Acute myeloid leukaemia in adults
Felicetto Ferrara, Charles A Schiffer

Introduction
Acute myeloid leukaemia is a clonal disorder of haemopoietic stem cells characterised by the inhibition of differentiation and the subsequent accumulation of cells at various stages of incomplete maturation, and by reduced production of healthy haemopoietic elements. Cytoptenias cause clinical manifestations, with symptoms of anaemia (eg, fatigue and dyspnoea), neutropenia (infections), and thrombocytopenia (haemorrhage), which are usually present at the time of diagnosis and are dominant throughout treatment. How growing leukaemic clones suppress normal polyclonal residual haemopoiesis is poorly understood, but this suppression is partly protective against the cytotoxic effects of chemotherapy because normal blood counts are regenerated when the leukaemia clone is reduced.

Clinical and genetic features
Acute myeloid leukaemia can occur in people of all ages, but is most common in older patients (older than 65 years). It can be caused by exposure to ionising radiation and drugs that damage DNA; a clear history of contact with known carcinogens in patients is unusual. Two types of chemotherapy-related acute myeloid leukaemia exist. Drugs that target topoisomerase II, such as anthracyclines and epipodophyllotoxins, can cause patients to develop rapidly proliferative disease with a monocytic histology and cytogenetic abnormalities at the MLL gene locus at chromosome 11q23, within months to 2 years of treatment.1 More common is the so-called alkylator agent-induced disease occurring 5–6 years after exposure, characterised by a myelodysplastic prodrome with complex karyotypes and deletions in chromosomes 5 and 7.2 Notably, these changes and clinical course are more often seen in older patients, suggesting that, as yet unquantifiable, repeated exposure to environmental carcinogens could contribute to acute myeloid leukaemia in these patients.

How these distinct types and other cancers develop is poorly understood. The contribution of inherited polymorphisms to metabolism of different toxins and repair of DNA is under investigation.1 In vitro and preclinical models have shown that a multistep series of mutations are needed to produce acute myeloid leukaemia. Leukaemogenesis needs, at a minimum, activating mutations in class I genes that stimulate signal transduction pathways and induce cellular proliferation, in conjunction with mutations in class II genes that affect transcription factors and compromise normal differentiation.3 4 Mutations leading to activation of the receptor tyrosine kinase FLT3, KIT, and RAS signalling pathway belong to class I mutations. RUNXI/ETO, CBFβ/MYH11, and PML/RARα, which are fusion transcripts generated by well known recurring chromosomal abnormalities such as t(8;21), inv(16), and t(15;17), respectively, are examples of class II mutations.4 Likewise, mutations of the transcription factors RUNX1, CEBPα, and MLL fall in this group (table 1). A third class of genes encoding epigenetic modifiers, including, but not limited to, DNMT3A, IDH1, IDH2, TET2, ASXL1, and EZH2, have a major role in pathogenesis, although the mechanisms by which these aberrations contribute to the leukaemia phenotype are poorly understood. Most of these abnormalities are associated with a worse patient outcome and are frequent in older patients.5

Acute myeloid leukaemia is a clinically and biologically heterogeneous disease with distinct clinical presentations.

Search strategy and selection criteria
We searched Medline for articles published in English from Jan 1, 2007 to Oct 30, 2012, using the search terms “acute myeloid leukaemia”, “prognostic factors”, “pathogenesis”, “epidemiology”, and “treatment”. Relevant references published before the search period were also included and references from relevant articles were also searched. Review articles and book chapters are cited to provide readers with more details and more references than this Seminar has room for.

Reference
Lancet 2013; 381: 484–95
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in different morphological and cytogenetic subtypes. Molecular analyses have expanded our understanding of this heterogeneity and have the potential to point to new directions for treatment. Although morphological appearance is much the same for most leukaemic blasts in individual patients, only about 0.5% of these cells with an immature CD34+, CD38– immunophenotype are clonogenic with the potential for repetitive colony formation in vitro and the ability to establish leukaemia when transplanted into immunodeficient mice. More recently, studies have shown that many subclones with different patterns of molecular abnormalities are present at diagnosis, and that different subclones might become predominant under the selective pressure of serial chemotherapy treatments. The heterogeneity of leukaemia cells in individual patients has implications for the use and development of treatments that specifically affect the products of these gene mutations. This heterogeneity in the so-called leukaemia stem cells could also complicate the targeting of these progenitors with specific antibodies or drugs.

### Cytogenetics and molecular genetics

The importance of cytogenetic findings related to initial response and long-term cure rate was identified in the 1980s and supported by large collaborative groups (table 1). Patients with core binding factor acute myeloid leukaemia, including t(8;21) and abn16q22, have cure rates of over 60% with high-dose cytarabine-based chemotherapy alone, whereas those with other balanced translocations such as t(6;9) and abnormalities of chromosome 3q26, have very poor outcomes after chemotherapy. Major change in chromosome number, termed monosomal karyotype, is another distinctly unfavourable marker even in patients who receive allogeic stem-cell transplantation. Nevertheless, the mechanisms by which drug resistance or sensitivity is produced remain poorly understood. Many collaborative groups have suggested risk classifications according to karyotype.

<table>
<thead>
<tr>
<th>French, American, and British morphology</th>
<th>Affected genes</th>
<th>Typical average age (years)</th>
<th>Approximate incidence in de-novo AML</th>
<th>Outlook</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(8;21) M2</td>
<td>RUNX1/RUNX1T1</td>
<td>30</td>
<td>5-7%</td>
<td>Favourable</td>
<td>Auer rods usually present</td>
</tr>
<tr>
<td>t(15;17) M3</td>
<td>PML/RARA</td>
<td>40</td>
<td>5-8%</td>
<td>Favourable high cure rate with all-transretinoic acid-based therapy</td>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td>t(11;17) Similar to M3</td>
<td>ZBTB16/RARA</td>
<td>Unknown</td>
<td>&lt;1%</td>
<td>Poor response to all-transretinoic acid-based treatment</td>
<td></td>
</tr>
<tr>
<td>abn(16q22) M4 with eosinophilia</td>
<td>CBFB/MYH11</td>
<td>35-40</td>
<td>5%</td>
<td>Favourable</td>
<td>High reinduction rate post relapse</td>
</tr>
<tr>
<td>abn(11q23) M5</td>
<td>MLL and many partners</td>
<td>&gt;50</td>
<td>3%</td>
<td>Poor, except t(9;11)</td>
<td>Hyperleucocytosis and extramedullary disease</td>
</tr>
<tr>
<td>+8</td>
<td>Varied</td>
<td>&gt;60</td>
<td>About 3% if +8 alone</td>
<td>Poor</td>
<td>Often associated with other chromosomal additions and deletions</td>
</tr>
<tr>
<td>del 5, del 7, 5q-, 7q, or combinations</td>
<td>Varied, common in M6</td>
<td>&gt;60</td>
<td>15-20%</td>
<td>Poor</td>
<td>Common in patients with secondary acute myeloid leukaemia and prior myelodysplastic syndrome</td>
</tr>
<tr>
<td>inv 3</td>
<td>Abnormal megakaryocytes</td>
<td>Unknown</td>
<td>&lt;1%</td>
<td>Poor</td>
<td>Increased platelet count; other abnormalities common (del 5,7)</td>
</tr>
<tr>
<td>abn(p12)</td>
<td>Varied</td>
<td>TPS3</td>
<td>Probably &gt;60</td>
<td>5%</td>
<td>Poor</td>
</tr>
<tr>
<td>+13</td>
<td>Varied, sometimes undifferentiated</td>
<td>--</td>
<td>Probably &gt;60</td>
<td>About 1-2%</td>
<td>Poor</td>
</tr>
<tr>
<td>t(6;9)(p2;q34) M2/M4 with basophilia</td>
<td>DEK/NUP214</td>
<td>Unknown</td>
<td>&lt;1%</td>
<td>Poor</td>
<td>Prominent basophilia</td>
</tr>
<tr>
<td>t(9;22)</td>
<td>Usually M1</td>
<td>BCR/ABL1</td>
<td>Probably &gt;50</td>
<td>About 1%</td>
<td>Poor</td>
</tr>
<tr>
<td>t(1;22)</td>
<td>Often M7</td>
<td>RBM15/MKX1</td>
<td>Infants (aged 0-2 years)</td>
<td>&lt;1%</td>
<td>Poor</td>
</tr>
<tr>
<td>t(8;16)</td>
<td>M4 and M5</td>
<td>KAT6A/CREBBP</td>
<td>Unknown</td>
<td>&lt;1%</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Table 1: Cytogenetic abnormalities in acute myeloid leukaemia

Adapted with permission from PMPH USA.
shown that overexpression of Table 2: Molecular markers in acute myeloid leukaemia needed to assess the individual miRNA families and their interactions with other mutations.40–42 Some studies have Changes of miRNAs 15, 16, 155, and 181 among others, have been reported. The prognostic effect varies and studies are confi rmation. AML=acute myeloid leukaemia. CN AML=cytogenetically normal acute myeloid leukaemia. ITD=internal tandem duplication. TKD=tyrosine kinase domain. APL=acute promyelocytic leukaemia.

<table>
<thead>
<tr>
<th>Approximate frequency in de-novo AML.</th>
<th>Frequency in CN AML</th>
<th>Strong associations</th>
<th>Not recorded with</th>
<th>Outlook</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPM1</td>
<td>35%</td>
<td>50%</td>
<td>CN AML, FLT3-ITD, FLT3-TKD, DNMT3A, IDH1, IDH2</td>
<td>CEBPA double mutant</td>
</tr>
<tr>
<td>CEBPA</td>
<td>7%</td>
<td>8–19%</td>
<td>CN AML, FLT3-ITD</td>
<td>NPM1</td>
</tr>
<tr>
<td>FLT3-ITD</td>
<td>20–25%</td>
<td>30–35%</td>
<td>CN AML, APL, i(6,9), NPM1</td>
<td>Adverse in patients with CN AML; could vary with allelic burden; no clear effect in patients with APL20–24</td>
</tr>
<tr>
<td>FLT3-TKD</td>
<td>5%</td>
<td>14%</td>
<td>CN AML, NPM1</td>
<td>--</td>
</tr>
<tr>
<td>KIT</td>
<td>...</td>
<td>25%</td>
<td>Core binding factor leukaemias</td>
<td>Most other karyotypes</td>
</tr>
<tr>
<td>TET2</td>
<td>8–12%</td>
<td>23%</td>
<td>Possibly CN AML</td>
<td>IDH1, IDH2</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>14–22%</td>
<td>20–33%</td>
<td>CN AML, NPM1, FLT3</td>
<td>Core binding factor leukaemias, CEBPA, MLL translocations</td>
</tr>
<tr>
<td>IDH1, IDH2</td>
<td>8–16%</td>
<td>30%</td>
<td>CN AML, NPM1, FLT3</td>
<td>TET2, WT1</td>
</tr>
<tr>
<td>ASXL1</td>
<td>5–30%</td>
<td>About 10%</td>
<td>Uncommon with NPM1 and FLT3</td>
<td>Possibly CEBPA</td>
</tr>
</tbody>
</table>

Changes of miRNAs 15, 16, 155, and 181 among others, have been reported. The prognostic effect varies and studies are needed to assess the individual miRNA families and their interactions with other mutations.21 Some studies have shown that overexpression of BIALC,4–6 NPM1,14 and ERG6 genes is associated with poorer outcomes, but needs in confirmation. AML=acute myeloid leukaemia. CN AML=cytogenetically normal acute myeloid leukaemia. ITD=internal tandem duplication. TKD=tyrosine kinase domain. APL=acute promyelocytic leukaemia.

Table 2: Molecular markers in acute myeloid leukaemia

most recent revisions provided by the WHO and the European LeukaemiaNet.20,21 However, outcomes vary considerably within groups of patients with identical karyotypes, raising the question of whether additional abnormalities predictive of outcome could be identified. Additionally, the prognostic value of cytogenetic aberrations such as +8, 7q-, i(8;16), or +13 remains unclear, but some reports suggest a very poor prognosis for patients with abn(17p).18

Advent in molecular genetics initially focused on the characterisation of the heterogeneous group of patients with normal karyotypes (ie, the majority of patients with acute myeloid leukaemia). Molecular biological techniques identified many mutations, alone or in combination, in these patients (table 2), and mutations in the NPM1 and FLT3 genes are now routinely tested for. Although patients with NPM1 mutations have an improved outcome with chemotherapy alone, mutations in FLT3, which lead to constitutive receptor activation, dysregulation of FLT3 signal transduction pathways, and stimulation of cell proliferation, are associated with a worse prognosis, with a larger negative effect if the mutations are homozygous.45–50 In combination (ie, NPM1 and FLT3 mutated), FLT3 mutations cancel out the better effects of NPM1 and the outcome is poorer than when NPM1 is mutated and FLT3 is germline.27,11,12 Several other mutations have been identified (table 2); however, the prognostic effect of many of these findings is uncertain, with discrepant results reported by different groups. Although some mutations can be detected in combination with two or three other mutations, thereby increasing the molecular heterogeneity, others are mutually exclusive, suggesting that in some patients, these single mutations might be essential drivers that could be targets for treatment.13–15 Other mutations or abnormal recurrent patterns of gene expression will probably be detected with whole-genome sequencing of leukaemia cells and studies of the less differentiated stem-cell subpopulation.33 The challenge, as was originally presented by the discovery of recurrent chromosomal abnormalities, will be to elucidate the mechanisms by which these changes affect the response to treatment and to develop more rational, individualised treatments. These aims might be difficult to achieve because changes in patterns of microRNA expression46,47 and epigenetic modification of gene expression38,49,50 also contribute to the AML phenotype.51

Treatment

Advanced age and the presence of comorbidities, which are often summarised as performance status, affect a patient’s ability to survive the side-effects of intensive chemotherapy.15 Several existing comorbidity indices are able to reliably quantify the presence and effect of other medical and psychosocial factors, helping to guide treatment decisions and comparisons across clinical trials that focus on high-risk older patients.51,52 Major advances in supportive care have taken place, including widespread availability of high-quality platelet transfusions,62 improved and less toxic broad-spectrum antibiotics and antiviral drugs, elimination of post-transfusion hepatitis, and new antifungal agents.63 Perhaps less appreciated are the salutary effects of improved antiemetics, so that patients no longer develop erosive esophagitis and inanition from poor nutrition. The 30-day mortality of older patients entered on clinical trials with intensive chemotherapy is now less than 10%,64 largely related to improved supportive care, although it must be acknowledged that patients entered on clinical trials are a highly selected population.65,66

Conventional treatment for acute myeloid leukaemia has two phases—induction and consolidation, which includes stem-cell transplantation (table 3). The aim of induction is to achieve complete remission (CR) whereas consolidation is designed to eliminate residual leukaemia cells that persist after induction. CR is defined as bone marrow blasts less than 5% in a normocellular bone marrow, absence of extramedullary leukaemia, neutrophil count greater than 1000/μL, and a platelet count greater than 100 000/μL.67 In addition, the patient should be
transfusion independent. These criteria of morphological CR define response to induction treatment in routine practice; however, more sensitive technologies with flow cytometry and PCR can quantify much lower amounts of leukaemic burden, beyond the sensitivity of the light microscope. As a result, CR definitions will continue to evolve and, if shown to correlate with clinical outcome, could be used in future clinical trials.

After induction, some patients can achieve reduction of marrow blasts to less than 5%, but their neutrophil or platelet count, or both, might not reach 1000/μL and 100 000/μL, respectively. In these cases, response is defined as CR with incomplete haematological recovery and the outcome is generally poorer than in patients achieving CR. More than 30 years after its introduction, the combination of an anthracycline, usually daunorubicin, given for 3 days with continuous infusion of cytarabine for 7 days (3+7) is still the standard induction regimen. CR rates of patients given 3+7 are about 70% in patients younger than 60. Numerous trials have been done to improve the rate and quality of CR, including the use of anthracyclines other than daunorubicin (eg, idarubicin hydrochloride and mitoxantrone), the addition of a third drug (usually etoposide), use of high-dose instead of conventional dose cytarabine, and the use of haemopoietic growth factors such as granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor, and the combination of anthracyclines with fludarabine phosphate or cladribine and intermediate-dose cytarabine. Overall, results have been disappointing, in that they have failed to show important and consistent improvements in outcome, although a recent trial from the Polish Adult Leukaemia Group showed higher CR rates and possibly improved overall survival with the addition of cladribine to daunorubicin (60 mg/m²) and cytarabine in patients older than 60 years; no benefit was seen when fludarabine was added to the 3+7 regimen. The greatest difference was in patients older than 50 years and in those with unfavourable karyotypes; whether these findings can be reproduced, perhaps in older patients, is important to investigate.

The benefits of these manipulations could be restricted to genetically distinct subgroups of acute myeloid leukaemia that could not be assessed in older clinical trials. A trial from the UK Medical Research Council AML group showed that the addition of gemtuzumab ozogamicin, an anti-CD33 monoclonal antibody conjugated with calicheamicin (a cytotoxic antineoplastic antibiotic), to chemotherapy produces major clinical improvement in patients with core binding factor acute myeloid leukaemia, and a possible advantage in those with intermediate cytogenetics. Two further studies in older patients with AML, given gemtuzumab ozogamicin, showed a survival advantage in those with intermediate, but not adverse karyotypes. A major challenge to the stratification of patients by their biological characteristics when assessing new induction drugs is that the diagnosis of acute myeloid leukaemia is generally regarded as a medical emergency that requires immediate treatment. However, apart from patients with hyperleucocytosis, who could be considered for leucapheresis or hydroxyurea, many groups have shown that it is feasible to select specific induction treatment for patients according to molecular subtyping, which could become the standard for future clinical trials.

So far, FLT3 is the only mutation that can be pharmacologically targeted, and several inhibitors are being assessed clinically. Inhibitors such as midostaurin and lestaurtinib can be combined with chemotherapy, and trials in newly diagnosed patients assessing standard chemotherapy with or without these inhibitors are in progress. One randomised trial with lestaurtinib in patients with first relapse showed no improvement, perhaps because the target was not wholly inhibited as a result of pharmacokinetic problems. Other FLT3 inhibitors are under investigation.

### Table 3: Treatments of acute myeloid leukaemia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>Daunorubicin (or idarubicin) plus cytarabine 3+7 regimen remains the standard treatment for adults of all ages; analyses of the possible benefit of the addition of gemtuzumab ozogamicin in AML subgroups, including young patients with CBF leukaemia and older patients with intermediate karyotype are in progress.</td>
</tr>
<tr>
<td>Consolidation</td>
<td>High-dose or intermediate-dose cytarabine Intermediate or high dose cytarabine for patients who are candidates for stem-cell transplantation; high-dose cytarabine of most benefit for patients with CBF AML</td>
</tr>
<tr>
<td>Allogeneic stem-cell transplantation</td>
<td>Consider for patients with intermediate karyotype, except those with NPM1 mutation in the absence of FLT3 internal tandem duplication and in all patients with unfavourable karyotypes. Consider reduced intensity conditioning for selected older patients</td>
</tr>
<tr>
<td>Autologous stem-cell transplantation</td>
<td>Consider for patients with CBF AML and NPM1 mutated/FLT3 germ line Useful discipline for investigation of new conditioning regimens; no proven benefit compared with high-dose cytarabine in randomised trials; might be interesting to assess in patients without evidence of minimal residual disease.</td>
</tr>
</tbody>
</table>

3+7=anthracycline for 3 days with continuous infusion of cytarabine for 7 days. AML=acute myeloid leukaemia. CBF AML=core binding factor acute myeloid leukaemia. Older than 60 years of age.
Trials have also addressed the optimum dose of daunorubicin in induction therapy. A trial from the USA in younger patients (aged 17–60 years), showed an advantage in those given 90 mg/m² compared with 45 mg/m², particularly in the heterogeneous group with intermediate-risk cytogenetics. This study has been criticised because the control group had an unusually low CR rate (54%), but because toxicity was much the same in the two groups, many institutions now use the 90 mg/m² dose. Others believe that outside a clinical trial, a daunorubicin dose of 60 mg/m² for 3 days would be reasonable. A trial of similar design to the USA trial has shown that 90 mg/m² is well tolerated and more effective in selected older patients with core binding factor acute myeloid leukaemia and in those aged 60–65 years. Some groups use so-called double induction, in which a second course of induction treatment is given on day 14 of treatment, irrespective of marrow status. The attending physician must judge the eligibility of a patient for second induction because nearly all patients are severely pancytopenic and can have fever or infections. About 80% of younger patients can tolerate double induction and a reasonable study might be to assess double induction, specifically in patients with persistent leukaemia, after morphological and flow cytometric bone-marrow examination.

After achievement of CR, all patients will eventually relapse without further treatment and thus consolidation treatment is essential (with the ultimate goal of cure), provided that patients have adequate organ function. In 1994, the Cancer and Leukemia Group B (CALGB) group randomised 596 patients to receive four cycles of high-dose cytarabine (3 g/m² every 12 h over 3 days) or four courses of intermediate-dose (400 mg/m²) or standard-dose (100 mg/m²) cytarabine. A survival advantage was seen in patients up to age 60 years who received high-dose cytarabine with long-term relapse-free survival of about 45%. Subsequent analysis showed greatest clinical benefit in patients with favourable cytogenetics, and no substantial improvement in those with high-risk cytogenetic subtypes. Similar overall survival rates have been reported by many groups with various high-dose cytarabine-based regimens, sometimes with the addition of other drugs. Optimum dose and number of cycles have not been definitively established, although three cycles of intermediate doses of cytarabine (1·5 g/m²) reduces toxicity without worsening treatment outcome, suggesting that this dose is reasonable for routine practice.

Clinical trials and registry data strongly suggest that much lower relapse rates occur after allogeneic stem-cell transplantation than autologous stem-cell transplantation or chemotherapy, because of the graft-versus-leukaemia effect. However, allogeneic stem-cell transplantation has a treatment-related mortality of 10–25% because of graft-versus-host disease and substantial adverse effects on quality of life, such that randomised trials have not shown a survival benefit from allogeneic stem-cell transplantation compared with chemotherapy in the overall population of acute myeloid leukaemia patients. However, most of these trials were based on matched sibling donor versus no-donor analysis, a methodology that is not straightforward, especially with the increasing use of transplants with matched unrelated donors, partly mismatched donors, and umbilical cord blood. Additionally, both morbidity and mortality after allogeneic stem-cell transplantation are falling in allogeneic settings.

The present aim of clinical research is to identify subgroups of patients who respond poorly to chemotherapy alone and who might benefit most from allogeneic stem-cell transplantation, with matched sibling or alternative donors. Presently, the consideration of allogeneic stem-cell transplantation is appropriate in patients with unfavourable cytogenetics and in those with intermediate karyotype, with the exception of those with NPM1 mutation in the absence of FLT3 mutation. Patients with core binding factor AML should receive high-dose cytarabine, apart from those with KIT mutations, who could be considered for stem-cell transplantation. Because there are no data from randomised or prospective trials, controversy exists about the negative effect of the additional KIT mutation, especially in children and younger adults. Additionally, the relapse rate post-allogeneic stem-cell transplantation is about twice as high in FLT3-mutated patients than in FLT3-negative patients and is also higher in patients with adverse karyotypes and those transplanted with minimal residual disease.

In the past 20 years, reduced-intensity conditioning regimens have been developed that induce graft-versus-leukaemia and limit non-haematological toxicity. The number of patients eligible for allogeneic stem-cell transplantation, including those previously excluded because of age or comorbidities, has consequently increased. Studies have shown reduced mortality compared with standard conditioning regimens, although some data suggest increased relapse rate. Although we have no definite criteria for the selection of patients for reduced-intensity conditioning regimens, older age and the presence of toxicities accumulated during induction and consolidation treatment are considerations. The role of high-dose treatment with autologous stem-cell transplantation support is unclear and the procedure is more popular in Europe than in the USA. Randomised trials have shown similar outcomes with autologous stem-cell transplantation compared with repeated courses of high-dose cytarabine, perhaps because of the presence of minimal residual disease, which might also contaminate the graft. Overall, autologous stem-cell transplantation represents an arena where new conditioning regimens and experimental post-transplant maintenance treatments should be investigated. Attempts have also been made to identify subgroups of patients who might benefit from an autologous approach, potentially leading
to a more individualised approach to consolidation treatment.106 Figure 1 shows a practical approach to acute myeloid leukaemia management, and figure 2 a typical survival curve of patients with intensively treated acute myeloid leukaemia.

**Acute promyelocytic leukaemia**

Acute promyelocytic leukaemia is a distinct subtype of AML with a unique morphology characterised by hypergranulated promyelocytes and the presence of a t(15;17) translocation that results in an abnormal fusion protein termed PML/RARα. It is clinically characterised by a severe haemorrhagic diathesis. It is sensitive to anthracyclines, and studies show that a combination of anthracyclines and all-trans retinoic acid is the best induction approach, achieving CR rates of over 90% and, with various consolidation approaches, cure rates of roughly 80%.107 All-trans retinoic acid was the first, and perhaps the only, example of remission induction caused by differentiation of the leukaemia clone to a post-mitotic state. Arsenic trioxide is perhaps now the most effective single agent drug108 and small trials without any chemotherapy, with combinations of all-trans retinoic acid and arsenic trioxide,109 or arsenic trioxide alone110 have shown very promising results and are being assessed in large multicentre studies. The biggest challenge now is to increase diagnostic awareness about this highly curable disease to reduce early mortality from haemorrhage by prompt initiation of all-trans retinoic acid.

**Acute myeloid leukaemia in older patients**

More than half of patients with AML are older than 65 years and about a third are older than 75 years. Generally, older patients with AML have a very poor outcome—conventional induction treatment results in CR rates of 45–55%, and less than 10% of intensively treated patients survive for 5 years, with no improvement in these results in the decades.111,112 Of note, these results are from multicentre trials based on aggressive treatment aimed at CR achievement, and do not take into account the substantial proportion of older patients with acute myeloid leukaemia who are given only best supportive care and periodic treatment with hydroxyurea to control peripheral white blood count.113,114 Poor outcome is related to concomitant comorbidities, which make chemotherapy and transplantation more toxic or impossible to give, and the increased incidence of adverse biological features such as unfavourable cytogenetics, and AML after a previously diagnosed (or sometimes unrecognised) blood disorder, particularly myelodysplasia. As a consequence, a common dilemma in daily practice is the identification of older patients who can tolerate aggressive therapy and potentially derive benefit should CR be achieved. Predictive scores, based on clinical and biological features are being developed, which could help physicians to inform patients about the risks and benefits of treatment options (table 4).115,116 These discussions can be very difficult, because

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**Table 4.** Risk factors for survival and outcome

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;65 years</td>
</tr>
<tr>
<td>Performance status</td>
<td>1</td>
</tr>
<tr>
<td>Total leukaemic blast count</td>
<td>&gt;30%</td>
</tr>
<tr>
<td>Extramedullary involvement</td>
<td>Yes</td>
</tr>
<tr>
<td>Molecular genetics</td>
<td>FIP1L1/ PDGFRA, t(9;22)</td>
</tr>
</tbody>
</table>

**Figure 1: Practical approaches to management of acute myeloid leukaemia**

3+7 = anthracycline for 3 days with continuous infusion of cytarabine for 7 days.

**Figure 2: Overall survival of intensively treated patients with acute myeloid leukaemia according to age**

Survival curve of 428 consecutive patients with acute myeloid leukaemia treated at Cardarelli Hospital in Naples with intensive chemotherapy, according to age. The difference is highly significant (p<0.001, log-rank test) and relates to present therapeutic results in acute myeloid leukaemia (40-45% cure up to the age of 65 years; 10-15% in older patients). Results are similar to those reported by other institutions or most collaborative groups.117,118
Treatment options for older patients with acute myeloid leukaemia

AML=acute myeloid leukaemia. CR=complete remission. CBF AML=core binding factor acute myeloid leukaemia.

Conventional intensive induction chemotherapy with the 3+7 regimen

<table>
<thead>
<tr>
<th>Comment</th>
<th>Feasibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy patients</td>
<td>About 60% of patients aged &gt;60 years</td>
</tr>
</tbody>
</table>

Post-remission therapy with conventional or intermediate-dose cytarabine

<table>
<thead>
<tr>
<th>Comment</th>
<th>Feasibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>No proven benefit from high-dose cytarabine except in older patients with CBF AML or NPM1-mutated AML</td>
<td>Most patients who achieve CR</td>
</tr>
</tbody>
</table>

Attenuated chemotherapy aimed at complete remission achievement and disease control

<table>
<thead>
<tr>
<th>Comment</th>
<th>Feasibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose cytarabine; hypomethylating agents, low effect in more proliferative AML</td>
<td>&gt;80%</td>
</tr>
</tbody>
</table>

Supportive care and hydroxyurea for the control of leucocytosis

<table>
<thead>
<tr>
<th>Comment</th>
<th>Feasibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider in frail patients (often difficult to define)</td>
<td>100%</td>
</tr>
</tbody>
</table>

Allogeneic (reduced intensity) stem-cell transplantation

<table>
<thead>
<tr>
<th>Comment</th>
<th>Feasibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients need to achieve complete remission; medically fit without organ damage after induction and consolidation; limitations of donor availability</td>
<td>5–10%</td>
</tr>
</tbody>
</table>

Autologous stem-cell transplantation

<table>
<thead>
<tr>
<th>Comment</th>
<th>Feasibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients need to achieve complete remission; medically fit without organ damage after induction and consolidation; possible issues with successful mobilisation of stem cells</td>
<td>20%</td>
</tr>
</tbody>
</table>

Investigational treatments

<table>
<thead>
<tr>
<th>Comment</th>
<th>Feasibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with unfavourable cytogenetics aged &gt;70 years, all patients with early relapse (first complete remission &lt;2 months)</td>
<td>&gt;80%</td>
</tr>
</tbody>
</table>

Table 4: Treatment options for older patients with acute myeloid leukaemia

A study in France added fractionated doses of gemtuzumab ozogamicin (3 mg/m² per day on days 1, 4, and 7) to standard chemotherapy and noted improved event-free survival, and to a lesser degree, overall survival in patients aged 50–70 years. In the UK AML 16 study, a dose of 3 mg/m² gemtuzumab ozogamicin was given on day one of induction chemotherapy and showed a small but significant overall survival benefit in patients without unacceptable increase in toxicity. In both studies, gemtuzumab ozogamicin showed no benefit in patients with unfavourable cytogenetics. Gemtuzumab ozogamicin is no longer available, but should it be reintroduced—further studies of dose, schedule, and its effects in different patient subgroups would be needed.

The role of consolidation in older patients is less clear and CALGB trials showed that high-dose cytarabine does not increase overall survival and is more toxic than lower doses of cytarabine. Although no standard consolidation regimen for older patients with acute myeloid leukaemia has been established, one or two cycles of intermediate-dose cytarabine or other combination chemotherapy could be considered. Notably, a randomised phase 3 study conducted by the Acute Leukaemia French Association that tested the benefit of high-dose chemotherapy consolidation course versus small-dose ambulatory chemotherapy courses, suggested that many lower intensity cycles could be equivalent to, or even better than a reduced number of intensive cycles.

Reduced intensity conditioning regimens allow some older patients to have allogeneic stem cell transplantation, and studies have shown outcome and complication rates similar to myeloablative stem-cell transplantation in young patients. However, because only older patients with a good outlook were considered for reduced intensity conditioning haemopoietic stem-cell transplantation, these results are not applicable to most older patients in first CR. To address this issue prospectively, two studies explored the feasibility of allogeneic stem-cell transplantation in large consecutive cohorts of older patients with acute myeloid leukaemia. In both studies, only 5% of patients had allogeneic stem-cell transplantation; difficulties included inability to achieve CR, toxicity after induction or consolidation chemotherapy, and problems with identifying donors because of older sibling age and early relapse. Autologous stem-cell transplantation with peripheral blood stem cells is feasible in older patients; however, it can be difficult to mobilise adequate numbers of stem cells.

Many elderly patients with AML cannot tolerate standard treatment and need attenuated treatment or supportive care only. Low-dose cytarabine is the prototype of attenuated chemotherapy, but can be associated with substantial haematological toxicity. A Medical Research Council trial for patients with AML who were unsuitable for intensive chemotherapy, randomised 217 patients to receive low-dose cytarabine or hydroxyurea with best supportive care. 13 of 71 (18%) patients given low-dose cytarabine treatment achieved CR compared with one patient receiving hydroxyurea. Survival was substantially longer in patients taking low-dose cytarabine, although survival advantage was not recorded in patients with adverse karyotype, in whom CR was never achieved. Therefore, low-dose cytarabine is inadequate in terms of benefit-to-risk ratio for frail patients and in those with unfavourable cytogenetics.

The potential role of epigenetics in the pathogenesis of myeloid cancers has prompted interest in novel treatments that modify gene expression. The DNA hypomethylating drugs, azacitidine and decitabine, are approved for the treatment of patients with myelodysplastic syndrome and are frequently used in acute myeloid leukaemia. CR rates are about 15–20%, but both drugs can produce substantial haematological improvement in these disorders. Changes in global hypomethylation occur, but whether these changes cause re-expression of previously methylated, silenced tumour.
suppressor genes, or whether responses might be mediated by their low-level cytotoxic effects is unknown. A post-hoc subgroup analysis of a 2010 randomised trial119 with azacitidine compared with best supportive care, low-dose cytarabine, and intensive chemotherapy, which suggested a survival advantage even in the absence of CR in a patient population that was less suitable than healthy patients for standard induction chemotherapy, is intriguing, but needs confirmation in a larger study.120 AML in elderly patients, at both diagnosis and relapse, can be a fairly indolent disease that might not need immediate treatment. Most studies with hypomethylating agents exclude patients with high blast counts and these agents have not been adequately studied in AML with more rapidly proliferative features. In such patients, the discussion should focus on the pros and cons of standard induction treatment.

Recurrence of acute myeloid leukaemia remains a major challenge. Different patterns of relapse can be distinguished, including haematological (most frequent), extramedullary, and molecular relapse.121 In patients with acute promyelocytic leukaemia, molecular relapse should be treated to prevent haematological relapse.122 Older age, unfavourable cytogenetics at presentation, a duration of first CR of less than 12–18 months, and previous stem-cell transplantation are major determinants of low second CR rate and survival.123 Nonetheless, prognosis is generally poor and allogeneic stem-cell transplantation should be offered after second or further CR has been achieved. Patients with a low bone marrow blast count at relapse could be considered for allogeneic stem-cell transplantation without salvage chemotherapy,124 which is usually based on high-dose or intermediate-dose cytarabine regimens. Older patients with unfavourable cytogenetics or a first CR of less than 12 months and young adults in early relapse after allogeneic stem-cell transplantation or in advanced relapse should be selected for investigational treatment, to avoid toxicity that is not balanced by survival advantage (table 3).

With the decline in treatment-related mortality, drug resistance is the main cause of treatment failure. Many resistance mechanisms have been investigated, and clinical and laboratory studies have focused on cytarabine metabolism125 and ATP-binding cassette drug-efflux pumps found on the cell surface membrane.126 Overexpression of P-glycoprotein causes resistance to anthraclines by rapidly pumping these drugs out of the cell before their cytotoxic effects occur, and is associated with poor outcomes, particularly in older patients.127 Several clinical studies have used inhibitors of P-glycoprotein in combination with chemotherapy.128,129 However, randomised trials do not show an improvement and some suggest increased toxicity in patients receiving inhibitors such as ciclosporin, zosuquidar trihydro chloride,130,131 and valspodar.132 This increased toxicity is partly attributable to the inhibitors’ effect on the disposition of anthracyclines and epipodophyllotoxins, resulting in slowed metabolism and increased drug exposure.133 These drug resistance mechanisms are also exaggerated in leukaemia stem cells, presumably mimicking the overexpression in normal stem cells, which teleologically is designed to protect against the background of environmental toxins to which these cells are exposed.

Future considerations

Treatment outcome of adult acute myeloid leukaemia, particularly in older patients, has not improved in the past 20 years despite a great improvement in our understanding of many of the biological aspects of this complex disease. To translate this knowledge into new treatments is difficult because the many mechanisms of resistance inherent in the stem cells responsible for AML cannot be targeted with available drugs. Indeed, we might have reached the limits of the benefits achievable with chemotherapy. Most studies have focused on mechanisms of drug resistance,134 but what can we learn from the study of treatment successes—why are certain patients cured with crude, non-specific chemotherapy? We do know that the most potent anti-leukaemic effect is mediated by the immune system, as evidenced by the potent graft-versus-leukaemia effect after allogeneic transplantation. Efforts to separate this effect from the limiting toxicities of graft-versus-host disease continue, although the solution remains elusive. Is it possible that patients who have been cured have somehow overcome the immune tolerance that permitted their acute myeloid leukaemia to prosper? Assessments of reactivity against the leukaemia of T-cell subsets in patients in long-term CR could be important and, if present,135 efforts to expand and stimulate this population would be of interest. Studies that use interleukin-2 in the post-remission setting have produced mixed and, at best, modest results.136,137 Whether more targeted approaches derived from further molecular characterisation of the leukaemia cells will be of benefit remains to be seen. Hopefully, this new biological information will contribute to less empirical approaches to treatment, although drug discovery and development remains to be seen. Hopefully, this new biological information will contribute to less empirical approaches to treatment, although drug discovery and development will be challenging, especially if individual patients with unique mixtures of genetic, epigenetic, and microRNA abnormalities need different treatments.

Contributors

FF and CAS conceived and drafted the paper.

Conflicts of interest

FF has received consultancy fees from Janssen, Celgene, and Genzyme. CS has received consultancy fees from BMS, Novartis, Celgene, Genzyme, Pfizer, Teva, Genzyme, and Eisai. CS has received grants from BMS, Novartis, Celgene, Pfizer, and Ariad.

References


Seminar


