Therapeutic Advances in Acute Myeloid Leukemia
Alan Burnett, Meir Wetzler, and Bob Löwenberg

ABSTRACT

The choice of treatment approach and outcome in acute myeloid leukemia (AML) depends on the age of the patient. In younger patients, arbitrarily defined as being younger than 60 years, 70% to 80% enter complete disease remission with several anthracycline-based chemotherapy combinations. Consolidation with high-dose cytarabine or stem-cell transplantation in high-risk patients will restrict overall relapse to approximately 50%. A number of demographic features can predict the outcome of treatment including cytogenetics and an increasing list of molecular features (ie, FLT3, NPM1, MLL, WT1, CEBPα, EVI1). These are increasingly being used to direct postinduction therapy, but they are also molecular targets for a new generation of small molecule inhibitors that are in early development; however, randomized data have yet to emerge. In older patients who comprise the majority, which will increase with demographic change, the initial clinical decision to be made is whether the patient should receive an intensive or nonintensive approach. If the same anthracycline/cytarabine–based approach is deployed, the remission rate will be around 50%, but the risk of subsequent relapse is approximately 85% at 3 years. This difference from younger patients is explained partly by the ability of patients to tolerate effective therapy, and also the aggregation of several poor risk factors compared with the young. There remains a substantial proportion of patients older than 60 years who do not receive intensive chemotherapy. Their survival is approximately 4 months, but there is considerable interest in developing new treatments for this patient group, including novel nucleoside analogs and several other agents.

INTRODUCTION

Acute myeloid leukemia (AML) is a relatively rare cancer with a median age of presentation in the late 60s. In younger patients, the incidence is two to three per 100,000, which rises to 13 to 15 per 100,000 in the seventh and eighth decade.3 Considerable knowledge has accumulated which indicated that it is a highly heterogeneous disease or set of diseases in terms of morphology, cytochemistry of the leukemic population, immunophenotype, cytogenetics, and molecular abnormalities, which may either be mutations or gene overexpression. Since the morphology of the leukemic cells (blasts) in the bone marrow may not be straightforward as to whether it is of lymphoid or myeloid origin, cytochemistry and/or immunophenotyping is an essential part of the diagnosis. It has been recognized for 20 years that nonrandom chromosome abnormalities occur in 50% to 60%2,3 of patients. In some instances, such as the acute promyelocytic subtype, cytogenetic corroboration is essential confirmation of that subtype, which is now regarded and treated as a separate entity.7 However, the importance of the cytogenetic information is that it is highly prognostic both for the outcome of first-line treatment, but also after relapse, and as such is being increasingly used to direct treatment. The accumulation of molecular information provides powerful additional prognostic information, and adds a further layer of prognostic insight within the cytogenetic strata. This not only refines prognostic information, which may optimize existing treatments, but also could lead to the development of additional molecularly targeted approaches. Some of these abnormalities only occur in a small minority of patients, which means that, in a rare disease, the development of molecular therapy will be challenging.

In this review, we provide an outline of the current and developing treatments, and where they are relevant, with attention paid to the emerging molecular knowledge.

CURRENT TREATMENT OUTCOMES

What to expect from treatment for a particular patient has been derived from several collaborative group trials. While there may be differences in treatment schedules and study inclusion/exclusion criteria in trials, some general expectations can be suggested. In patients younger than 60...
years, between 70% and 80% should enter complete remission (CR) after one or two induction treatments.5-8 While the conventional definition of CR is virtual absence of morphologic evidence of disease to fewer than 5% blasts in the marrow with recovery of marrow function, it is known that without further treatment a very high proportion will relapse. Therefore, additional courses, which may include transplantation for the patients at highest risk, are given as consolidation which are capable of reducing the risk of relapse to 50% to 55%, so from diagnosis 40% to 45% of patients will be cured. This represents a steady improvement over the past 30 years, even although the chemotherapy used has not involved new drugs. Much of the improvement can be attributed to a better understanding and deployment of supportive care to carry patients through the inevitable period of severe pancytopenia caused by effective treatment. The picture in older patients who are given the same chemotherapy is not as good, and more worryingly shows modest, if any, improvement over the years. Approximately 40% to 65% will achieve remission, but 85% will relapse within 2 to 3 years (Fig 1).3-13

Induction Therapy

Cytarabine has been the backbone of treatment for several decades combined with an anthracycline, usually daunorubicin. The combination of 3 days of daunorubicin and 7 days of cytarabine (3 + 7) has been accepted as the standard of care for induction treatment. Even after more than 40 years, nothing has convincingly displaced this combination; although, there is a general acceptance that more intensification is feasible and may produce more and better qualities of remission. Several attempts have been made to increase the daily dose and the duration of cytarabine without conclusively improving overall survival (OS). So whether cytarabine is given in a daily dose of 200 mg/m² by continuous infusion or twice per day bolus, doubling5 to 400 mg/m², extending to 10 days or escalating14,15 to a 3g/m², has not made a major impact. Several studies have compared alternatives to daunorubicin, again without convincingly establishing benefit.16 However, there are questions about dose equivalence between daunorubicin, mitoxantrone, and idarubicin. For example, a 12-mg dose of idarubicin is more myelosuppressive than a 50- or 60-mg dose of daunorubicin.17 Improvement may show itself not just by the proportion of patients entering CR, but also in reducing relapse. Mitoxantrone can reduce the risk of relapse without improving the remission rate. However, this may come at a cost of more procedural mortality or failure to deliver postinduction treatment.

The addition of a third drug has been tested with mixed results for either etoposide or thioguanine.18-20 There is no convincing evidence of benefit for a third drug.

Dose escalation of daunorubicin has been less frequently explored, because of concerns about the cumulative dose. A recent study6 claimed a potential new standard of care at a dose level of 90 mg/m² for three days. The problem is that the CR achieved was at least matched by many other schedules involving lower doses, and, although there was a significant difference in younger patients the outcome in the controls was lower than is usually accepted. However, this study may stimulate further interest in daunorubicin dose. A comparison21 of an 80-mg daunorubicin dose and idarubicin showed no difference suggesting that the traditional dose of daunorubicin may be suboptimal but equivalent to idarubicin at 12 mg/m². Treatment with fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin has recently been shown to significantly reduce the relapse rate without improving CR, but was compromised by more myelosuppression and failure to deliver postinduction treatment.7 Several other schedules have been developed including the addition of antibody directed chemotherapy which will be mentioned later.

CR, based on an international consensus,22 requires marrow blast lower than 5% and adequate recovery of peripheral counts. Where counts have not recovered, designated CRi (ie, CR with incomplete platelet recovery), survival is inferior.11,23 Failure to achieve CR with one or two treatment courses suggests a poor prognosis even if a CR is subsequently achieved. Survival for patients who are primarily refractory is unlikely unless they undergo allogeneic stem-cell transplantation (SCT), which offers about a 10% chance of cure for younger patients.

Postinduction Therapy

Having reached CR, further treatment is necessary to reduce the risk of relapse. Currently, this comprises further chemotherapy of similar intensity; however, the precise number of courses is unclear. Large studies from the United Kingdom Medical Research Council (MRC) have addressed this issue for a number of years and currently conclude that a total of four,5 including induction, is sufficient. The most widely accepted schedule is high-dose cytarabine comprising 3g/m² given on days 1, 3, and 5 given for four courses.24 However, only the minority of patients will actually receive all four courses. Lesser doses, such as 400 mg/m², were inferior. The recent MRC AML15 trial

Fig 1. Change in overall survival with time. (A) Age 15 to 59 years; (B) 60 or more years.
compared their favored amsacrine, etoposide, and cytarabine followed by mitoxantrone and cytarabine with high-dose cytarabine at doses of 3 g/m² and 1.5g/m² and found no overall difference in OS between the three options. However, the amsacrine, etoposide, and cytarabine/mitoxantrone and cytarabine was more myelosuppressive. In general, it is less often possible to deliver all the planned consolidation treatment if induction has been intensified. Examples are the introduction of mitoxantrone to induction in a large German study, and the inclusion of fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin in the United Kingdom MRC AML12 trial, and in the United Kingdom AML15 trial.

### Role of Transplantation

An alternative approach is SCT. Several prospective trials evaluated autologous SCT, which although associated with an improved antileukemic effect compared with chemotherapy, did not consistently improve OS. SCT from a well-matched sibling donor has been part of standard care for 25 years, but there remains debate about which patients benefit in terms of OS, and in whom such an aggressive treatment should be reserved for salvage in a second CR. The decision relates to balancing the relapse risk that the patient faces with chemotherapy alone against the risk of the procedure itself. Several prognostic factors (discussed below) can be used to assess the risk in both instances. In general, patients with low relapse risk will also have a higher chance of responding again if they relapse, so delaying SCT to second CR is practical. But in patients with high-risk disease, SCT offers the best option because if such patients relapse the prospect of getting a second response is low. The main controversy centers around the majority of patients with an intermediate risk. The risk of the SCT can be affected by such factors as the age of the recipient and donor, the cytomegalovirus status of donor and host, the parity of a female donor, the degree of matching, and the comorbidities present in the patient, which can be quantitated in a risk score. A further complication in assessing the data for SCT in first CR, is the method of assessment. Traditionally, this has been done by sibling donor versus sibling no donor as a surrogate for an intent to treat in the absence of randomized studies of which there is only one which was negative, but may be less valuable with the emergence of unrelated donation, and the deployment of SCT to second CR for some patients. Age is a prognostic factor for a standard SCT with the benefit restricted to patients, 35 or 40 years old. It is feasible to harness the antileukemic effect without conditioning the patient with myeloablative chemotherapy. So-called reduced intensity conditioning allograft is feasible, although it might be associated with an increased risk of graft-versus-host disease. It appears that the results are similar with a matched sibling or unrelated donor as the source of stem cells. Further prospective studies will establish the relative benefit of this option compared with standard chemotherapy.

### Molecular Genetic Implications for Diagnosis and Therapeutics

Cyto genetics have major prognostic value (Table 1). Core-binding factor (CBF) leukemias comprise 15% to 20% of patients with a favorable prognosis, but 30% of adults, but apparently not children, have a KIT mutation which increases the risk of relapse from 40% to 50% to around 70%, which created the rationale for testing agents such as the tyrosine kinase inhibitor, daesatinib, in combination with chemotherapy.

Of the 60% of patients who are intermediate risk, of whom 60% to 70% will have normal cytogenetics (CN), recent molecular revelations have defined additional prognostic cohorts (Table 2). Activating mutations in the FMS-like tyrosine kinase 3 (FLT3), a tyrosine kinase receptor, which is important in the development of myeloid and lymphoid lineages, occur in 25% to 30% due to internal tandem duplications (ITDs) in the juxtamembrane domain or mutations of the activating loop of the kinase. FLT3 ITD provides proliferative advantage and antiapoptotic signals and predicts shorter CR duration. Further prognostic subdivision is proposed based on the FLT3-ITD wild type (WT) allele ratio (high ratio conferring higher risk), the length of the duplication (increasing size associated with decreasing survival), and the location of the insertion (the more C-terminal, the longer the insertion). This information can inform the decision to undertake allogeneic SCT although the evidence of benefit is not unanimous. Several tyrosine kinase inhibitors with FLT3 inhibitory activity have had modest effects as monotherapy, but at least three
randomized trials are underway in combination with chemotherapy, which will also take into account the molecular subsets. Fifty percent of CN-AML and some of the other intermediate group have nucleophosmin1 (NPM1) mutations resulting in its delocalization into the cytoplasm.32 NPM1 mutation in the absence of FLT3-ITD confers a favorable outcome similar to CBF leukemia33 in young AML patients. These patients benefit from consolidation chemotherapy and do not require SCT in first CR. There is a suggestion that NPM1 patients should receive additional all-trans-retinoic acid therapy,34 but this has not been corroborated.35 Of note, the prognostic value of the molecular biomarkers (eg, NPM1) may also be useful to predict outcome in older patients.36,37

<table>
<thead>
<tr>
<th>Aberration</th>
<th>Prognostic Impact</th>
<th>ELN Classification</th>
<th>Possible Therapeutic Considerations</th>
<th>Standard Testing</th>
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</table>

Abbreviations: AML, acute myeloid leukemia; ELN, European LeukemiaNet; CBF, core-binding factor; SCT, stem-cell transplantation; TKI, tyrosine kinase inhibitor; FLT3, FMS-like tyrosine kinase 3; ITD, internal tandem duplication; MLL, mixed lineage leukemia; PTD, partial tandem duplication; EVI1, ecotropic virus integration site 1; IDH, isocitrate dehydrogenases; NPM1, nucleophosmin1; C/EBPα, CCAAT enhancer binding protein α; ERG, ets erythroblastosis virus E26 oncogene homolog (avian); WT1, Wilms tumor 1.

*In normal cytogenetic AML.

of the juxtaposed related MDS-EVI1 gene frequently carry cryptic 3q26 abnormalities.40 Transplant should be considered in EVI1-positive AML as well as inv(3)(q21q26)/t(3;3)(q21q26) AML.

Recently, mutations in the genes encoding isocitrate dehydrogenase (IDH1 and IDH2) were described in approximately 33% of CN-AML.42-45 Their adverse prognostic significance has been suggested but early studies have not yet generated a consistent picture about their value in particular genotypic subsets (eg, in NPM1+/FLT3-ITD- CN AML and NPM1-/FLT3-ITD- AML).42-45 Specifically, the R172 IDH2 mutations characterize a novel subset of patients with CN-AML lacking other prognostic mutations and associate with unique gene- and microRNA-expression profiles that may lead to the discovery of novel, therapeutically targetable leukemogenic mechanisms.

Approximately 10% of CN-AML carry mutations in the transcription factor CCAAT enhancer binding protein (C/EBPα).46,47 Half are biallelic, which convey a favorable outcome similar to NPM1+/FLT3-, which is maintained in other karyotypic subgroups, thus identifying a further group of young AML who may not need to be referred for allogeneic SCT in first CR.

Low expression of the brain and acute leukemia, cytoplasmic (BAALC) gene, the human member of a novel mammalian neuroectoderm gene lineage that is implicated in hemopoiesis and acute leukemia, is also associated with favorable outcome in CN-AML,48 but not in association with FLT3, NPM1, and C/EBPα, and may not be prognostic in older patients.49 However, low ERG expression predicted even better OS in patients who had low BAALC expression, reaching 70% survival at 5 years,45 removing the need for allogeneic SCT in first CR.

Low expression level of the tumor suppressor Wilms tumor (WT1) gene was associated with longer OS in AML in some patients but not others.50 While WT1 mutations correlate with poor DFS and
OS in normal and abnormal karyotype.\textsuperscript{51-54} Patients with AML in some but not all studies which might be explained by the small numbers studied or different treatments. A recent study demonstrated that a single nucleotide polymorphism in the WT1 mutational hotspot predicted favorable outcome in CN-AML.\textsuperscript{54} Since this single nucleotide polymorphism was also detected in normal volunteers, its role may be related to drug metabolism or other yet unclear function. In summary, the story of WT1 is not completed clear.

Genomewide search and new technologies represent different opportunities to subcategorize AML. For example, microRNAs are small RNAs of 19 to 25 nucleotides that are regulators of gene expression. Specific microRNA signatures associate with particular genotypes in AML thus providing evidence for their pathophysiologic role.\textsuperscript{55} It was initially shown that patients with high expression of miR-191 and miR-199a had significantly worse event-free survival (EFS) and OS in AML (all ages, all karyotypes).\textsuperscript{56} Later, a signature of eight microRNAs was found to be associated with EFS in patients younger than 60 years of age with FLT3-ITD and NPMI-WT (poor molecular group) CN-AML. Of these eight, the levels of miR181a and miR-181b were negatively associated with outcome while the levels of miR-124, miR-128-1, miR-194, miR-219-5b, miR-220a, and miR-320 were positively associated with outcome. These results will need to be validated by other groups. Whether microRNAs or their downstream targets are potential targets for therapeutics remains to be seen.

**Epigenetic Implications for Diagnosis and Therapeutics**

Epigenetic mechanisms are important in the regulation of cellular processes involved in cell growth and cell differentiation. One such mechanism that has received considerable attention with potential therapeutic impact is DNA cytosine methylation, which can modify gene expression. Abnormal methylation patterns have been recognized in AML by genome-wide analysis.\textsuperscript{57,58} Specific methylation patterns were associated with particular AML genotypes, such as t(8;21), t(15;17), mutations in C/EBP\textalpha, or high EVII. Further, unique AML subtypes were identified solely based on distinctive DNA methylation signatures even without a common molecular or cytogenetic abnormality and these were found to independently predict survival in AML.\textsuperscript{57} Such subgroups may be candidates for demethylating therapies.

The wealth of emerging novel molecular data may create confusion as regards practical utility. For the time being, different prognostic biomarkers may be used in clinical practice. This area of research will continue to evolve that ultimately should lead to generally accepted algorithms with validated clinical relevance.

### Treatment of Older Patients

The great majority of patients with AML are older than 60 years. Median age is around 70 years, and physicians or patients are reluctant to undertake intensive chemotherapy.\textsuperscript{59,60} High age independently defines unfavorable disease outcome. Reduced anthracycline sensitivity and RAS, SRC, and TNF pathway activation have recently been reported in particular in older patients with AML.\textsuperscript{61} These deregulated signaling pathway variations appear to contribute to poor survival and more specifically chemotherapy resistance at older age, a phenomenon less common in younger adults. Unfavorable cytogenetics are more common among patients older than 60, while favorable cytogenetic prognostic factors (CBF) are less frequent.

Among older patients, reproducible prognostic factors including increasing age,\textsuperscript{2,61,62} poor performance status, secondary leukemia, overexpression of P-glycoprotein, adverse cytogenetics,\textsuperscript{63,64} splenomegaly, and extramedullary disease independently predict for lower CR rates. Monosomal karyotype\textsuperscript{13} recognizes a subcategory of particularly bad disease with an excessively low CR rate and dismal OS and EFS. CBF cytogenetics predicts for better OS and DFS consistent with published data in younger patients.\textsuperscript{12,13,61-64} Reduced performance status, splenomegaly, increased WBC count, and again, unfavorable cytogenetics confer negative prognostic impact in regards to OS and EFS, while mutations in the NPM1 gene show somewhat better outcome. It is of interest that mutations catalyzing methylation of DNMT3A are recurrent in patients with de novo AML with intermediate karyotype and are associated with poor outcome.\textsuperscript{64a}

**Remission Induction Treatment in Older Patients**

Physicians are often reluctant to recommend full-dose chemotherapy in patients of older age because of toxicity concerns. However, there is a prevailing opinion that intensive remission induction chemotherapy in the so-called fit elderly provides an outcome that overall is superior to a wait-and-watch approach or dose-attenuated cytoreductive treatment.\textsuperscript{10} The attainment of a CR is regarded a prerequisite not only for better OS as well as better quality of life, so it is the first treatment objective. For the past 20 years, it has been standard practice among the major cooperative groups to use daunorubicin at doses of 45 to 50 mg/m\textsuperscript{2} for 3 days in combination with cytarabine 100 to 200 mg/m\textsuperscript{2} for 7 to 10 days in older patients, which induces CR in 45% to 65% of patients.\textsuperscript{65} A slightly higher dose of 60 mg/m\textsuperscript{2} is employed by some, but has not been evaluated in direct comparisons.\textsuperscript{66} Prospectively evaluated regimens of mitoxantrone and etoposide or combinations with idarubicin (12 mg/m\textsuperscript{2}) or mitoxantrone (12 mg/m\textsuperscript{2}) do not appear any better than standard 45 to 50 mg/m\textsuperscript{2} daunorubicin and cytarabine. The traditional dose level of daunorubicin has recently been challenged in a large randomized study.\textsuperscript{13} Doubling the dose of daunorubicin (90 mg/m\textsuperscript{2} for 3 days) in a single cycle, did not increase early mortality, prolong myelosuppression, increase transfusion dependence or hospitalization. Apart from the feasibility of applying an enhanced dose intensity of daunorubicin, a profound dose-response relationship for daunorubicin was apparent up to 90 mg/m\textsuperscript{2}. Not only more CRs were attained with the escalated dose regimen, but more early CRs were attained after cycle 1. The high-dose regimen did not impact on OS in the study but the younger subgroup age 60 to 65 gained advantage from daunorubicin intensification in regards to all the major clinical endpoints. In this subgroup substantial improvements in CR rate, EFS, and OS were noted while patients with CBF leukemias appeared to benefit from high-dose daunorubicin and cytarabine, irrespective of age. This is consistent with the trial of daunorubicin dose in younger patients referred to above.\textsuperscript{6} Of interest in this respect is that another recent comparative study did not reveal differences in outcome in patients between 50 and 70 years of age between comparative regimens of cytarabine plus daunorubicin at 80 mg/m\textsuperscript{2} for 3 days or idarubicin at 12 mg/m\textsuperscript{2} for 3 or 4 days\textsuperscript{21} suggesting therapeutic equivalence between these two drugs at these doses. However, another large study\textsuperscript{11} comparing 50 versus 35 mg of daunorubicin for two cycles in older patients showed no difference in outcome, which suggests that high peak concentrations of daunorubicin rather than total dose impact on response.

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Postremission Treatment in Older Patients

In general, CRs obtained after remission induction chemotherapy in patients of older than 60 years are short lived. This results in an OS probability of around 10% at 5 years from diagnosis.11-13,63 While it is striking that almost all remissions are subsequently lost within 3 years, various efforts have been undertaken to develop more active therapeutic regimens for the elimination of residual leukemia in remission and thereby stabilizing these remissions more effectively. These efforts in patients older than 60 years unfortunately have generally been unsuccessful. Studies based on the use of cytarabine according to various dose intensification schedules did not produce therapeutic benefits.24,67 Two studies have produced an improvement of disease-free survival (DFS) in a comparison between low-dose cytarabine and no maintenance chemotherapy but OS was similar.65,68 A comparison between one additional cycle of combination chemotherapy for remission consolidation with four additional cycles showed no differences in OS.9 When three successive versus four successive cycles of intensive chemotherapy were directly compared, no differences in outcome were noted either.11 Neither did the use of interferon after CR result in any significant positive effect on outcome.9 One study compared one single intensive consolidation cycle in remission with low-dose chemotherapy delivered in an outpatient setting produced ambiguous results.69 The study compared a single additional intensive cycle of chemotherapy during hospitalization with six repeated cycles of lower dose ambulatory combination chemotherapy in first CR. It suggested an OS and DFS advantage at 2 years for the ambulatory regimen but whether this benefit was maintained during longer follow-up remains to be seen. High-dose cytarabine while offering effective postremission treatment in young and middle-age adults appears too toxic in patients older than 60 and therefore its use is generally discouraged in older individuals.24 A recent study comparing no maintenance chemotherapy with three cycles of gemtuzumab ozogamicin, an anti-CD33-calicheamicin immunoconjugate, failed to show a benefit in favor of postremission treatment.70 Hence, there is no generally established postremission treatment in elderly patients with AML.

Reduced-intensity allogeneic SCT has been applied in highly selected subgroups of patients and appears feasible with encouraging results but awaits critical evaluation in prospective trials.71

Nonfit Patients With AML

In clinical practice, there are a substantial proportion of older patients who are not treated with intensive treatment by choice or because it is considered unsuitable.50,64 Unsuitable in this context can mean that the patient is medically unfit and such treatment might curtail survival. It may also mean that the patient is medically fit, but unlikely to benefit due for example to adverse features of the disease (eg, cytogenetics or secondary disease). Comorbidity scores and/or disease related scores can be used to more accurately individualize the treatment prospect.72,73 but in the absence of randomized data, which has proved difficult to obtain, it is still difficult to be sure which treatment approach to deploy. Such patients have been managed with best supportive care; however, this has been shown in a randomized trial to be inferior to low-dose cytarabine.74 In these patients alternatives such as hypomethylating agents are widely used, but there is so far no randomized data to show that they are superior to low-dose cytarabine. Such patients have become a focus for new drug development.

Table 3. New Treatments in Development

<table>
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<tr>
<th>Parameter</th>
<th>Treatment</th>
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<td>Nucleoside analogues</td>
<td>Clolarabine, sapacitabine, elacytarabine</td>
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<tr>
<td>FLT3 inhibitors</td>
<td>Midostaurin, leustaurtinib, sorafenib, AC220</td>
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<tr>
<td>Antibody based</td>
<td>Gemtuzumab ozogamicin, CLS123</td>
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<tr>
<td>Demethylating agents</td>
<td>Azacytidine, decitabine</td>
</tr>
<tr>
<td>Other agents</td>
<td>Aurora kinase inhibitor/Aminopeptidase inhibitor Tosedostat/mTOR inhibitor voroxolin/amonofide/ceplene</td>
</tr>
</tbody>
</table>

Abbreviations: FLT3, FMS-like tyrosine kinase 3; mTOR, mammalian target of rapamycin.

NEED FOR NOVEL DRUGS

It is surprising that relatively few new drugs have been approved for AML in the past 20 years. However, new strategies and treatments are emerging and under current assessment. These are presented in Table 3. Gemtuzumab ozogamicin is the first example of antibody directed chemotherapy targeting the CD33 epitope, and although approved for older patients in relapse for whom conventional therapy was not thought to be suitable, randomized trials so far have not shown an OS benefit,70,77 with the exception of a single study in good risk younger patients when added to chemotherapy.76 In this study, patients with poor risk did not benefit but the application of simple prognostic factors was able to identify 70% of patients who had a 10% improvement in OS. It is regrettable that this agent has recently been withdrawn based on the failure of the pivotal trial to show an OS benefit, and an excess induction death risk (5.4%) versus an unusually low risk (1.4%) in the control arm. The combination of low-dose of interleukin 2 combined with histamine as maintenance prolonged remission,77 but is not yet widely used. As mentioned above emerging molecular knowledge offers potential for new therapies. Studies targeting the FLT3 mutation have shown limited activity as monotherapy but randomized trials in combination are underway. Targeting RAS and other farnesylated peptides and P-glycoprotein has been disappointing. Several new agents show promise in phase II trials but require randomized evidence (including clolarabine, voroxolin, spactibine, elacytarabine, tosedostat). Novel strategies of prolonging survival with hypomethylating agents without necessarily improving remission rates may be particularly suitable for older patients, or patients with particular methylation patterns, but randomized data is needed. Given that AML is a relatively rare disease new approaches to trial design are also required.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Information page of the Journal or go to Cancer.org/COI.
REFERENCES

CORRECTIONS

Author Corrections


In Table 1, in the visceral involvement row, the number of patients in the fulvestrant 500 mg treatment group was given as 239 (66%), whereas it should have been 205 (57%). Also, the number of patients in the fulvestrant 250 mg treatment group was given as 232 (62%), whereas it should have been 198 (53%).

In Figure 3, the results depicted for no visceral involvement showed an HR of 0.74 (95% CI, 0.56 to 0.98), whereas it should have been HR of 0.72 (95% CI, 0.57 to 0.92). Also, the results depicted for visceral involvement represent an HR of 0.82 (95% CI, 0.67 to 1.00), whereas it should have been an HR of 0.86 (95% CI, 0.70 to 1.06).

In the Results section, under Efficacy, an HR of 0.78 (95% CI, 0.67 to 0.92; P = .003) was given for the PFS analysis in the first sentence of the second paragraph, whereas it should have been an HR of 0.79 (95% CI, 0.68 to 0.93; P = .004), as follows: “The PFS analysis adjusted by predefined covariates resulted in an HR of 0.79 (95% CI, 0.68 to 0.93; P = .004).”

In the Discussion section, P = .801 was given for the global interaction test in the second sentence of the fourth paragraph, whereas it should have been P = .796, as follows:

“The planned subgroup analysis according to six pre-defined covariates suggests that the type of treatment effect seems to be consistent across the investigated subgroups (global interaction test, P = .796; Fig 3).”

The authors believe that these errors do not affect the overall results and conclusions of the study, and apologize to the readers for the mistakes.

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In Table 1, the column heading “GIMEMA/AML 10” should have been labeled “EORTC/GIMEMA.” Also, in the Abbreviations list, EORTC should have been listed as the European Organisation for Research on Treatment of Cancer.

The authors apologize to the readers for the mistake.

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In the Authors’ Disclosure of Potential Conflicts of Interest section, Catherine Van Poznak’s work as a consultant/advisor for Amgen was listed as compensated (C), whereas it should have been listed as uncompensated (U).

The authors apologize to the readers for the mistake.

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