin for daunorubicin. In the UK MRC AML 9 study, patients were randomised to receive DAT in a 1 + 5 or a standard 3 + 10 regimen: patients receiving DAT 1 + 5 were less likely to achieve CR, and required more time in hospital and more blood product support (Rees et al, 1996). An EORTC study (Lowenberg et al, 1998) randomised patients over 60 years of age to mitoxantrone and cytarabine or daunorubicin and cytarabine induction chemotherapy; although CR rates were improved in patients receiving mitoxantrone, there was no difference in RFS or OS. A meta-analysis of trials comparing idarubicin with daunorubicin has similarly failed to demonstrate a survival advantage with this agent (AML Collaborative Group, 1998). The MRC AML 11 study (Goldstone et al, 2001) randomised 1314 patients to receive DAT (daunomycin, cytarabine and 6-thioguanine) 3 + 10, ADE or mitoxantrone and cytarabine (MAC) as induction chemotherapy: the remission rate in the DAT arm was significantly better than for either ADE or MAC, although there were no differences with respect to OS at 5 years. A SWOG randomised study demonstrated no improvement in outcome when mitoxantrone and etoposide were compared with daunorubicin and cytosine arabinoside in AML arising in this age group (Anderson et al, 2002).

The role of MDR modulators is unclear although MDR expression is more prevalent. A study examining the role of PSC-833, a ciclosporin analogue with MDR-blocking activity, was stopped prematurely due to an unexpectedly high death rate in the PSC-833 arm (Baer et al, 2002).

Haemopoietic growth factors, G-CSF and granulocyte–macrophage CSF (GM-CSF) reduce the duration of hospitalisation and febrile episodes after induction therapy but have no effects on CR rate, CR duration or OS (Rowe et al, 1995; Lowenberg et al, 1997a,b; Goldstone et al, 2001).

The optimal postremission therapy remains unclear as there is no benefit from high-dose cytosine arabinoside-containing consolidation regimens (Stone et al, 2001). In the EORTC/ HOVON study (Lowenberg et al, 1998) patients attaining CR received one further course of the drugs used for induction and were then randomised to receive low-dose cytosine arabinoside or no further treatment: there was a marginal improvement in DFS for those given low-dose cytarabine, but no difference in OS.

There does not seem to be a role for extended consolidation treatment (Goldstone et al, 2001) or for maintenance with either low-intensity chemotherapy (Rees et al, 1996) or interferon (Goldstone et al, 2001).

Aggressive salvage chemotherapy is seldom appropriate for elderly patients unless the patient has good performance status and has had a prolonged first remission. In a recent phase II study (Sievers et al, 2001) of 142 patients with relapsed AML, GO was infused at a dose of 9 mg/m² on days 1 and 14: the overall response rate was 30%, with half of these patients achieving standard CR. However, caution must be exercised following reports of cases of veno-occlusive disease in treated patients (Giles et al, 2001).

Recommendations

1 For patients in whom intensive chemotherapy is deemed justified (e.g. age < 70 years, good performance status, white cell count <100 x 10⁹/l), no adverse cytogenetic abnormalities or MDR expression), standard induction chemotherapy with daunorubicin (or an equivalent
anthracycline) for 3 d plus cytarabine for 7–10 d is recommended (grade A recommendation, level Ib evidence). Where possible patients should be entered into clinical trials.

2 There is no firm evidence to date to support the use of MDR-blocking agents as an adjunct to induction chemotherapy (grade A recommendation, level Ib evidence).

3 Similarly there is insufficient evidence to support routine use of G-CSF or GM-CSF with induction chemotherapy in patients over 60 years of age, although this may be appropriate if it is desirable to reduce hospitalisation or antibiotic usage (grade A recommendation, level Ib evidence).

4 The optimal postremission chemotherapy for older adult patients with AML remains unclear. There does not seem to be a role for extended consolidation chemotherapy or maintenance treatment (grade A recommendation, level Ib evidence).

5 GO shows promise as a salvage agent in patients with relapsed disease, and may be preferable to further intensive chemotherapy in this setting (grade B recommendation, level Ib evidence).

9.2. Non-intensive (palliative) chemotherapy

The aim of treatment is to control the white blood cell count whilst minimising hospitalisation and providing the best QoL. Low-dose cytarabine has been widely used (Cheson & Simon, 1987; Powell et al, 1989; Detourmignies et al, 1993), but potentially useful oral agents include hydroxyurea, 6-mercaptopurine and etoposide. The LRF AML 14 trial has shown a highly significant survival benefit for low-dose cytarabine, with no excess toxicity or supportive care requirements compared with hydroxyurea (Burnett et al, 2004b). While not curative, this treatment should now be considered the standard against which to evaluate new treatments.

Recommendations

1 Unless patients opting for palliative chemotherapy are entered into clinical trials, treatment should be offered with low-dose cytarabine (grade A; level Ib evidence).

10. Conclusions

Acute myeloid leukaemia is a complex group of disorders with an expanding range of potential therapies. It requires specialist care provided within the context of an experienced multidisciplinary team. Patients should be treated, wherever possible, within an appropriate clinical trial. Outcomes have been steadily improving over the last two or three decades. There has been an increasing understanding of the risk factors that influence outcome. New therapeutic options will become available in the next few years including both new cytotoxic agents, e.g. clofarabine, and targeted agents, e.g. FLT-3 antagonists; with the introduction of an expanding range of molecular markers to enhance risk stratification and increasing use of MRD monitoring, they are likely to herald a new era involving a more tailored approach to the treatment of AML.

Disclaimer

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References


Guideline


Appendix 1

Classification of evidence levels

Ia. Evidence obtained from meta-analysis of randomised controlled trials.

Ib. Evidence obtained from at least one randomised controlled trial.

IIa. Evidence obtained from at least one other type of well-designed controlled study without randomisation.

IIb. Evidence obtained from at least one other type of well-designed quasi-experimental study.

III. Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlational studies and case studies.
IV. Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Classification of grades of recommendations

A. Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing specific recommendation (evidence levels Ia and Ib).

B. Requires the availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation (evidence levels IIa, IIb and III).

C. Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality (evidence level IV).