



Paul Gauguin. *Still Life with Onions, Beetroot and a Japanese Print*, 1889. Oil on canvas.

*Treatment regimens for acute myelogenous leukemia should be based on biologic and prognostic factors rather than on patient age.*

# Management of Acute Myelogenous Leukemia in the Elderly

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**Background:** Acute myelogenous leukemia (AML) is a hematopoietic neoplasm that primarily affects older adults. Despite scientific advances into the epidemiologic, genetic, and biological features of AML, this disease remains fatal to the majority of patients, particularly older individuals.

**Methods:** We review the biologic and clinical characteristics of AML in the elderly and the treatment options that have emerged for them during the past several years.

**Results:** Several biologic features of AML differ between older and younger individuals. Older patients often have disease that expresses multidrug resistance phenotype and cytogenetic abnormalities, which may be responsible in large part for the poor outcomes observed in older-aged subgroups. Traditional cytotoxic chemotherapy is associated with a low complete response rate and a high treatment-related mortality in older patients, which explains in part the poorer outcomes in cohorts over 60 years of age. Research into the pathophysiology of AML has revealed an abundance of intracellular signaling events that govern proliferation and survival of the malignant cell. Such discoveries have promoted recognition of new molecular and antigenic targets (eg, *Flt-3* kinase, *Ras*, *CD33* antigen) to which therapeutic development may be aimed.

**Conclusions:** New therapies directed against these unique targets may add to the current arsenal of antileukemic regimens and improve response rates and survival in older patients.

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## Introduction

Acute myelogenous leukemia (AML) is the most common type of leukemia among adults in the United States, and it afflicts the elderly more frequently than the young. However, little progress has been made in the long-term survival of older adults with AML. Conventional cytotoxic chemotherapy for AML can be asso-

ciated with serious adverse effects and, as a result, often cannot be tolerated by older patients. This age-related consequence raises conflicting issues. On one hand, the effect of modern therapy for AML in the elderly may be skewed by the underrepresentation of the elderly in clinical trials. In leukemia trials, less than 10% participants in NCI-sponsored cooperative group cancer treatment trials were older than 65 years, even though this cohort represents more than 55% of patients with leukemia.<sup>1</sup> On the other hand, results reported in the literature, largely based on cooperative group trials (using selected cohorts of patients who are well enough to enter such studies) probably grossly overestimate the true response rates, the duration of remission, and overall survival (OS) rates. A prospective British study of AML in the elderly found that only 89 of 200 patients newly diagnosed with AML were considered fit enough to receive treatment with curative intent.<sup>2</sup> This finding emphasizes that the elderly are frequently afflicted with comorbidities that preclude aggressive therapy.

This article reviews the biologic and clinical characteristics of AML in the elderly population and the treatment options that have emerged during the past several years.

## Epidemiology

The incidence of AML is relatively low. Approximately 10,500 new cases of AML are diagnosed annually in the United States, accounting for less than 1% of all cancers and 34% of all leukemias.<sup>3</sup> AML has a slight male predominance (1.2:1.0).<sup>3</sup> Age-specific incidences differ dramatically between acute lymphocytic leukemia (ALL) and AML, with a median patient age at diagnosis of 10 years and 65 years, respectively.<sup>4</sup> The incidence of AML is rare below the age of 40 but increases progressively with age, from approximately 1 per 100,000 at age 40 to more than 15 per 100,000 at age 75 and older.<sup>4</sup>

Risk factors for the development of AML include benzene exposure, which imparts a 1.9- to 10-fold increase in relative risk to exposed populations, and radiation exposure, which can result in a 2- to 6-fold increase in relative risk.<sup>5,6</sup> Secondary leukemias arising from previous chemotherapy for other malignancies are also well described. For example, patients with Hodgkin's disease receiving chemotherapy based on nitrogen mustard have an estimated 167-fold increase in relative risk for developing secondary AML.<sup>7</sup> An increased risk has also been observed in patients treated with regimens containing cisplatin or etoposide.<sup>7</sup> Because secondary AML is more common in the elder-

ly, and also because common malignancies are often treated with cisplatin or etoposide, the increased frequency of AML in the elderly may be attributable, at least in part, to these iatrogenic risks.

## Prognostic Factors

It is well known that successful treatment is far less common in elderly patients with AML than in younger patients. Comorbid disease with decreased therapeutic tolerance in the host, and particularly the adverse biology of the underlying disease, undoubtedly account for the differences in outcomes.

### *Cytogenetic Abnormalities*

Abnormal karyotypic features are common in AML. The importance of karyotype in defining the pathophysiology, natural history, and response to therapy in acute leukemia is a key concept.<sup>8,9</sup> Perhaps the most supportive evidence in this regard is the increased prevalence of various chromosomal abnormalities in older adults compared with younger patients with AML. The genetic mutations most often associated with treatment failure in young patients with AML (eg, abnormalities of chromosome 5 or 7 or complex karyotypes) are considerably more common in the elderly, occurring in 32% to 57% of patients.<sup>10</sup> Conversely, all of the "favorable" cytogenetic abnormalities, such as t(8;21), t(15;17), or inv(16), are more common in younger subjects and are responsible in part for their better disease-free survival.<sup>8</sup>

Results from the UK Medical Research Council AML 11 trial, in which the median age was 66 years, have identified the following prognostic groups<sup>10</sup> (Table 1):

- Favorable group [t(15;17), t(8;21), and inv(16)] — complete remission (CR) rate of 72% and 5-year OS rate of 34%
- Intermediate group (normal karyotype or non-complex karyotype) — CR rate of 53% to 63% and 5-year OS rate of 10% to 15%
- Poor prognosis group (complex karyotypes) — CR rate of 26% and 5-year OS rate of 2%

These categories are similar to those that have been defined for younger adults, although the survival rates are inferior. A report from the Southwest Oncology Group (SWOG) included 211 elderly patients with AML (mean age = 68 years).<sup>11</sup> Unfavorable cytogenetics were present in 32%; these patients had a much

Table 1. — Complete Remission Rates and 5-Year Survival Rates in Older Adults With Acute Myelogenous Leukemia Based on Initial Karyotypic Profile

Abnormality	No. of Patients	Complete Remission Rate (%)	Overall 5-Year Survival Rate (SE)
Favorable:			
t(15;17)	43	63	38 (8.2)
t(8;21)	23	87	35 (9.9)
inv(16)	12	75	17 (10.8)
Intermediate:			
No abnormality	507	63	15 (1.7)
Sole +8	41	51	5 (3.4)
11q23 (excludes patients with 11q23 in a favorable karyotype and in an adverse karyotype)	7	86	0 (0.0)
Other intermediate (includes all patients not otherwise classified as favorable or adverse risk)	221	54	11 (2.2)
Adverse:			
Noncomplex adverse (includes patients with 7,del(5q), -5, and abnormal (3q) alone and in combination with up to 3 other cytogenetic abnormalities)	66	45	7 (3.9)
Complex (with no favorable)	145	26	2 (1.2)
Overall:	1,065	55	13 (1.1)

From Grimwade D, Walker H, Harrison G, et al. The predictive value of hierarchical cytogenetic classification in older adults with acute myeloid leukemia (AML): analysis of 1065 patients entered into the United Kingdom Medical Research Council AML11 trial. *Blood*. 2001;98:1312-1320. Copyright American Society of Hematology, used with permission.

lower CR rate than those with favorable or intermediate cytogenetics (21% vs 55%). Similar results have been reported from the German AML Cooperative Group<sup>12,13</sup> and from a large Swedish study.<sup>14</sup>

The presence of certain cytogenetic abnormalities may be used to guide therapy. As an example, a study from the Cancer and Leukemia Group B (CALGB) included 42 patients with isolated trisomy 8, 60% of whom were more than 60 years of age.<sup>15</sup> Median survival was lower in patients over the age of 60 than in younger patients (4.8 vs 17.5 months). There were no long-term survivors among the older patients. The only long-term survivors were those younger than 60 years of age who were treated with autologous or allogeneic stem cell transplantation while in first CR.

### *Treatment-Related Acute Myelogenous Leukemia*

A clear cause of leukemia can be found in a minority of patients with a history of prior chemotherapy or radiation therapy. Such secondary leukemias, most of which are myeloid, are difficult to treat. Exposure to alkylating agents such as melphalan and cyclophosphamide increases the risk for secondary AML.<sup>16,17</sup> The risk of secondary AML is greatest between 2 and 9 years after therapy; 85% of cases occur before the 10th year and are often associated with abnormalities of chromosome 5 and/or chromosome 7. Another recognized type of secondary leukemia develops after exposure to agents that inhibit the DNA repair enzyme

topoisomerase II, such as etoposide, teniposide, and anthracyclines. This type of secondary AML has a shorter latency period and is associated with abnormalities of the long arm of chromosome 11.<sup>18</sup> The chromosomal abnormalities often observed in secondary leukemias are associated with poor prognosis, even when observed in patients without a history of prior therapy or toxic exposure. Particularly in the case of the alkylating agent-induced leukemias, the response to therapy is poor.<sup>19</sup>

### *Antecedent Hematologic Disorders*

Preexisting myelodysplastic or myeloproliferative disorders are common in older patients with AML, occurring in 24% to 40% of cases.<sup>20</sup> AML in elderly patients may evolve through a myelodysplastic phase characterized by the stepwise accumulation of genetic abnormalities; this process is analogous to the evolution of new chromosomal abnormalities that occurs as chronic myelogenous leukemia, myelofibrosis, or polycythemia vera evolves into the blast phase. Patients with “secondary” AML due to prior hematologic disease have a lesser response to therapy than those with de novo disease. In the series from SWOG, for example, the CR rates were 24% and 52%, respectively.<sup>11,20</sup>

### *MDR1 Phenotype and P-Glycoprotein*

The MDR1 phenotype may emerge during the evolutionary process of the leukemic cells. In the report from the SWOG noted above, 71% of elderly patients

with AML expressed MDR1 compared with 30% in younger subjects.<sup>11</sup> Patients with MDR1-positive disease were less likely to have a CR. The significance of this finding is unclear, since other studies have indicated that the presence of the MDR1 phenotype is or is not associated with reduced OS in AML.<sup>21,22</sup> On the other hand, in the SWOG study, elderly patients who had MDR1-negative AML cells and favorable or intermediate cytogenetics had a CR rate of 81%.<sup>11</sup> In another study involving 153 previously untreated patients with AML, positivity for P-glycoprotein (Pgp) did not adversely affect attainment of CR or OS unless Pgp was expressed along with lung resistance-related protein (LRP). The mean age of this latter subpopulation (LRP+/Pgp+) was 64 years, whereas that of the other groups (LRP+/Pgp-, LRP-/Pgp+, and LRP-/Pgp-) was 48 years ( $P=.009$ ), indicating that this adverse prognostic combination was more common in the elderly.<sup>23</sup>

### Comorbid Conditions

Increasing age and comorbid conditions are poor prognostic factors in elderly patients with AML.<sup>17</sup> Many of these patients are unable to withstand the rigors of intensive chemotherapy and its attendant complications. Acute toxicity from chemotherapy is greater in patients with age-related chronic cardiac, pulmonary, hepatic, or renal disorders. As an example, the age-related reduction in left ventricular ejection fraction may limit the use of anthracyclines or mitoxantrone. Older patients may also have lesser bone marrow regenerative capacity, even after successful leukemia cytoreduction. Their inability to tolerate long periods of pancytopenia and malnutrition as well as the nephrotoxicity of aminoglycosides or amphotericin are the major barriers to successful treatment.

## Treatment Considerations

The therapeutic strategy for most patients with AML has been divided into two general phases: remission induction and postremission therapy.

### Induction Therapy

The remission induction therapy in leukemia is designed to produce the rapid restoration of normal bone marrow function. The term *complete remission* is reserved for patients who have full recovery of normal peripheral blood counts with recovery of normal bone marrow cellularity; less than 5% blast cells are present in the bone marrow, and none can have a leukemic phenotype or cytogenetic abnormality. Induction therapy aims to reduce the total body leukemia cell population from approximately  $10^{12}$  to

below the cytologically detectable level of approximately  $10^9$  cells.<sup>24</sup>

For more than 20 years, standard remission induction chemotherapy has included an anthracycline and cytarabine. The most common regimen combines 3 days of daunorubicin with 7 days of continuous infusion of cytarabine. Using this regimen, in most prospective studies CR is achieved in 65% to 75% of patients younger than 60 years and in approximately 50% of those older than 60 years.<sup>25,26</sup> The reduced likelihood of CR among older patients is the result of an increased risk of resistant disease as well as increase risk of death from complications of pancytopenia. Other factors associated with the lower rate of CR after induction therapy include the presence of adverse cytogenetics, preceding hematologic disorders, and poor performance status at diagnosis, as described earlier. Drug types and doses in these larger trials were similar and typically consisted of daunorubicin 45 to 60 mg/m<sup>2</sup> for 3 days plus cytarabine 100 to 200 mg/m<sup>2</sup> over 7 days.

Given the relatively low response rate to standard therapy in the elderly, some investigators have attempted dose-intensive induction therapy. The German AML Cooperative Group has suggested that in older adults, 60 mg/m<sup>2</sup> of daunorubicin leads to a higher CR rate compared with 30 mg/m<sup>2</sup>.<sup>27</sup> The CALGB explored the benefit of adding additional drugs such as etoposide during induction in older patients. To date, no obvious change in the remission or mortality rates has become evident.<sup>28,29</sup>

A few prospective, randomized trials,<sup>30,31</sup> including one with older adults,<sup>32</sup> have compared the newer anthracycline, idarubicin, to daunorubicin in induction therapy, suggesting that idarubicin may be associated with higher CR rates. As these trials compared idarubicin doses of either 12 or 13 mg/m<sup>2</sup> to standard doses of daunorubicin (45 to 50 mg/m<sup>2</sup>), it is not clear that any improvement represents inherent biological advantage rather than biological dose equivalence. A recent Eastern Cooperative Oncology Group (ECOG) study in an older population showed no difference among three different anthracyclines when given in conjunction with cytarabine.<sup>33</sup> Another study in older adults comparing mitoxantrone to daunorubicin showed no benefit to mitoxantrone.<sup>34</sup>

At the present time, no induction regimen has been proven superior to daunorubicin 45 mg/m<sup>2</sup> for 3 days and cytarabine 100 mg/m<sup>2</sup> by continuous infusion for 7 days.

### Postremission Therapy

Postremission therapy is directed toward further reduction in the in the residual leukemic cell number,

which may be as high as  $10^8$  to  $10^9$  cells at initial CR. The elimination of these residual leukemic cells may be accomplished by either cytotoxic chemotherapy, causing significant myelosuppression and even myeloablation (eg, requiring autologous stem cell rescue) or by replacement of a patient's stem cells through allogeneic transplantation, a procedure combining myeloablation and immunotherapy. Selecting the optimal therapeutic approach for elderly patients who achieve a CR remains a subject of debate.

One approach to postremission therapy has been the use of high-dose cytarabine. The CALGB completed a large trial in adult AML using high-dose, intermediate-dose, or low-dose cytarabine as postremission therapy. In this trial, 596 patients in CR were randomized to consolidation with 4 cycles of conventional-dose cytarabine ( $100 \text{ mg/m}^2$  per day  $\times$  5 days), intermediate-dose cytarabine ( $400 \text{ mg/m}^2$  per day  $\times$  5 days) or high-dose cytarabine ( $3 \text{ g/m}^2$  total of 6 doses over 5 days). Among patients 60 years of age and younger, the 4-year disease-free survival rate was 44% in those receiving high-dose cytarabine compared with 24% in those who received conventional-dose cytarabine. However, patients older than age 60 did poorly regardless of the type of consolidation they received; less than 20% achieved durable remission, although only one third of patients in this age group received all 4 courses of high-dose cytarabine, primarily as a result of central nervous system toxicity.<sup>25</sup> A subsequent CALGB trial failed to demonstrate a benefit to modified high-dose cytarabine plus mitoxantrone in the consolidation setting.<sup>35</sup>

Thus, consolidation or maintenance chemotherapy for elderly patients with AML has not been proven beneficial. Caution is needed in extrapolating results from younger patients.

High-dose therapy followed by autologous or allogeneic stem cell transplant is another postremission therapeutic strategy. In younger patients, the advantage of high-dose myeloablative chemotherapy with autologous peripheral blood stem cell transplant for AML is not clearly established.<sup>36-38</sup> The role of transplantation in older adults is undefined, mainly due to exclusion of these patients from such trials. However, nonmyeloablative stem cell transplant regimens, which are believed to induce less treatment-related toxicity, are now being explored and developed and may have applicability in the elderly population.

Overcoming the drug resistance that frequently occurs in elderly patients with AML remains a major challenge to successful treatment. As such there has been much interest in applying allogeneic bone marrow transplant with its associated benefits of graft-vs-

leukemia effect to older adults with AML. However, this strategy does not appear feasible because treatment-related mortality in elderly patients (especially related to graft-vs-host disease) is high. Deeg et al<sup>39</sup> have recently reported a nonrelapse mortality of 39% in 50 MDS patients (16 with transformation to leukemia) who were between 55 and 66 years of age (median = 58.8) and were treated with conventional allogeneic stem cell transplantation. Encouraging results with low-intensity nonmyeloablative stem cell transplant in elderly AML patients have recently been reported,<sup>40</sup> thereby rekindling interest in utilizing allografting in such patients.

### *Supportive Care vs Antileukemic Chemotherapy*

Considering the high morbidity and mortality rates associated with standard induction therapy for AML in the elderly, coupled with low CR and survival rates, the potential benefits of any antileukemic therapy must be questioned. To this point, older adults with AML treated in cooperative group studies achieved only a 10-month median survival, with a 10% likelihood of long-term disease-free survival.<sup>35</sup>

The European Organization for Research and Treatment of Cancer (EORTC) performed a randomized clinical trial in patients over the age of 65 that compared daunorubicin, cytarabine, and vincristine therapy with a "watch and wait" strategy, using supportive care and resorting to cytoreductive chemotherapy only for relief of AML-related symptoms. The outcome was better with initial chemotherapy. The 31 patients receiving remission induction chemotherapy survived significantly longer (median, 21 weeks vs 11 weeks) than those in the supportive care group. Interestingly, the percent of remaining days spent in the hospital was similar in the two groups (54% vs 50%).<sup>41</sup>

Hence, the approach to withhold antileukemic treatment in elderly patients is not supported by published data. To the contrary, it appears that antileukemic therapy should be pursued and may offer longer survival for a considerable proportion of elderly patients.

### *Hematopoietic Growth Factors*

Hematopoietic growth factors have been tested in clinical trials in an attempt to reduce the toxicities that occur with dose-intensive treatments in older adults. The majority of the fatal events emerge from uncontrolled infections that have a frequency and severity closely related to the duration of neutropenia. Shortening this critical period by application of hematopoietic growth factors, such as granulocyte and granulo-

cyte-macrophage colony-stimulating factors (G-CSF and GM-CSF), might reduce the incidence of such complications. Initially, there was concern about the use of a myeloid growth factor in AML; however, a clinical trial conducted in patients with relapsed disease did not demonstrate stimulation of leukemic cells when G-CSF was used in support of chemotherapy.<sup>42</sup> Given the conflicting data in the early studies, several large randomized trials were conducted in an attempt to clarify the role of growth factors in AML treatment. However, only one trial, conducted by ECOG, has shown improvement in median OS in an intent-to-treat analysis for patients receiving GM-CSF (10.6 months vs 4.8 months).<sup>43</sup> In most other trials, hematopoietic growth factors were shown to shorten the period of neutropenia after induction therapy. In general, the CR and OS rates are not improved.<sup>44-49</sup>

Some studies have explored a novel application of growth factors to modify drug sensitivity. Both G-CSF and GM-CSF have been used before and during induction chemotherapy (as priming) in an effort to increase leukemia cell proliferation and sensitivity to cell cycle-specific agents. None of these trials have demonstrated any survival benefit in this strategy.<sup>46,50</sup>

Hence, despite intensive investigation, there is still no consensus regarding growth factors in AML therapy other than the observation that their use is safe and reduces the neutropenic period.

### Novel Therapeutic Approaches

Despite major advances in treatment and supportive care, a high percentage of elderly patients remain refractory to primary therapy or they relapse later with conventional cytotoxic therapy. Several different categories of new therapies are under development, including multidrug resistance (MDR) reversal agents, immunomodulatory therapies, and signal transduction targeting. Some of these targets being pursued in trials are listed in (Table 2).

**MDR Modulation:** Most of the trials with MDR modulators in AML have included patients with high-risk disease who are either in relapse or over 60 years of age. In a SWOG study of AML refractory to induction chemotherapy or in relapse following a chemotherapy-induced remission,<sup>51</sup> 226 patients received daunorubicin 45 mg/m<sup>2</sup> per day × 3 days plus cytarabine 3 g/m<sup>2</sup> per day × 5 days. Half were randomized to receive cyclosporine A 16 mg/kg per day by continuous infusion on days 6–8. The addition of cyclosporine A reduced the frequency of resistance to induction chemotherapy (31% vs 47%,  $P=.0077$ ). Whereas the CR rate was not significantly improved (39% vs 33%,

Table 2. — Targets for New Agents for Acute Myelogenous Leukemia

Targets	Agents
CD33	Gemtuzumab ozogamicin
CD45	<sup>131</sup> I-anti-CD45
MDR1/Pgp	Cyclosporine, PSC-833
Angiogenesis and/or VEGF	Thalidomide, SU-5416, bevacizumab antibodies
Hypermethylated chromatin	Decitabine
Histone deacetylase	Phenylbutyrate trichostatin A, trapoxin
Bcl-2	Bcl-2 antisense
S-phase checkpoint	UCN-01
20S proteasome	PS-341
Tyrosine kinase (c-kit receptor)	STI-571
Flt-3 kinase	CEP-701
Farnesyl transferase	BMS-214662, R115777

$P=.14$ ), the relapse-free survival rate (34% vs 9% at 2 years,  $P=.031$ ) and the OS rate (22% vs 12%,  $P=.046$ ) were significantly increased with cyclosporine A.

The CALGB conducted a phase III trial of Pgp modulator PSC-833 in untreated patients with AML who were 60 years of age and older. This trial was prematurely topped due to excessive early mortality in the PSC-833 arm. Despite this disappointing result, it was suggested that patients whose pretreatment cells exhibited PSC-833–modulated dye efflux in vitro actually benefited from PSC-833.<sup>29</sup> Further trials of MDR agents in older patients must await the design of less-toxic regimens.

**Immunotherapy:** CD33 is a membrane glycoprotein that is expressed in blasts from 80% to 90% of those with AML and is not expressed in nonhematopoietic tissues. Gemtuzumab ozogamicin (GO) is a humanized monoclonal antibody targeted against the CD33 antigen, which is conjugated to a highly potent antitumor antibiotic calicheamicin.

The combined results of three multicenter phase II trials of GO have recently been reported.<sup>27</sup> In these studies, 142 patients with AML in first relapse were treated with 9 mg/m<sup>2</sup> of GO on days 1 and 14. Overall, 30% of the patients achieved remission, defined as less than 5% blasts in marrow, recovery of red cell and neutrophil counts to normal, and platelet transfusion independence. Grade 3/4 elevations in transaminases occurred in 17% of patients and 1 patient died of apparent veno-occlusive disease of the liver. Based on its activity and favorable safety profile, GO was approved by the US Food and Drug Administration for the treatment of CD33+ AML in first relapse in patients 60 years of age

and older who are not good candidates for aggressive reinduction regimens.<sup>52</sup> In their recent small case-control study, Estey et al<sup>53</sup> concluded that single-agent GO (with or without the addition of interleukin-11) is less active than standard cytotoxic chemotherapy in front-line therapy of elderly patients with AML high-risk myelodysplastic syndrome, albeit the remission rates with GO were unexpectedly low. Gemtuzumab ozogamicin is now being combined with other cytotoxic agents. A recent report from the 44th American Society of Hematology Annual Meeting indicated that GO can be safely combined with traditional induction chemotherapy ("7+3") in previously untreated younger patients, with response rates similar to those seen with chemotherapy alone.<sup>54</sup> Median durations of response and survival have not yet been reached.

**Signal Transduction Inhibitors:** Inhibitors of cellular signal transduction, designed to inhibit proliferation and survival signals within leukemic cells, represent perhaps the most promising class of new agents for the treatment of AML in the elderly. Interruption of signal transduction can occur at the level of the cell surface, such as through inhibition of a growth factor receptor or through the inhibition of cytoplasmic enzymes that help to propagate these signals. One potential limitation of this anticancer approach is the diversity and redundancy of signal transduction pathways that lead to a certain cellular event. It appears that these agents will achieve their greatest potential when combined with other drugs that work through different mechanisms.

Farnesyl transferase inhibitors (FTIs) make up a promising new class of signal transduction inhibitors in AML. These agents selectively inhibit farnesyl transferase, a key enzyme. In a phase I study, R115777 given orally at doses of 100 to 200 mg twice daily  $\times$  4 weeks every 6 weeks induced two CRs and six partial remissions in 25 patients with high-risk acute leukemias (mainly relapsed/refractory AML). The dose-limiting toxicity was a central neurotoxicity.<sup>55</sup> Future research should address whether the molecular techniques can identify patients most likely to respond to an FTI. In addition, optimal administration schedules for these need to be defined, as well as the value of incorporating an FTI into combination regimens for difficult-to-treat hematologic malignancies.

The Flt-3 tyrosine kinase is also the target of a new inhibitor. Flt-3 plays an important role in the generation of cellular proliferation signals. A mutation of the gene for this receptor tyrosine kinase, which causes it to be in a constitutively activated state, is present in approximately 30% of AML cases.<sup>56,57</sup> Hence, Flt-3 is an attractive therapeutic target that may be preferentially more

active in AML cells than in normal cells. Inhibitors of Flt-3 tyrosine kinase are currently being tested in clinical trials.<sup>58,59</sup>

## Conclusions

Treatment of AML in the elderly remains a challenge. A higher frequency of unfavorable biologic and prognostic factors, rather than age per se, is the major determinant for the inferior prognosis for elderly patients. Therefore, treatment regimens should be individualized. Intensive chemotherapy with curative intent should be offered to older individuals who are otherwise healthy and without unfavorable cytogenetic features. Patients with unfavorable karyotypes and particularly with complex chromosome abnormalities have low expectations for current treatment modalities. In the frail elderly patients with unfavorable prognostic features, it may be acceptable to withhold treatment. A better understanding of the pathophysiology of AML in the elderly will lead to treatment approaches that are more targeted and less toxic. Until that goal is achieved, the priority is to ensure patient access to adequately designed clinical studies.

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