Recent Developments in Acute Myelogenous Leukemia Therapy

MARY E. KING, a JACOB M. ROWE b

aMedical & Scientific Communications, Boulder, Colorado, USA; bDepartment of Hematology and BMT, Rambam Medical Center and Technion, Israel Institute of Technology, Haifa, Israel

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ABSTRACT
Recent progress has been made in several areas in the treatment of acute myelogenous leukemia (AML): prognostic factors, allogeneic bone marrow transplantation, and new and targeted therapies. Delineation and clarification of prognostic factors have led to improved risk determination, with research moving from cytogenetics to an examination of molecular markers. Trends in the area of allogeneic bone marrow transplantation include broad adoption of reduced-intensity conditioning despite the lack of prospective comparative studies. Although the preponderance of data has established this as a feasible option, a true understanding of how much of an advantage it conveys needs to be established in prospective studies. The use of alternative donors is another advance, and recent data are promising, but survival is poor if transplantation is performed when disease is active, especially during refractory relapse or refractory disease. When haploidentical matched donors are used, survival rates appear similar to those reported with matched unrelated-donor transplants. Analysis of the data for allogeneic transplantation shows that HLA-identical sibling transplants to patients in the first complete remission (CR1) provide the highest probability of long-term survival, compared with HLA-identical sibling transplants to patients in later remissions. Similarly, unrelated-donor transplants to high-risk patients in CR1 lead to a greater degree of success than unrelated-donor transplants to patients in CR2 or later remission. Cord blood has also been established as a suitable source for hematopoietic transplantation in AML. A third area of recent progress involves new and targeted therapies. Multiple new agents with tremendous potential are in development and clinical trials. Therapy can even be tailored to several specific genetic subtypes of AML. The Oncologist 2007;12(suppl 2):14–21

INTRODUCTION
Three areas are considered in this discussion of recent progress in the treatment of acute myelogenous leukemia (AML): prognostic factors, which are improving risk discrimination; improvements in the availability and outcome of allogeneic bone marrow transplantation; and new and targeted therapies.

PROGNOSTIC FACTORS
One of the most important areas in the development of state-of-the-art therapy for AML has been the delineation and clarification of prognostic factors, leading to much-improved risk determination. Over the past decade, virtually all major cooperative groups that have studied the treatment of AML in a prospective fashion have reported that the most important prognostic factor is the cytogenetics of patients at presentation. The U.S. intergroup (Eastern Cooperative Oncology Group [ECOG] and Southwest Oncology Group [SWOG]) study E3489/S9034 [1], the U.K. Medical Research Council (MRC) AML 10 trial [2], and the Cancer and Leukemia Group B (CALGB) 8461 study [3] each demonstrated that overall survival is greatest in patients with the most favorable cytogenetics, intermediate in those with intermediate-risk cytogenetics, and poorest in patients with unfavorable cytogenetics.

Correspondence: Jacob M. Rowe, M.D., Department of Hematology and BMT, Rambam Medical Center, Haifa 31096 Israel. Telephone: 011-972-4-8542541; Fax: 011-972-4-8542343; e-mail: rowe@jimmy.harvard.edu Received June 18, 2007; accepted for publication August 31, 2007. ©AlphaMed Press 1083-7159/2007/$30.00/0 doi: 10.1634/theoncologist.12-S2-14

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Research in defining prognostic factors in AML has moved from cytogenetics to an examination of molecular markers, beginning with enormous interest in the P-glycoprotein transmembrane transporter proteins, which are the product of the multidrug resistance gene (MDR-1). Unfortunately, most of the studies attempting to overcome MDR-1 have been negative. More recently, various mutations resulting in overexpression of specific genes have been shown to be associated with specific prognoses. Unfavorable prognosis is associated with several of these, including: the Wilms tumor gene, WT1; the genes for the apoptosis regulators B-cell lymphoma protein 2 (BCL-2), BCL-2, and BCL-2-associated X protein, BAX; the brain and acute leukemia, cytoplasmic gene, BAALC; the ecotropic viral integration site 1 gene, EVII; the FMS-like tyrosine kinase type 3 gene, FLT3; and KIT, ERG, and the mixed-lineage leukemia gene, MLL. Some mutations of specific genes confer a more favorable prognosis; most notably, mutations in the genes for CCAAT enhancer binding protein-α (C/EBP-α), CEBPA, and nucleophosmin, NPM1. These prognostic determinants have been particularly important for patients with AML and a normal karyotype.

The difficulty with using cytogenetic grouping as a risk factor is that most patients fall in the intermediate-risk group, and the majority of these have a normal karyotype (Table 1) [4]. Between 40% and 50% of young adult AML patients in the U.S. and United Kingdom have been found to have a normal karyotype [1–4]. The intermediate group, unlike the favorable or the unfavorable cytogenetics group, has a greater heterogeneous mix of patients, with some having a poor prognosis and others having a better prognosis.

One example of the significance of prognostic factors in patients with a normal karyotype is shown by the presence or absence of the most common gene mutation in AML, FLT3 internal tandem duplication. In a study of 854 patients with AML, 27% had this mutation [5]. The mutation was associated with a lower complete remission rate, a higher risk for relapse, and lower disease-free survival, event-free survival, and overall survival rates. The occurrence of the FLT3 mutation was the most significant prognostic factor linked with relapse risk and disease-free survival (p < .0001) [5]. Other studies have shown that, in adult patients with AML and normal cytogenetics, the presence of the MLL partial tandem duplication is associated with a very poor prognosis [6]. Similarly, the expression of WT1 has been shown to be of major prognostic significance and is associated with a lower disease-free survival rate in AML patients, including those with a normal karyotype [7]. In addition, when hierarchical cluster analysis was used to study gene-expression profiling in patients with AML and a normal karyotype, two distinct groups with statistically different Kaplan–Meier estimates of overall survival were identified (p = .009) [8].

These studies demonstrate to clinicians that the largest group in AML with an assigned specific prognosis, the intermediate group, is, in fact, enormously heterogeneous, raising questions about how to assign specific therapies to this group based solely on cytogenetics. This group of patients with AML is a prime target for the development of better prognostic tools.

Even among patients with a favorable karyotype, genetic mutations can further refine prognosis. The KIT gene encodes a transmembrane glycoprotein that is part of the type 3 receptor tyrosine kinase family. In a recent report, researchers from the CALGB demonstrated that, in 43 patients with the 8;21 translocation, the incidence of relapse was significantly higher among patients with KIT mutations than among those with wild-type KIT (p = .017) [9]. Similarly, among 50 patients with inversion 16, the overall survival duration was significantly shorter for those patients who had any type of KIT mutation than for those with wild-type KIT (p < .009) [9].

The reports are in line with other published data for patients with the 8;21 translocation, indicating that CD56 expression [10], trisomy 4 [11], and mutations in the receptor tyrosine kinase pathway [12] may each independently confer a poor prognosis, even among this group with so-called favorable cytogenetics.

**Table 1.** Percentage of newly diagnosed young adults who present with specific cytogenetic subtypes

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Intermediate-risk group (%)</th>
<th>Normal karyotype (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG/SWOG [1]</td>
<td>46</td>
<td>40</td>
</tr>
<tr>
<td>MRC AML [2]</td>
<td>66</td>
<td>42</td>
</tr>
<tr>
<td>CALGB [3]</td>
<td>71</td>
<td>48</td>
</tr>
</tbody>
</table>


Abbreviations: AML, acute myelogenous leukemia; CALGB, Cancer and Leukemia Group B; ECOG, Eastern Cooperative Oncology Group; MRC, Medical Research Council; SWOG, Southwest Oncology Group.

**Allogeneic Bone Marrow Transplantation**

Considerable progress has also occurred in the area of allogeneic bone marrow transplantation, making this option available to a greater number of patients with AML. Such developments have occurred through the increasing use of reduced-intensity conditioning, something that would have been quite revolutionary 10 years ago; through better under-
standing and use of alternative donors, including matched unrelated donors and haploidentical related donors; and through a better understanding of the need for transplantation during the first complete remission (CR1) in patients with unfavorable cytogenetics.

**Reduced-Intensity Conditioning**

Reduced-intensity conditioning has become a fact of life, often without supporting data. Despite its wide use, to date there have been no prospective comparative studies. Available information is based on data from phase II clinical studies [13] and some retrospective comparative data. The best data in patients with AML have come from a multicenter study in the U.S. and Europe, referred to as the Consortium Study [14]. The immunosuppression regimen involved minimally toxic total body irradiation of 2 Gy, most often with fludarabine, before and a combination of cyclosporine and mycophenolate mofetil after allogeneic hematopoietic stem cell transplantation (HSCT). The regimen was used for both related- and unrelated-donor transplantations. The postgrafting immunosuppression both enhanced engraftment and mitigated serious graft-versus-host-disease (GVHD). Serial analyses for chimerism were performed on days 28, 56, 84, 180, and 360 after HSCT [14].

One hundred twenty-two AML patients, with approximately equal numbers of related and unrelated donor–recipient pairs, were included in this study. Three quarters of the patients were in complete remission, either CR1 or CR2, and about 25% had advanced disease. The most important reason for reduced-intensity conditioning was age or significant comorbidity. Engraftment was prompt in all patients, as indicated by the percentages of donor chimerism in natural killer cells, granulocytes, and T cells during the first 180 days post-transplantation. The overall survival rate at 2 years was 48%, and patients receiving transplantation during CR1 had 2-year overall survival rates of 44% (related HSCT) and 63% (unrelated HSCT). Cumulative incidences of acute GVHD (grades 2–4) were 35% at 180 days after related HSCT and 42% after unrelated HSCT. The probability of one of the most important complications, chronic GVHD, was 36% at 2 years [14].

Although data from prospective studies are not available, a retrospective comparison of standard and reduced-intensity conditioning was published recently [15]. Researchers studied transplantation outcomes in 150 patients, over the age of 40 years, with myelodysplastic syndrome (MDS) or acute AML transformed from MDS. Most patients (n = 112) received standard conditioning, but 38 patients received reduced conditioning because of older age or the presence of comorbidities (Table 2). At 3 years post-transplantation, the overall survival rates were not statistically different in the two groups, and the nonrelapse mortality rates were also similar [15]. Patients in the reduced-intensity group were older and sicker, which may explain the results. The preponderance of data has established reduced-intensity conditioning as a feasible option, but how feasible and how important this is in the management of AML, and how much of a difference it will make, still needs to be established in prospective studies.

**Alternative-Donor Transplantation**

The Center for International Blood & Marrow Transplant Research has published data summarizing the probability of survival after allogeneic transplantation for AML, categorized by donor type and remission status. Data covering the years 1994 through 1999, for example, show that HLA-identical sibling transplants to patients in CR1 confer the highest probability of long-term patient survival, followed by HLA-identical sibling transplants to patients in later remissions, unrelated-donor transplants to patients in CR1, and unrelated-donor transplants to patients in CR2 or later remission. More than one third of patients who are in CR1 or subsequent remissions can be cured with unrelated-donor transplantation. These data have been confirmed by many other groups.

**Haploidentical Transplantation in AML**

The problem with matched unrelated-donor (MUD) transplantation is twofold. First, while there is no doubt that these transplants work, the difficulty is the availability of a donor. Although the National Marrow Donor Program network reports that one can find a stem cell donor for over 80% of individuals, this is limited to the white population. Second, the time required to find a donor and initiate a transplantation is in the range of 1–6 months, and the median time of 3 months is often too long for a patient with acute leukemia. In fact, only about one third of pediatric patients with acute lymphoblastic leukemia (ALL) who have a planned, unrelated-donor transplantation actually undergo the procedure [16].

When transplantation does take place, and haploidentical matched donors are used, however, survival rates appear

<table>
<thead>
<tr>
<th></th>
<th>Standard conditioning</th>
<th>Reduced-intensity conditioning</th>
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<tbody>
<tr>
<td>n</td>
<td>112</td>
<td>38</td>
</tr>
<tr>
<td>Median age</td>
<td>53</td>
<td>62</td>
</tr>
<tr>
<td>AML</td>
<td>31%</td>
<td>53%</td>
</tr>
<tr>
<td>MDS</td>
<td>69%</td>
<td>47%</td>
</tr>
</tbody>
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Abbreviations: AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome.
similar to those reported with MUD transplants [17]. The importance of these data is that almost everyone has a haploidentical donor, such as a parent, a child, or 75% of one’s siblings. In some communities, an uncle or a cousin may be a haploidentical donor. Because such donors are readily available, transplantation can be done very rapidly once the decision has been made.

This approach is based on the concept of complete T-cell depletion and the use of megadoses of stem cells, on the order of $10^5 - 10^6$ CD34+ cells/kg [17]. No GVHD prophylaxis is given, which also makes this approach attractive. Infections remain a major problem in these patients, with a slow recovery of CD4 cells, and for patients who are transplanted during a complete remission, the 2-year mortality rate was around 30% ($n = 67$) [17]. This mode is being adopted by other groups, but it is coming slowly to the U.S., partly because of legal considerations. But results appear to be similar to those seen with MUD transplants in AML [17, 18]. Few long-term data have been published about the use of MUD transplants in advanced AML. A study from Sierra and colleagues has shown that, among patients transplanted during relapsed disease, long-term survival is poor, only 7% at 5 years [18]. Relapsed disease is a major problem in patients with advanced AML who undergo MUD or haploidentical transplantation.

**Umbilical Cord Blood Transplantation in AML**

Cord blood (CB) has now become established as a suitable source for hematopoietic transplantation. Since first performed in 1988, over 4,000 such transplants have taken place for malignant and nonmalignant diseases [19]. Compared with MUD transplants, several advantages exist. First is the immaturity of the immune system, allowing for unrelated donors with less restrictive HLA compatibility requirements. At least as important is the fact that, given the availability of these donors in the bank and the lack of any further requirement for procurement, the time for this transplant is far more rapid than for MUD transplants. Finally, is the absence of any risk for mothers or donors. Its major disadvantage relates to the small amount of stem cells infused, which is generally 1 log lower than for non-CB allogeneic transplants, resulting in delayed engraftment and greater mortality. CB transplantation has become increasingly used in hematologic malignancies, especially AML, mostly in children [20]. CB transplants have been used in adults with some reported success and certainly are an alternative when a matched unrelated donor or a haploidentical donor is not available [21–23]. Recent attempts to augment the graft cell dose have been made through the transplantation of two partially HLA-matched umbilical cord blood units. Considerable success has been reported [24]. The potential for this is immense, such that in select cases, because of the rapid availability, this may even be preferable to a MUD transplant. The possibility that reduced-intensity regimens may also be used in umbilical CB transplantation may make this procedure even more attractive by reducing its toxicity [25, 26].

To summarize this section, the data for using alternative donors are exciting, provided the patients are in complete remission at the time of transplantation. But survival is poor if the transplantation is performed when disease is active, and especially if patients are in refractory relapse or have refractory disease. However, when comparing data from MUD transplants and haploidentical transplants, it is important to note the time of the transplantation. An intent-to-treat analysis of MUD transplantations in AML has never been performed. Most patients with advanced disease simply do not make it to transplantation. In other words, those patients who do receive MUD transplants for advanced AML are a select group who survived long enough to undergo transplantation. In comparison, haploidentical transplant recipients represent a group of patients who are transplanted much sooner after the decision was made to have a transplantation, and many of them would never have survived long enough to undergo an MUD transplantation.

**Alternative Donors in Patients with AML and Unfavorable Cytogenetics**

Another area of AML transplantation where there has been major progress is the use of alternative-donor cells for patients with unfavorable cytogenetics, and transplanting them during CR1. This is a fairly novel concept. While transplantations are performed for ALL in CR1 patients who have risk factors associated with a particularly poor prognosis, such as the Philadelphia chromosome (Ph), until recently almost no AML patient with unfavorable cytogenetics would be sent for an alternative-donor transplantation during first remission. Some very recent and exciting data suggest that this approach ought to be considered more frequently.

Data on adult patients who are Ph positive from German ALL studies (D. Hoelzer, personal communication) and the international ALL study (ECOG E2993/MRC UKALL XII) [27] demonstrate a very low survival rate for those who did not undergo a transplantation during CR1. Data from the U.S. intergroup study [1] and the MRC AML 10 trial [2] for subgroups of patients with AML and unfavorable cytogenetics yielded overall survival curves that are virtually superimposable on the survival curve for patients with Ph-positive ALL. Yet few MUD transplantations take place during CR1 in AML patients with
unfavorable cytogenetics, while clinicians do not hesitate to perform MUD transplantations during CR1 in comparable patients with Ph-positive ALL.

While the rationale exists for transplanting during CR1 in these AML patients, very few data are available. A German group did do a prospective study of this issue and released data at the 2005 and 2006 meetings of the American Society of Hematology (ASH) [28, 29]. All patients were treated with a first cycle of conventional induction therapy ($n = 520$). Bone marrow was examined on day 15. Patients who had a favorable karyotype and those who had a normal karyotype with aplastic bone marrow at day 15 were considered to be at standard risk. The standard-risk group did not undergo MUD transplantation. The high-risk group was composed of 249 individuals who had unfavorable cytogenetics and those who had a poor response to initial induction despite having a normal karyotype. They received a second cycle of induction therapy, and if they went into remission they received one cycle of consolidation therapy. If they had an allogeneic sibling, they went on to a matched-family-member allogeneic transplantation. Those who did not have a sibling were assigned to an unrelated-donor transplantation, if a donor was available ($n = 32$); otherwise, they received an autotransplantation. Therefore, this study allowed researchers to assess the possible impact of an MUD transplantation in a prospective manner.

About 520 patients entered this study and, interestingly, they split almost equally into high-risk and standard-risk groups [28, 29]. The high-risk group contained 249 patients and the upper age limit (as for all patients in the study) was 60 years. One third had a poor response to initial induction therapy, one third had an adverse karyotype, and the other third had both high risk factors. Data shown at the ASH meetings indicated overall very acceptable results for MUD transplantation in patients with AML and unfavorable cytogenetics during CR1. Each of the high-risk subgroups had a similar rate for overall survival at 70 months, approximately 25% [28, 29].

**New and Targeted Therapies**

A third area of recent progress in AML involves new and targeted therapies. The period between 1985 and 1995 was marked by the remarkable rediscovery of all-*trans* retinoic acid for use in acute promyelocytic leukemia [30]. Arsenic was rediscovered a few years later. During the next decade, 1995–2005, one of the most important leaps in the treatment of myeloid leukemias occurred through translational research into the design of targeted therapy with inhibitors of breakpoint cluster region–Abelson (BCR-ABL) tyrosine kinase for the treatment of chronic myeloid leukemia, specifically the use of imatinib mesylate [31].

Table 3 lists some of the developments that can be expected during the decade 2005–2115 [32]. It is fair to say that there have never been so many targeted and other novel agents with such enormous potential. We may be moving into an era of combinations of multiple targeted therapies for the treatment of AML. Therapy can even be tailored to several specific genetic subtypes of AML, including acute promyelocytic leukemia, CD33+ AML, AML with FLT3 mutations, AML with KIT mutations, and AML with MLL partial tandem duplications.

One broad class of mutations associated with acute leukemia comprises the proliferation/survival mutations that do not affect differentiation (Fig. 1) [33]. Examples include mutations that activate tyrosine kinases such as BCR-ABL or FLT3 and oncogenic RAS mutations that enhance the proliferative and survival advantage of cells. These mutations can be targeted by small-molecule inhibitors of the respective tyrosine kinases or, potentially, by farnesyltransferase inhibitors. A second class of mutation comprises loss-of-function mutations in hematopoietic transcription factors, as exemplified by AML1ETO or PMLRARA gene rearrangements, or point mutations in AML1 [33]. Treatments targeting this class of mutations can include agents that specifically induce differentiation and apoptosis of leukemic cells, for example, all-*trans* retinoic acid in acute promyelocytic leukemia, or the class of agents known as histone deacetylase inhibitors.

**Table 3. Potential advances in targeted therapy and other novel treatments for AML, 2005–2015**

<table>
<thead>
<tr>
<th>Treatment</th>
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<tbody>
<tr>
<td>Gentuzumab ozogamicin</td>
</tr>
<tr>
<td>Multidrug resistance inhibitors</td>
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<tr>
<td>Farnesyltransferase inhibitors (tipifarnib)</td>
</tr>
<tr>
<td>FLT3 inhibitors (PKC-412, CEP-701)</td>
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<tr>
<td>Apoptosis inhibitors</td>
</tr>
<tr>
<td>Antiangiogenesis agents</td>
</tr>
<tr>
<td>Histone deacetylase inhibitors</td>
</tr>
<tr>
<td>Hypomethylating agents (decitabine)</td>
</tr>
<tr>
<td>Deoxyadenosine analogues (clofarabine)</td>
</tr>
<tr>
<td>Sulfonylhydrazine alkylators (VNP40101M)</td>
</tr>
<tr>
<td>Small-molecule inhibitors (tandutinib)</td>
</tr>
<tr>
<td>Inhibitors of multiple receptor kinases (XL999)</td>
</tr>
<tr>
<td>IL-2</td>
</tr>
<tr>
<td>IL-2 plus histamine</td>
</tr>
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Abbreviations: AML, acute myelogenous leukemia; FLT3, FMS-like tyrosine kinase type 3; IL, interleukin.
deacetylase inhibitors. Members of a third class, consisting of genes and pathways that are responsible for the self-renewal potential of leukemic stem cells (e.g., $WNT$, $Notch$, $HOX$) are not known to be mutant in leukemia, but they too may be candidates for molecularly targeted therapy [33]. Examples of new agents include the FLT3 tyrosine kinase inhibitors PKC-412 and CEP-701, the farnesyltransferase inhibitor tipifarnib, the apoptosis inhibitor oblimersen sodium, and the deoxyadenosine analogue clofarabine. FLT3 tyrosine kinase has been an obvious target since the publication of data showing the poor prognosis associated with internal tandem duplication of $FLT3$ [5]. A phase II study of PKC-412 ($n = 20$) (Novartis Pharmaceuticals, Basel, Switzerland) [34] and a phase I–II study of CEP-701 ($n = 17$) (Cephalon, Inc., Frazer, PA) [35] had no patients with complete remissions, although both studies revealed reductions in blood and bone marrow blasts in at least some patients. The authors of each study suggest that these agents may have a role in combination with chemotherapy [34, 35], and a phase III international trial is planned that will combine PKC-412 with daunorubicin and cytarabine, in an adjuvant setting, for newly diagnosed patients with AML.

Tipifarnib was evaluated in a phase II trial in previously untreated, high-risk patients with AML [36]. A complete response rate of 14% with a median duration of response of 7.3 months was achieved in a cohort of approximately 150 patients [36]. Research proceeded to a U.S. intergroup phase II trial (ECOG-SWOG-S0432) evaluating four dosing schedules. That trial, begun in 2004, is closed, but results have not yet been released. Because overexpression of the gene $BCL2$ is associated with poor outcome in AML, the antisense oligodeoxynucleotide oblimersen sodium was evaluated in conjunction with fludarabine, cytarabine, and G-CSF salvage chemotherapy in a phase I study of patients with refractory or relapsed AML or ALL [37]. The results were sufficiently encouraging to lead researchers to design a phase III trial (CALGB 10201), currently under way, that is comparing treatment with the combination of daunorubicin and cytarabine with or without oblimersen in older patients with previously untreated AML.

Finally, the agent clofarabine is a deoxyadenosine analogue intentionally designed to combine the favorable properties of fludarabine and cladribine, with multiple mechanisms of action, including inhibition of DNA replication and repair and disruption of mitochondrial function, leading to apoptosis. Clofarabine is active in both dividing and nondividing cells. This agent has been the subject of phase II trials in patients with AML, and results have been encouraging when it is used as a single agent [38, 39]. It will be further tested in a proposed ECOG study for newly diagnosed patients with AML who are over the age of 60.

Several other active agents, some of which are in clinical trials, are awaiting correlation with specific genetic subtypes. These include VNP40101M, a sulfonylhydrazine alkylating agent; tandutinib (MLN518), a small-molecule inhibitor of type 3 receptor tyrosine kinases; XL999, which inhibits multiple receptor kinases; low-dose decitabine; and the combination of arsenic plus low-dose cytarabine. Other
studies are anticipated for agents that may be active in specific genetic subtypes of AML—for example, the tyrosine kinase inhibitors imatinib and dasatinib in CKIT AML. Both histone deacetylase inhibitors and DNA methyltransferase inhibitors will likely be evaluated in MLL partial tandem duplication variants of AML [40], and an inosine monophosphate dehydrogenase inhibitor may be evaluated in BCR-ABL–positive AML [41].

References


