Acute Myeloid Leukemia and Myelodysplastic Syndromes in Older Patients

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ABSTRACT

The median age of patients with acute myeloid leukemia (AML) is 65 to 70 years. The majority of older patients with AML probably do not receive specific treatment, and those who receive standard regimens have a median survival time of less than 1 year. This suggests that, in general, older patients should receive investigational therapy; however, factors other than age influence survival after administration of standard treatment and need to be accounted for when making treatment recommendations. In some cases where investigational therapy is unavailable, palliative care may be the best option. Like AML, myelodysplastic syndrome (MDS) is a disease of the elderly. It is divided into higher and lower risk groups. The natural history of higher-risk MDS leads to consideration of reduction in transfusion needs and improvement in quality of life as primary goals of therapy. Lenalidomide, azacitidine, and decitabine, each recently approved by the US Food and Drug Administration, are useful in achieving these objectives.


Any discussion of acute myeloid leukemia (AML) in a geriatric population should begin with recognition of the difficulty in accurately defining such a population. In particular, it seems that each additional year of age above age 5 to 10 years is associated with a worse outcome.1 Thus, although clinical trials often consider patients aged 60 years and older to be elderly, there is less difference in outcome between, for example, a 58-year-old patient and a 61-year-old patient than between the same 61-year-old patient and a 69-year-old patient, although the 58-year-old patient would be considered young, and both the 61-year-old and 68-year-old patients would be considered elderly. However, for practical purposes, age ≥ 60 years is a commonly accepted criterion for elderly AML (with 60 years being 5 to 10 years less than the median age of all AML patients). Importantly, the effect of age is not constant throughout a patient’s course of treatment. Rather, approximately 1 year after treatment begins, the effect of age on prognosis disappears; this reflects the disproportionate influence of age on early death.2

Clinical trials typically include as eligible all older patients except those with a poor performance status, abnormal organ function, or active infection. These exclusions suggest that factors (covariates) other than age affect outcome. Such outcome is a sum of the probability of treatment-induced death (TID) and the probability of therapeutic resistance. Resistance means either a transient remission or no remission, with the inability to maintain a remission incompatible with survival. The distinction between TID and resistance is arbitrary, with overlap between the two categories, but often, deaths occurring within the first 6 weeks after beginning therapy are considered TID, with deaths occurring later ascribed to resistance; using this definition, resistance is the cause of death in 75% of older patients. Of particular note, at any given age, the risk of TID depends on, among other factors, performance status, bilirubin and creatinine (even within the normal range), the presence of infection, albumin, and beta2-microglobulin.3 The major predictor of resistance is not age but leukemia-cell cytogenetics, with a normal karyotype and the very rare cases with inv(16) or t (8;21) associated with the best outcome, abnormalities of chromosomes 5 and/or 7 associated with the worst outcome (except when, rarely, present as single abnormalities), and other karyotypes associated with an intermediate outcome. Furthermore, at any given age, an abnormal blood count for at least 1 month before diagnosis of AML (antecedent hematologic disorder [AHD]) or AML arising after chemotherapy for another disease (secondary AML) confers a worse prognosis, usually independent of cytogenetics.4 Leith et al5 found that presence of a protein (MDR1, also called P-glycoprotein) that promotes extrusion
of anthracyclines commonly used to treat AML was associated with a lower complete response (CR) rate, but not relapse-free survival rate, in older patients. In contrast, internal tandem duplications (ITD) of the FLT3 gene (but seemingly not mutations that do not affect the gene’s length) decrease relapse-free survival time but not CR rate; such ITDs are most commonly seen in the normal cytogenetic group.10 However, although older age is associated with poorer performance status, −5/−7, an AHD, secondary AML, and MDR1 (but not FLT3 ITDs), the deleterious effect of advancing age generally remains after accounting for these covariates.1,3-5 None-}

gelderly. The characteristics of untreated patients, as a group, are often the contention that there is no standard therapy for AML of the elderly patients probably do not receive anti-AML therapy, leading to the tendency to treat only very fit older patients.17,18 Indeed, most elderly patients probably do not receive anti-AML therapy, leading to the contention that there is no standard therapy for AML of the elderly. The characteristics of untreated patients, as a group, are often not known in adequate detail. Hence, the natural history of AML becomes difficult to specify, particularly compared with outcome with standard anti-AML therapy. In one of the few randomized studies to address the issue, the European Organisation for Research and Treatment of Cancer assigned patients aged more than 65 years to immediate 3+7 or to observation/supportive care, with use of chemotherapy (hydroxyurea or LDAC) if blood counts worsened or symptoms developed.19 Median survival time was 21 weeks in the 3+7 arm and 10 weeks in the observation arm, and the number of days spent in hospital was essentially identical. However, the degree to which the enrolled patients represented AML in the elderly is in some doubt because the enrolled patients had a performance status of less than 3 and relatively normal organ function, and 50% of the patients randomly assigned to observation had to begin therapy within 1 month, suggesting that they were on the verge of progression when randomly assigned. In contrast, it is commonly observed that AML in older patients can have an indolent course for months if not longer. However, regardless of their relative merits, 3+7, LDAC, and supportive care only are not appealing approaches for the majority of older patients with AML.

**General Inadequacy of Standard Anti-AML Therapy**

Two types of regimens may be considered standard. The first, known as 3+7, consists of 3 days of an anthracycline (usually daunorubicin or idarubicin) and 7 days of cytarabine (ara-C). Table 1 lists series reporting outcome with 3+7 in older patients. Despite variations in postremission therapy in these studies and possible differences in therapy after relapse, the table indicates that the average older patient with untreated AML can expect to live 8 to 12 months if administered 3+7 as initial therapy.11-15 The second standard regimen omits anthracyclines and reduces the dose of ara-C (low-dose ara-C [LDAC]). In one of the only randomized comparisons of 3+7 and LDAC, which involved 87 patients aged more than 65 years, Tilly et al16 found median survival times of 9 months with LDAC and 13 months with 3+7; however, patients administered LDAC spent less time in hospital (median time, 28 v 34 days, respectively) and required fewer transfusions (median, seven v 10 transfusions, respectively).

Reported survival data likely overestimate the effectiveness of standard therapy in older patients. This overestimation results from the tendency to treat only very fit older patients.17,18 Indeed, most elderly patients probably do not receive anti-AML therapy, leading to the contention that there is no standard therapy for AML of the elderly. The characteristics of untreated patients, as a group, are often not known in adequate detail. Hence, the natural history of AML becomes difficult to specify, particularly compared with outcome with standard anti-AML therapy. In one of the few randomized studies to address the issue, the European Organisation for Research and Treatment of Cancer assigned patients aged more than 65 years to immediate 3+7 or to observation/supportive care, with use of chemotherapy (hydroxyurea or LDAC) if blood counts worsened or symptoms developed.19 Median survival time was 21 weeks in the 3+7 arm and 10 weeks in the observation arm, and the number of days spent in hospital was essentially identical. However, the degree to which the enrolled patients represented AML in the elderly is in some doubt because the enrolled patients had a performance status of less than 3 and relatively normal organ function, and 50% of the patients randomly assigned to observation had to begin therapy within 1 month, suggesting that they were on the verge of progression when randomly assigned. In contrast, it is commonly observed that AML in older patients can have an indolent course for months if not longer. However, regardless of their relative merits, 3+7, LDAC, and supportive care only are not appealing approaches for the majority of older patients with AML.

**Most Elderly Patients Are Candidates for Investigational Therapies**

The data in Table 1 indicate that a principal reason to recommend investigational therapy for older patients with AML is the unsatisfactory outcome with standard therapy. Although scientific promise is a frequently cited reason for recommending an investigational therapy, history suggests that the promise of many therapies is not borne out by clinical trials. Furthermore, investigational therapies can prove worse than standard therapies. (An example is a trial of the MDR1 antagonist PSC-833 in older patients with untreated AML.)20 If this was not the case, random assignment between standard and investigational therapies would be problematic. Nonetheless, I believe that, in the majority of older patients with AML, the results with newer therapy cannot be much worse than those obtained with standard or no therapy. The view that elderly patients with AML are typically candidates for investigational therapy is widespread. For example, the National Comprehensive Cancer Network,21 a consortium of

| Table 1. Outcomes in Older Patients Administered Anthracycline Plus Cytarabine for AML |
|----------------------------------|-------|-----------|----------|------------|----------|--------|--------------|-----------------|
| Study                          | Group or Institution | No. of Patients | Age of Patients (years) | Median Survival Time (months) | Probability of Survival at 2 Years (%) | CR Rate (%) | Induction Death Rate (%) | Comment                      |
| Rowe et al11                    | ECOG   | 234       | ≥ 56      | 7-8        | ~ 20     | 41      | 19            | Results same with daunorubicin, idarubicin, or mitoxantrone and ± GM-CSF priming |
| Goldstone et al12              | NCRI (formerly MRC) | 1,314     | ≥ 56      | ~ 12       | ~ 25     | 62      | 16            | Results same with 1 or 4 courses after CR and ± G-CSF starting 8 days after end of induction |
| Anderson et al13               | SWOG   | 161       | ≥ 56      | 9          | 19       | 43      | 15            | Survival worse with mitoxantrone + etoposide |
| Van der Holt et al14           | HOVON  | 211       | ≥ 60      | ~ 10       | ~ 25     | 48      | 15            | Results same ± PSC-833 |
| Estey et al15                  | M.D. Anderson Cancer Center | 31        | ≥ 65      | ~ 12       | ~ 20     | 48      | Not given      | Cytarabine at 1.5 g/m² daily × 3; survival worse with single-agent gemtuzumab |

Abbreviations: AML, acute myeloid leukemia; CR, complete response; ECOG, Eastern Cooperative Oncology Group; GM-CSF, granulocyte-macrophage colony-stimulating factor; NCRI, National Cancer Research Institute; MRC, Medical Research Council; G-CSF, granulocyte colony-stimulating factor; SWOG, Southwest Oncology Group; HOVON, Stichting Haemato-Oncologie voor Volwassenen Nederland.
prominent American cancer centers, explicitly cites clinical trial as the preferred option in patients with untreated AML who are aged 60 years and elders.

Thinking in terms of covariates other than age allows identification of groups of older patients for whom standard therapy (3 + 7 or LDAC) might be reasonable. From the preceding discussion, one such group might be patients with the following characteristics: aged 60 to 69 years, performance status less than 2, normal bilirubin and creatinine, neither an AHD nor secondary AML, and no pretreatment infection. Such patients have a median survival time of 14 months after administration of various ara-C–containing regimens at M.D. Anderson Cancer Center over the past decade, with a 38% actuarial survival rate at 2 years, a 5% TID rate at 6 weeks, and a 70% CR rate (Table 2). Because investigational therapy can be worse than standard therapy, some patients in this group might prefer standard therapy.

The same might be said, although to a lesser extent, of patients aged 70 to 79 years but with an otherwise favorable configuration of performance status, bilirubin/creatinine/infection, and AHD/secondary AML (Table 2; the number of such patients aged 80 years and older is too small to warrant comment). However, patients less than age 80 years with otherwise favorable features composed only 17% of the patients seen during this time. The outcome of the remaining 83% of patients after ara-C–containing therapy is more problematic (Fig 1). For example, those patients aged ≥ 80 years only had an 11-week median survival time, with 39% dead within 6 weeks of beginning therapy (Table 2), which is similar to reports from an earlier period. The dominant effect of performance status is seen in the 21-month median survival time and 24% 6-week mortality rate in otherwise favorable patients who have a performance status more than 1. Patients with an AHD or secondary AML as their only unfavorable characteristic still had a median survival time of only 35 weeks, despite only a 9% 6-week TID rate. All of these patients are candidates for standard therapy. However, if such therapy is unavailable, then the preferred option in those patients aged ≥ 80 years or with a performance status more than 1 would seem to be supportive care only given their high early death rates; in contrast, 3 + 7 or LDAC might be more plausible in patients with only an AHD or secondary AML. As the number of unfavorable covariates increases, so should the reluctance to give standard therapy rather than investigational therapy.22,23

Any discussion of choice of therapy must refer to the observations of Sekeres et al24 that 74% of older patients estimated that their chances of cure with 3 + 7 were at least 50%; in contrast, 85% of their physicians estimated this chance to be less than 10%. Although the most plausible cause of this discrepancy is patients’ natural tendency to believe what they want to believe, there may also be gaps in communication between physicians and patients.

Role of Cytogenetics

Optimally, cytogenetics would inform initial management of untreated AML. For example, considering the most favorable patients in Table 2 (row 1), median survival time was 90 weeks in patients with a normal karyotype or, more rarely, an inv(16) or t (8;21) karyotype, with 46% alive at 2 years, versus a median survival time of 40 weeks in patients with other karyotypes, with 20% alive at 2 years (Fig 2). Accordingly, the former might be less receptive than the latter to investigational therapy. However, results of cytogenetic tests are often unavailable for at least 1 week, necessitating that physicians decide whether it is riskier to delay initiation of therapy or to administer potentially toxic standard therapy that is unlikely to be effective given the patient’s cytogenetics (or, in the case of a normal karyotype, to administer investigational therapy when standard therapy might be reasonably successful). The Eastern Cooperative Oncology Group reported that the 113 patients aged ≥ 55 years in whom logistical reasons necessitated a 3- to 5-day delay in beginning

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Table 2. Outcome According to Indicated Covariates After Cytarabine-Containing Therapy for AML at M.D. Anderson Cancer Center 1996 to 2006

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Performance Status</th>
<th>AHD or Secondary AML</th>
<th>Bilirubin/Creatinine (mg/dL)</th>
<th>Infection/FUO</th>
<th>No. of Patients</th>
<th>Median Survival Time (weeks)</th>
<th>% of Patients Dead By Day 42</th>
<th>CR Rate (%)</th>
<th>Probability of Survival at 2 Years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-69</td>
<td>0-1</td>
<td>No</td>
<td>&lt; 2</td>
<td>No</td>
<td>64</td>
<td>58</td>
<td>5</td>
<td>70%</td>
<td>38%</td>
</tr>
<tr>
<td>70-79</td>
<td>0-1</td>
<td>No</td>
<td>&lt; 2</td>
<td>No</td>
<td>51</td>
<td>46</td>
<td>2</td>
<td>59%</td>
<td>28%</td>
</tr>
<tr>
<td>≥ 80</td>
<td>Any</td>
<td>Yes or no</td>
<td>Any</td>
<td>Yes or no</td>
<td>46</td>
<td>11</td>
<td>39</td>
<td>39%</td>
<td>11%</td>
</tr>
<tr>
<td>60-79</td>
<td>&gt; 1</td>
<td>No</td>
<td>&lt; 2</td>
<td>No</td>
<td>21</td>
<td>21</td>
<td>24</td>
<td>67%</td>
<td>5%</td>
</tr>
<tr>
<td>60-69</td>
<td>0-1</td>
<td>Either or both</td>
<td>&lt; 2</td>
<td>No</td>
<td>127</td>
<td>35</td>
<td>9</td>
<td>55%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Abbreviations: AML, acute myeloid leukemia; AHD, antecedent hematologic disorder; FUO, fever of unknown origin; CR, complete response.
induction therapy had a CR rate of 38% compared with a CR rate of 50% in the 235 similarly aged patients who began the same therapies without such delay.11 M.D. Anderson Cancer Center data (unpublished data) suggest that a 1-week delay in beginning therapy in older patients with WBC counts less than 50,000/μL is associated with decreases in median survival time ranging from 4 to 28 weeks depending on other covariates.

If it does not enter into initial management decisions, cytogenetic information should be used in planning postremission therapy. In particular, patients with an abnormal karyotype would generally be poorer candidates for ara-C or anthracycline plus ara-C than patients with a normal karyotype.

**Investigational Approaches**

The first three agents listed in Table 3 (tipifarnib,25 lestaurtinib,26 and decitabine27) are examples of targeted therapy, although, particularly with tipifarnib and less so with lestaurtinib and decitabine, there is no direct correlation between response and the pretreatment status of, or the effect of the drug on, the presumed target. As seen in Table 3, response rates seem higher when the new agent is not a targeted therapy but bears more resemblance to a traditional cytotoxic agent (eg, dofarabine28 or VNP40101M [Cloretazine; Vion Pharmaceuticals, New Haven, CT]29). Accordingly, it is generally assumed that many targeted agents will eventually be combined with cytotoxic agents, as has been done with gemtuzumab ozogamicin (GO)30 and oblimersen sodium (Marcucci et al, submitted for publication; Table 3. In younger patients with favorable or intermediate karyotypes, gemtuzumab ozogamicin plus chemotherapy has been reported to lengthen relapse-free survival time32; whether the same is true in older patients is unknown.) Although not exhaustive, Table 3 makes several other relevant points. First, there is an increasing tendency to report responses (eg, CR with incomplete platelet recovery) less demanding than CR. Although it is known that achievement of CR prolongs survival, the effect of these lesser responses on survival remains to be established.33 Second, although patients are more interested in the number of PR1-specific CTLs; in contrast, there was no relationship between response and the number of CTLs directed against the control antigen PP65.43,44 Immune response was more common in patients in remission when beginning vaccination, leading to a soon to be initiated trial comparing PR1 vaccination with no further therapy in patients who are HLA-A2 positive and have completed three courses of postremission therapy.

Numerous studies comparing allogeneic stem-cell transplantation (SCT) with standard chemotherapy in patients less than age 60 years have found that the likely greater anti-AML effect of SCT is counterbalanced by greater TID, resulting on average in equivalent survival.37-41 Current thinking assigns more of a role to an immuno-logically mediated graft-versus-leukemia effect than to high-dose chemotherapy as the principal mediator of the anti-AML effect of SCT.41 If this is the case, it becomes feasible to use reduced-intensity conditioning (RIC) SCT (minitransplantation) to reduce TID. Estey et al42 described a systematic attempt to perform RIC-SCT in first CR in all M.D. Anderson patients aged ≥50 years with an abnormal karyotype and a sibling or matched unrelated donor. Matching for known prognostic factors suggested that the 14 patients who received transplantation had longer survival time than the 83 patients who did not receive transplantation, but these 14 patients represented only 5% of all treated patients aged more than 50 years with abnormal karyotypes. These results question the general applicability of RIC-SCT and suggest that it should be performed before patients enter first CR to increase the number of patients who might be candidates given the low CR rates in older patients. For example, older patients might initially receive a new agent. While waiting to see this agent’s effect, a donor search might be completed, as might various logistical arrangements. RIC-SCT would be performed once response to the new agent is known.

Cytotoxic T lymphocytes (CTLs) are proposed mediators of graft-versus-leukemia.45 Mølldrem et al46 have identified PR1, an HLA-A2-binding peptide derived from protease-3, as a myeloid leukemia-associated antigen for CTL, finding PR1-specific high-avidity CTLs in 11 of 12 patients with CML responding to interferon compared with none of seven patients without a response. They suggested that failure of myeloid leukemia patients to spontaneously develop an immune response to their disease resulted from overexpression of protease-3, leading to apoptosis of PR1-specific high-avidity CTLs.45 Clinical responses have followed PR1 vaccination of patients with AML and have occurred only in patients in whom there was an immune response, which was defined as ≥two-fold increase in the number of PR1-specific CTLs; in contrast, there was no relationship between response and the number of CTLs directed against the control antigen PP65.43,44 Immune response was more common in patients in remission when beginning vaccination, leading to a soon to be initiated trial comparing PR1 vaccination with no further therapy in patients who are HLA-A2 positive and have completed three courses of postremission therapy.

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**Fig 2.** Influence of cytogenetics on survival in patients in the better group described in Figure 1 who were aged 60 to 69 years (log-rank test, P = .02).
Clinical Practice Issues

Several practices that may have little effect on mortality but considerable effect on patients’ lives should be mentioned. First is hospitalization; given the more serious nature of hospital-acquired infection compared with community-acquired infection, the use of routine hospitalization after completion of a course of therapy should be questioned. The second practice involves masks and avoidance of crowds. The advice to avoid crowds seems inconsistent with observations that bacteria and fungi, rather than viruses, are the typical causes of infection in AML. The bacteria are invariably residents of the patients’ own skin, mouth, or intestines. The fungi are similarly found on the skin or are airborne. However, because of the organism’s size, it is unclear whether masks will restrict entry of *Aspergillus* into the nose. The third practice involves consumption of fresh fruits and vegetables. There is conflicting data as to whether avoidance of these foods lessens the risk of infection. An ongoing M.D. Anderson Cancer Center trial suggests that patients who are encouraged to eat fresh fruits and vegetables have similar infection rates as patients randomly assigned to not eat them (unpublished data).

**Table 3. Investigative Therapies in Patients Age ≥ 60 Years With Untreated AML**

<table>
<thead>
<tr>
<th>Type of Drug</th>
<th>Example</th>
<th>Study</th>
<th>No. of Patients</th>
<th>Median Age (years)</th>
<th>CR Rate (%)</th>
<th>Response &lt; CR Rate (%)</th>
<th>Effect on Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farnesyltransferase inhibitor</td>
<td>Tipifarnib</td>
<td>Lancet et al25</td>
<td>158</td>
<td>74</td>
<td>14</td>
<td>9</td>
<td>Median survival time, 5.3 months</td>
</tr>
<tr>
<td>FL73 inhibitor</td>
<td>Lestaurtinib (CEP701)</td>
<td>Knapper et al26</td>
<td>27</td>
<td>73</td>
<td>0</td>
<td>11</td>
<td>Not given</td>
</tr>
<tr>
<td>Hypomethylating agent</td>
<td>Decitabine (plus all-trans-retinoic acid)</td>
<td>Lubbert et al27</td>
<td>29</td>
<td>72</td>
<td>14</td>
<td>17</td>
<td>Median survival time, 7.5 months</td>
</tr>
<tr>
<td>Nucleoside analog</td>
<td>Clofarabine</td>
<td>Burnett et al28</td>
<td>66</td>
<td>71; included only patients aged ≥ 65</td>
<td>29</td>
<td>20</td>
<td>Median survival time, 5 months</td>
</tr>
<tr>
<td>Alkylating agent</td>
<td>VNP40101M (Clorezatine)</td>
<td>Karp et al29 (no AHD or secondary AML)</td>
<td>45</td>
<td>72</td>
<td>49</td>
<td>—</td>
<td>22% survival at 1 year</td>
</tr>
<tr>
<td>Anti-CD33 antibody attached to toxin</td>
<td>Gemtuzumab ozogamicin (+ ara-C)</td>
<td>De Angelo et al30</td>
<td>21</td>
<td>67</td>
<td>43</td>
<td>—</td>
<td>48% of patients alive with median follow-up time of 7 months</td>
</tr>
<tr>
<td>Bcl-2 antagonist: enhances apoptosis</td>
<td>Oblimersen sodium (added or not added to 3+7)</td>
<td>Marcucci et al (submitted for publication)</td>
<td>503</td>
<td>—</td>
<td>48 in patients who received oblimersen sodium; 82 in patients who did not receive oblimersen sodium</td>
<td>—</td>
<td>None; 1-year survival rate: 36% with oblimersen sodium, 40% without oblimersen sodium</td>
</tr>
<tr>
<td>MDR1 antagonist</td>
<td>PSC-833 Added or not added to 3+7 plus etoposide</td>
<td>Baer et al21</td>
<td>120</td>
<td>70</td>
<td>39 in patients who received PSC-833; 46 in patients who did not receive PSC-833</td>
<td>—</td>
<td>Median survival time of 2 months with PSC-833 and 7 months without PSC-833; study was stopped because of excess early deaths with PSC-833</td>
</tr>
<tr>
<td></td>
<td>Zosuquidar Added or not added to 3+7</td>
<td>Cripe et al31</td>
<td>442</td>
<td>67</td>
<td>—</td>
<td>None; median survival time of 7.7 with zosuquidar and 9.4 months without zosuquidar</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** AML, acute myeloid leukemia; CR, complete response; AHD, antecedent hematologic disorder; AML, acute myeloid leukemia; ara-C, cytarabine; 3+7; 3 days of an anthracycline and 7 days of cytarabine.

### MYELODYSPLASTIC SYNDROME

Like AML, myelodysplastic syndrome (MDS) is a disease that has an onset usually after age 60 years. Patients are usually classified as high or low risk.

**High-Risk MDS**

High-risk MDS generally implies International Prognostic Scoring System (IPSS) scores of intermediate-2 or high. All patients with 10% to 20% marrow blasts will meet these criteria, as will patients with two to three cytopenias and either 5% to 10% blasts and intermediate cytogenetics or less than 5% blasts and unfavorable cytogenetics, as defined by the IPSS. Life expectancy without treatment is typically less than 1.5 to 2 years. Thus, the natural history of high-risk MDS bears more resemblance to that of AML than to that of an indolent smoldering disease, which is how MDS, at times, is regarded. Furthermore, patients with AML and patients with high-risk MDS have similar outcomes when treated identically, after accounting for the older age of MDS patients and their tendency to have −5/−7 and longer
durations of abnormal blood counts. Indeed, the boundary between high-risk MDS and AML is malleable; previously defined by a narrow blast count of 30%, AML is now diagnosed when more than 20% blast counts are seen. Although there are undoubtedly biologic differences between high-risk MDS and AML, there is also likely to be biologic overlap, given the somewhat arbitrary distinction between the two entities.

Given the natural history of high-risk MDS, the primary goal of therapy is to lengthen survival. The US Food and Drug Administration has recently approved lenalidomide, decitabine, and azacitidine for treatment of MDS. However, too few patients with high-risk MDS have received lenalidomide to draw conclusions. Approval of decitabine in MDS was based on a randomized trial comparing supportive care plus decitabine (15 mg/m² every 8 hours for 3 days intravenously repeated every 6 weeks) with supportive care alone; approximately 70% of patients had high-risk MDS, with 25% of these patients having 20% to 30% blasts. Decitabine produced a response rate (CR + partial response + hematologic improvement, as defined by List et al53) of 30%, reduced RBC transfusion need, and improved quality of life. An analogous trial randomly assigning patients to either supportive care or supportive care plus azacitidine (75 mg/m² subcutaneously on days 1 through 7) prompted approval of azacitidine.58,59 Unlike the decitabine trial, crossover was permitted for patients in the supportive care group who remained transfusion dependent, developed worsening cytopenias, or had increased blasts. Forty-six percent of the patients for whom IPSS scores were known had high-risk MDS, and substantial numbers of these patients had AML, using the 20% blast criterion. The CR + partial response + hematologic improvement rate was 47% in the azacitidine arm compared with 17% in the supportive care arm. Both decitabine and azacitidine produced statistically significant delays in time to AML or death (eg, median time, 12.0 months for decitabine v 6.8 months for supportive care in high-risk patients). But neither drug resulted in a more than 5-month delay in median time to death; in the decitabine trial, the median time to death was 14.0 months for decitabine compared with 14.9 months for supportive care, with data not broken down by risk group; and in the azacitidine trial, the median time to death in patients who would probably currently be considered as high risk was 18 months in the azacitidine arm compared with 13 months in the supportive care arm. Although the ability to cross over to azacitidine decreased the difference in survival between supportive care and azacitidine, such a crossover would of course be done in clinical practice. The inability of azacitidine and decitabine to have more of an effect on survival may reflect the low CR rates each drug produced (9% for decitabine and 10% for azacitidine). In general, I believe time to AML or death is considerably less important than time to death; after all, patients presumably care little about whether they die with or without AML, and the definition of AML is itself arbitrary.

Given the data, I believe that decitabine, azacitidine (as administered in the randomized trials), and lenalidomide are not satisfactory options for patients with high-risk MDS. Accordingly, like older patients with AML, older patients with high-risk MDS are primarily candidates for investigational treatments.

Besides the investigational treatments noted earlier and in Table 3, there are other investigational therapies to consider. The first is low-dose decitabine. Two confounding factors in any analysis of the effects of azacitidine and decitabine are the number of courses administered and the interval between courses. Thus, in 50% of patients, at least three courses are needed to observe response to azacitidine,58,59,25% of responses or best responses were seen between course 5 and course 17. A similar phenomenon occurs with decitabine.57 Use of lower doses (eg, 20 mg/m² daily for 5 days) facilitates administration of more courses at more frequent intervals (eg, every 4 to 5 weeks). Using such an approach, Kantarjian et al50 reported a CR rate of 34% in 95 MDS patients, two thirds of whom were high-risk patients. In contrast, the CR rate was 9% in the randomized (higher dose, fewer and less frequent courses) trial.57 A similar approach might be taken with azacitidine.

Another investigational therapy is hypomethylating agents plus histone deacetylase inhibitors. The effect of azacitidine and decitabine is believed to be mediated by removal of methyl groups from various tumor suppressor genes, with hypomethylation restoring gene expression.61 Through a different mechanism, histone deacetylase inhibitors are also postulated to reactivate transcription of tumor suppressor genes.62 The possibility of synergy between these two classes of epigenetic-acting drugs has led to their combination (eg, azacitidine plus valproic acid, decitabine plus suberoylanilide hydroxamic acid) in ongoing clinical trials. Given the overlap between high-risk MDS and AML, low-dose decitabine and combination epigenetic therapy are also plausibly effective in AML.

Lower Risk MDS

Lower risk MDS includes patients with IPSS scores of intermediate-1 or low.68 The natural history is quite variable, but median survival times usually range from 2 to 10 years. This more benign natural history leads to consideration of reduction in RBC transfusion need and concomitant improvement in quality of life as primary goals. Table 4 presents an approach to management of lower risk MDS in transfusion-dependent patients. Lenalidomide is particularly effective in patients with deletion of the long arm of chromosome 5 (5q–).65 Sixty-seven percent of 148 patients with this abnormality became transfusion independent within a median of 4.6 weeks (range, 1 to 49 weeks) of beginning lenalidomide 10 mg daily for 21 days every 4 weeks, with independence maintained for at least 1 year in 62% of patients. There was no relationship between the complexity of the 5q karyotype and the likelihood of response, but multivariate analysis indicated that response was less likely in patients with thrombocytopenia or who required more than 4 units of RBCs in the 8 weeks before study entry.

Preliminary data suggest that lenalidomide may also be effective (but less so) in patients with a normal karyotype.66 However,
at present, I recommend erythropoietin (EPO) or darbepoetin (± granulocyte colony-stimulating factor) for patients without 5q– with a serum EPO level of less than 500 mU/mL, primarily because these drugs have fewer adverse effects than lenalidomide. Such patients have a 25% to 75% response rate, with the specific rate inversely related to the transfusion rate (eg, < 2 v 2 units/month).6,3

Some patients with MDS respond to immunosuppressive therapy (eg, antithymocyte globulin [ATG]), reflecting the autoimmune nature of MDS; indeed, there is overlap between aplastic anemia and MDS. ATG-responsive patients tend to be positive for HLA-DR15 and have an age in years and a duration of RBC transfusion dependence in months summing to less than 72.6,4

Patients who are not candidates for lenalidomide, EPO, or ATG are candidates for azacitidine, decitabine, or investigational therapies. One example of the latter is the PRI vaccine discussed in the section on AML.43

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SUMMARY

Most patients with untreated AML or high-risk MDS should receive investigational therapy. Covariates other than age affect outcome and should be used in deciding whether specific patients receive investigational or standard therapy or supportive care only in cases where investigational therapy is not feasible. There are several problems with the approaches used to conduct trials of new agents. Supportive care practices for older patients with AML or high-risk MDS should be questioned. Lenalidomide, azacitidine, and decitabine are important advances for patients with lower risk MDS.

AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author indicated no potential conflicts of interest.


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