Acute promyelocytic leukemia: evolving therapeutic strategies

Martin S. Tallman, Chadi Nabhan, James H. Feusner, and Jacob M. Rowe

Acute promyelocytic leukemia (APL) is now the most curable subtype of acute myeloid leukemia in adults. All-trans retinoic acid (ATRA), which induces differentiation of the leukemic cells into mature granulocytes, represents the important advance. The incorporation of ATRA in induction results in a high complete remission rate, leads to rapid resolution of the characteristic life-threatening coagulopathy, and, most importantly, decreases the relapse rate compared with treatment with chemotherapy alone. However, ATRA is associated with unique toxicities not observed with conventional cytotoxic chemotherapy. A number of clinical trials have been performed to define the optimal role of ATRA in the treatment of patients. The therapeutic strategies have rapidly evolved as a result of both single institution and large cooperative group trials. Arsenic trioxide and stem cell transplantation are effective treatments for patients with APL who relapse after or are refractory to ATRA-based therapy. As experience with ATRA and arsenic trioxide in patients with APL accumulates, a number of important questions arise that need to be addressed. (Blood. 2002;99:759-767)

Induction therapy

Role of cytarabine

Before 1992, induction therapy for patients with acute promyelocytic leukemia (APL) was similar to all other patients with acute myeloid leukemia (AML) and included an anthracycline and cytarabine. However, the leukemic cells from patients with APL are peculiarly sensitive to anthracyclines, perhaps because of significantly lower P-glycoprotein expression and other resistance markers in APL cells compared with other subtypes of AML.1-3

Both daunorubicin and idarubicin as single agents induce complete remission (CR) in 55% to approximately 90% of patients (Table 1).4-10 Two retrospective comparisons showed no difference in the CR rate between patients treated with daunorubicin alone or with daunorubicin and cytarabine.6,7 In addition, in a prospective randomized trial comparing idarubicin plus cytarabine to idarubicin alone, no difference in the CR rate was observed.10 In that trial, the CR rate was 76.3% with the single agent alone compared with 66.6% in the combination arm. The event-free survival (EFS) was 35% in the idarubicin arm compared with 35% in the combination arm (P = .0429). This finding suggests that omission of cytarabine may permit higher doses of anthracycline to be given. However, the dose of idarubicin in the single-agent arm was 72 mg/m² compared with 40 mg/m² in the combination arm. Therefore, patients in the monotherapy arm received 1.8 times as much anthracycline as in the combination arm. In a retrospective analysis, the Southwest Oncology Group showed excellent survival in patients with APL when a daunorubicin dose of 70 mg/m² per day was used compared with the dose used in most studies of 45 to 50 mg/m² per day, but without a change in cytarabine dose.11

The introduction of all-trans retinoic acid (ATRA) has prompted several study groups to exploit this peculiar sensitivity to anthracyclines by omitting cytarabine during induction (Table 2). Estey et al12 reviewed sequential studies at the MD Anderson Cancer Center and compared the current regimen of ATRA plus idarubicin with an earlier study of cytarabine with doxorubicin, amsacrine or daunorubicin without ATRA. The CR rate was 77% among patients treated with ATRA and idarubicin, which was not different from the historic cohort of patients. The Italian Cooperative group GIMEMA and the Spanish Cooperative group PETHEMA each combined ATRA with single-agent idarubicin given in conventional doses (12 mg/m² per day on days 2, 4, 6, and 8) and showed CR rates in the range of 70% to 95%.13-15

Nevertheless, the evidence appears compelling that cytarabine can be omitted during induction when an anthracycline is given with ATRA. The European APL Group is currently conducting a trial in which patients presenting with a white blood cell (WBC) count of 10,000/µL or fewer are prospectively and randomly assigned to ATRA and daunorubicin or to ATRA plus daunorubicin and cytarabine. The results of this trial should provide important information on the role of cytarabine in the treatment of APL.

Choice of anthracycline

There is no clear choice of anthracycline in induction in APL. Fenaux et al16 prospectively randomized patients to either rubidizone plus cytarabine or to amsacrine plus cytarabine, and the CR rate was 86% without any difference between the anthracyclines. Berman et al17 published a retrospective analysis in a preliminary form investigating prognostic factors in APL and suggested that idarubicin is associated with an improved outcome compared with daunorubicin or amsacrine. No prospective randomized trial has compared daunorubicin and idarubicin in APL. Therefore, no clear evidence proves that one anthracycline is clearly superior to another in APL. Despite theoretic considerations suggesting idarubicin may be better such as its relatively long half-life and good absorption,
central nervous system penetration, daunorubicin and idarubicin appear equally effective. It appears that what may be critical is the dose of anthracycline.\textsuperscript{31}

Combining ATRA with chemotherapy

Although early phase II trials showed a high CR rate with ATRA alone, the remission durations were short.\textsuperscript{16-21} Furthermore, some patients treated with ATRA alone developed a rapid increase in WBC count that in some, but not all, studies was associated with retinoic acid syndrome (RAS).\textsuperscript{22-27} Therefore, most cooperative groups initiated trials combining ATRA with intensive antileukemic chemotherapy. The European APL group has conducted a prospective randomized trial in which concurrent ATRA plus chemotherapy was compared with a sequential approach of ATRA followed by chemotherapy as postremission therapy.\textsuperscript{28} The EFS at 2 years was 84% among patients receiving the concurrent approach compared with 77% in the sequential arm. This difference was attributable to a significant decrease in the risk of relapse (at 2 years, 6% in the concurrent group versus 16% in the sequential group, $P = .04$). This benefit was observed even among patients presenting with a low WBC (< 5000/\mu L). Although the CR rate has not clearly increased and early mortality rate has not clearly decreased with the concurrent approach, the combination of ATRA plus chemotherapy as initial therapy has become an attractive strategy for all patients. This approach has the additional benefit of possibly reducing the incidence of RAS from approximately 25% with ATRA\textsuperscript{25,26} to approximately 10% with concurrent chemotherapy and ATRA (Table 3).\textsuperscript{13,14} Whether more intensive postremission chemotherapy with, for example, higher doses of anthracycline than has been customarily administered would have a similar effect on the relapse rate is not known. It appears reasonable to begin treatment first with ATRA for 2 to 4 days to ameliorate the coagulopathy before initiating chemotherapy, provided the WBC is not high (< 10 000/\mu L).

Table 1. Anthracycline monotherapy in acute promyelocytic leukemia

<table>
<thead>
<tr>
<th>Study, y</th>
<th>Anthracycline</th>
<th>No. of patients</th>
<th>Complete remission (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernard et al.,\textsuperscript{4} 1973</td>
<td>Daunorubicin</td>
<td>34</td>
<td>55</td>
</tr>
<tr>
<td>Collins,\textsuperscript{5} 1978</td>
<td>Daunorubicin</td>
<td>7</td>
<td>71</td>
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<tr>
<td>Party et al.,\textsuperscript{6} 1984</td>
<td>Daunorubicin</td>
<td>83</td>
<td>64</td>
</tr>
<tr>
<td>Petly et al.,\textsuperscript{7} 1987</td>
<td>Daunorubicin</td>
<td>30</td>
<td>67</td>
</tr>
<tr>
<td>Sanz et al.,\textsuperscript{8} 1988</td>
<td>Daunorubicin</td>
<td>34</td>
<td>68</td>
</tr>
<tr>
<td>Avvisati et al.,\textsuperscript{9} 1990</td>
<td>Idarubicin</td>
<td>27</td>
<td>81</td>
</tr>
<tr>
<td>Avvisati,\textsuperscript{10} 1999</td>
<td>Idarubicin</td>
<td>131</td>
<td>76</td>
</tr>
<tr>
<td>Fenaux et al.,\textsuperscript{11} 1991</td>
<td>Daunorubicin</td>
<td>35</td>
<td>88</td>
</tr>
</tbody>
</table>

Postremission therapy

Consolidation chemotherapy

It has become mandatory to administer consolidation chemotherapy after CR because early studies showed early relapse after ATRA alone. In most studies, consolidation chemotherapy has been anthracycline based. Three trials have included high-dose (1-3 g/m\textsuperscript{2}) cytarabine in consolidation.\textsuperscript{29,30} The North American Intergroup study administered one cycle of daunorubicin 45 mg/m\textsuperscript{2} per day for 3 days and standard-dose cytarabine 100 mg/m\textsuperscript{2} per day for 7 days as a first consolidation course followed by high-dose cytarabine 2 g/m\textsuperscript{2} twice daily for 4 days with 2 days of daunorubicin 45 mg/m\textsuperscript{2} per day for 2 days.\textsuperscript{30} Patients in the Medical Research Trial younger than 60 years received consolidation with cytarabine 1 g/m\textsuperscript{2} twice daily on days 1 to 3.\textsuperscript{30} The German AML Cooperative Group administered intensified double induction therapy including high-dose cytarabine with ATRA to newly diagnosed patients.\textsuperscript{31} Patients in CR received standard-dose cytarabine, daunorubicin, and 6-thioguanine consolidation and 3 years of monthly maintenance. The European APL group and the Japanese Adult Leukemia Study Group studies included standard-dose cytarabine as consolidation.\textsuperscript{23,32} However, just as there appears to be little role for cytarabine during induction, emerging data suggest that there is no role for high-dose cytarabine in consolidation. A prospective study published by the PETHEMA group suggests that patients do as well without cytarabine in either induction or consolidation.\textsuperscript{14} However, this study was not a randomized trial comparing idarubicin with or without cytarabine. It has become routine to administer at least 2 courses of postremission therapy after induction with ATRA and anthracyclines, although, as in all subtypes of AML, there are no prospective data establishing the number of courses of intensive postremission consolidation.\textsuperscript{33} The most important goal of postremission therapy is complete eradication of the leukemic clone as determined by the conversion to a polymerase chain reaction (PCR)–negative status, because persistence of such minimal residual disease (MRD) predicts relapse.\textsuperscript{30,34,37}

Role of maintenance therapy

Before the introduction of ATRA, several studies suggested a role for maintenance chemotherapy in patients with APL.\textsuperscript{6,38,39} Two large prospective randomized trials now suggest that maintenance therapy with ATRA is useful (Table 4).\textsuperscript{28,29,40} In the North American Intergroup study, patients in CR after 2 courses of consolidation chemotherapy were randomly assigned to either a year of daily maintenance ATRA at standard doses or to observation.\textsuperscript{29} This study showed a significant benefit when a year of daily maintenance ATRA is administered to patients whether they were induced into remission with chemotherapy alone or with ATRA. The best outcome was observed in patients who received ATRA during both induction and as maintenance with a 5-year disease-free survival of 74%.\textsuperscript{40} The European APL 93 trial randomly assigned patients in remission after anthracycline-based consolidation to one of 3 maintenance regimens or observation: ATRA in standard doses for 15 days every 3 months, or 6-mercaptopurine (6-MP) 90 mg/m\textsuperscript{2} per day plus methotrexate 50 mg/m\textsuperscript{2} per week, or the combination of ATRA and 6-MP/methotrexate as above.\textsuperscript{28} Patients receiving both ATRA and chemotherapy had the lowest relapse rate. In addition, overall survival (OS) was improved in patients receiving maintenance chemotherapy ($P = .01$), and there was a trend toward better survival in patients who received maintenance ATRA ($P = .22$). Furthermore, the combination of intermittent maintenance ATRA and continuous maintenance chemotherapy appeared to be particularly useful for patients presenting with a high WBC count. Therefore, at the present time, it appears that patients benefit from

Table 2. Anthracycline monotherapy with all-trans retinoic acid in acute promyelocytic leukemia

<table>
<thead>
<tr>
<th>Study, y</th>
<th>Anthracycline</th>
<th>No. of patients</th>
<th>Complete remission (%)</th>
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<tr>
<td>Estey et al.,\textsuperscript{12} 1997</td>
<td>Idarubicin</td>
<td>43</td>
<td>77</td>
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<tr>
<td>Avvisati,\textsuperscript{13} 1998</td>
<td>Idarubicin</td>
<td>480</td>
<td>93</td>
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<tr>
<td>Sanz et al.,\textsuperscript{14} 1999</td>
<td>Idarubicin</td>
<td>123</td>
<td>89</td>
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</table>
maintenance ATRA with or without continuous low-dose chemotherapy, particularly those at high-risk of recurrence such as those presenting with a high WBC count and older adults (> 60 years). The combination appears to be associated with the lowest relapse rate. However, the data on which these recommendations are made are based on small numbers of patients. The GIMEMA Cooperative Group is currently assigning patients in a randomized manner to the identical 3 maintenance regimens or to observation, and the North American Intergroup is currently assigning patients in CR in a randomized manner to either ATRA every other week with 6-MP and methotrexate or to ATRA alone. The results of these studies will aid in determining the optimal maintenance regimen and the patient population most likely to benefit. It is possible that higher doses of anthracyclines in induction or consolidation may obviate the need for maintenance therapy for some patients.

Prevention and management of RAS

The major toxicity of ATRA is RAS, a cardiorespiratory distress syndrome manifested by fever, weight gain, respiratory distress, interstitial pulmonary infiltrates, pleural and pericardial effusion, episodic hypotension, and acute renal failure. Among patients induced into remission with ATRA alone, the incidence is approximately 25% (Table 3). Among patients with the syndrome has declined over time (29% in the New York study versus 5% in the North American Intergroup study), likely reflecting earlier recognition and institution of dexamethasone. It is also possible that the risk factors for development of the syndrome were variable in the different studies. No factors are clearly predictive of the syndrome, including WBC count, although the presence of microgranular variant (M3v) morphology was protective in one study. An important issue concerns the potential difficulty in establishing an accurate diagnosis of the syndrome because patients may develop toxicities and complications of therapy, such as pneumonia, congestive heart failure, and sepsis, with manifestations that mimic RAS.

The concurrent administration of chemotherapy with ATRA may decrease the incidence of the syndrome. However, this decrease has not been clearly established. In the first report of the GIMEMA (ATRA plus idarubicin) trial in which all patients received concurrent therapy, the incidence of the syndrome was 10%. As experience with concurrent ATRA plus idarubicin accumulated, the incidence of the syndrome decreased to approximately 4%. In the Japanese Adult Leukemia Study Group trial in which chemotherapy was introduced early for the prevention of hyperleukocytosis, the incidence of the syndrome was 6%. An overall incidence of 15% was reported by the European APL group with a mortality rate of 8%. A review of the first North American Intergroup trial showed that 26% of patients treated with ATRA developed the syndrome at a median of 11 days; however, none of the patients who received ATRA as maintenance therapy developed the syndrome. No difference in the incidence of the syndrome was observed among patients treated with concurrent versus sequential ATRA and chemotherapy. The Australian Leukemia Study Group has explored the benefits of prophylactic corticosteroids in patients who develop leukocytosis (WBC > 10,000/μL). In a small nonrandomized study, 87 patients received prophylactic corticosteroids at a dose of 75 mg prednisone per day, and 16% of patients developed the syndrome that was fatal in 3%. This approach cannot be routinely recommended for all patients because no prospective randomized trial has confirmed the benefits given the potential toxicities of several weeks of corticosteroids in this setting. Therefore, it appears reasonable to evaluate the benefits of prophylactic corticosteroids in a prospective randomized fashion. This evaluation can likely be done safely because a small study has shown that dexamethasone did not unfavorably influence the induction of terminal differentiation by ATRA in NB4 cells.

It has been suggested that development of the syndrome may be associated with an increased incidence of extramedullary relapse. A number of reports have emerged, suggesting that the incidence of extramedullary relapse in APL, particularly in the central nervous system, is higher among patients previously exposed to ATRA than historically observed in patients treated with chemotherapy alone. This incidence may be related to modulation of adhesion molecules by ATRA.

Prognostic significance of a positive molecular test for the promyelocytic-retinoic acid receptor-α fusion transcript after chemotherapy

Reverse transcriptase (RT)–PCR has been shown to be an effective method to detect MRD in patients with APL in apparent CR. It is now clear that approximately 95% of patients are molecularly negative after intensive consolidation chemotherapy. However, a negative PCR test does not guarantee the absence of relapse. Overall, there is general agreement that a positive promyelocytic-retinoic acid receptor-α (PML/RARα) test after consolidation reliably predicts subsequent hematologic relapse, whereas repeatedly negative results are associated with long-term survival in most patients.

Table 3. Comparison of the incidence and outcome of the retinoic acid syndrome

<table>
<thead>
<tr>
<th>Study, y</th>
<th>N</th>
<th>Induction</th>
<th>Incidence (%)</th>
<th>Mortality (%) of patients with RAS</th>
<th>Mortality (%) of all treated patients due to RAS</th>
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<tr>
<td>Fenaux et al, 1999</td>
<td>413</td>
<td>ATRA + Chemo</td>
<td>15</td>
<td>8</td>
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<td>Tallman et al, 1997</td>
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<td>ATRA</td>
<td>26</td>
<td>5</td>
<td>1</td>
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<tr>
<td>Asou et al, 1998</td>
<td>196</td>
<td>ATRA + Chemo</td>
<td>6</td>
<td>9</td>
<td>0.5</td>
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<tr>
<td>Firkin et al, 1999</td>
<td>87</td>
<td>ATRA + Chemo</td>
<td>16</td>
<td>21</td>
<td>3</td>
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<td>Avvisati et al, 1998</td>
<td>480</td>
<td>ATRA + Chemo</td>
<td>9</td>
<td>4</td>
<td>0.4</td>
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<tr>
<td>Sanz et al, 1999</td>
<td>123</td>
<td>ATRA + Chemo</td>
<td>6</td>
<td>17</td>
<td>0.8</td>
</tr>
</tbody>
</table>

CT indicates chemotherapy (6-mercaptopurine plus methotrexate).

Table 4. Maintenance therapy in acute promyelocytic leukemia

<table>
<thead>
<tr>
<th>Study, y</th>
<th>N</th>
<th>Maintenance</th>
<th>Relapse rate (%)</th>
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<tr>
<td>Fenaux et al, 1999</td>
<td>270</td>
<td>ATRA + CT</td>
<td>5</td>
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<td>Sanz et al, 1999</td>
<td>123</td>
<td>ATRA + CT</td>
<td>20</td>
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<td>Tallman et al, 1997</td>
<td>94</td>
<td>ATRA + CT</td>
<td>32</td>
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<tr>
<td>Fenaux et al, 1999</td>
<td>270</td>
<td>ATRA + CT</td>
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<td>Sanz et al, 1999</td>
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<td>Tallman et al, 1997</td>
<td>94</td>
<td>ATRA + CT</td>
<td>32</td>
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</table>
| CT indicates chemotherapy (6-mercaptopurine plus methotrexate).
patients were induced into remission by ATRA combined with chemotherapy and were tested at regular pre-established time intervals after the end of treatment. Of 21 patients, 20 who converted to a positive PCR relapsed within a median of 3 months, whereas the 3-year estimate of relapse risk for patients who tested negative at least twice after consolidation was less than 10%. The molecular tests were carried out at similar time points from CR (at the end of consolidation, every 3 months during the first and second year, and then every 6 months during the third and fourth years), and the duration of follow-up was similar. Because patients who convert to a positive PCR can be salvaged early with chemotherapy before overt disease, this approach resulted in a significantly improved outcome compared with delaying treatment until morphologic evidence of relapse. It is anticipated that therapy at the time of molecular relapse will be associated with a lower mortality rate than that observed with reinduction of overt disease. Furthermore, aggressive chemotherapy such as high-dose cytarabine may be effective for patients who fail to achieve molecular remission with ATRA and daunorubicin. It is currently accepted that the persistence of a negative PCR is associated with long-term survival. A reasonable schedule of testing is to obtain at least 2 successive marrow samples at the end of treatment, every 3 months for the first 2 years of CR, and then every 6 months for the next 3 years. The use of quantitative PCR in the future will likely improve the ability to predict relapse because it is more sensitive in detecting minimal residual disease.

Should children with APL be treated differently than adults?

APL constitutes 6.2% to 8.7% of AML in children in the United States and up to 31% in some areas of Italy. Why is there is such an extreme variation in incidence is unknown and suggests the need for an international epidemiologic investigation. It is possible that the variability may be explained by the apparent increased incidence of APL in patients of Latino and Hispanic origin with AML. The typical clinical features of APL in adults, which include low WBC count at diagnosis, lack of hepatosplenomegaly or adenopathy, high incidence of coagulation abnormalities and signs of clinical hemorrhage, rarity of central nervous system leukemia, and special features of the microgranular variant, are also seen with this disease in children.

The results of contemporary treatment of children with APL also appear similar to those reported in adults. The CR rates for combination ATRA and anthracycline-based therapy have been reported to be 79% to 88% and long-term EFS of 64% to 76%.

There are, however, some special considerations in treating children with APL. The first special feature concerns the difficulty of some young patients to reliably swallow capsules. The pharmacokinetics of such delivery has not been studied, but there have been CRs in the few patients reported to have had nasogastric treatment. An alternative approach might be the use of a relatively newly developed liposomal ATRA compound. This agent may also be useful in intubated adult patients. It is given intravenously and has shown promising early results, but the responses of children in these trials have yet to be reported separately.

A second problem with the use of ATRA in pediatric patients (especially those younger than 10 years) is increased neurotoxicity. Both headache and pseudotumor cerebri have been shown to be more frequent in children compared with adults. Special recommendations are made for management of this problem that may necessitate withholding ATRA for a period of time, use of dexamethasone and/or acetazolamide, and then reinstitution of ATRA at a lower dosage. Because of this predisposition, children on maintenance ATRA should have periodic ophthalmologic examinations. This feature is not due to differences in the pharmacokinetics of ATRA in children compared with adults, because there are no apparent significant differences in this regard. It is speculated that the difference may be attributable to poorly understood end-organ sensitivity to ATRA in younger pediatric patients.

A final special circumstance for treating children with APL relates to a reluctance to expose children to daunorubicin doses larger than 400 mg/m² because of the cardiomyopathy reported in several studies. Because of this issue and the concern for additional cardiac toxicity that may be incurred if a marrow transplantation were required, the 2 major pediatric cooperative groups decided to limit the maximum daunorubicin exposure to children enrolled on the current North American Intergroup trial to a similar dose. In addition, frequent assessment of cardiac function is required for children on that trial. Whether delivery of daunorubicin by prolonged continuous infusion might decrease cardiac toxicity, as has been demonstrated in adults, has not been adequately studied in children. Other possible solutions, such as liposomal daunorubicin or the use of the cardioprotectant agent ICRF 187, require further study in children.

Should older adults with APL be treated differently than younger patients?

Older adults, arbitrarily defined in various studies as 65 to 70 years and older, with APL treated with ATRA appear to have a less favorable prognosis than younger adults. Age appears to be an important prognostic factor for both achievement of CR and overall survival. Despite the omission of potentially toxic consolidation that includes cytarabine and the addition of maintenance with both ATRA and low-dose chemotherapy, patients older than 70 years still had an inferior EFS compared with patients younger than 70 years. Most trials do indicate an inferior outcome in older adults, and it may be that even less intensive chemotherapy than reported by the PETHEMA group can favorably influence the outcome of older adults treated with ATRA/anthracycline-based therapy, because a high induction mortality appears to contribute to the inferior outcome in older adults. The death rate among patients in CR in the European APL93 trial (ATRA with either concurrent or sequential daunorubicin and cytarabine followed by daunorubicin plus cytarabine consolidation) was 19%, significantly higher than among patients aged 65 years or younger presenting with a WBC count less than 5000/μL or among all patients presenting with a WBC count more than 5000/μL. It is not clear whether older age itself confers a worse prognosis or rather a biologic issue unique to older adults that is as yet undefined. Because the major cause of failure in older adults is death in CR rather than failure to achieve CR, RAS, or relapse, alternative consolidation strategies such as liposomal ATRA, arsenic trioxide, or anti-CD33 antibody–based approaches should be explored.

Current role of arsenic trioxide in APL

Investigators from China reported that arsenic trioxide induces CR in patients with relapsed and refractory APL. Preclinical studies suggested that arsenic has several mechanisms of action, including apoptosis and leukemic cell differentiation. Soignet et al initiated a pilot study of 12 patients with relapsed APL who were treated with arsenic trioxide at doses ranging from 0.06 to 0.2 mg/kg per day until leukemic cells were eliminated.
from the bone marrow as determined by light microscopy. Eleven patients obtained CR, with 8 of the 11 patients who initially tested positive for the PML/RARα fusion transcript later becoming negative.99 This finding suggested a pivotal role for arsenic trioxide in patients with relapsed APL. A multicenter trial of 40 patients confirmed the high CR rate (85%).99 Furthermore, approximately 78% of patients had no evidence of the leukemic clone by PCR after 2 courses of arsenic trioxide.99 The most important toxicities include prolongation of the QTc interval and the APL differentiation syndrome, a cardiorespiratory distress syndrome with pulmonary infiltrates, reminiscent of the RAS, and responsive to dexamethasone.100 Two recent reports of sudden cardiac death with arsenic trioxide indicate that careful monitoring is warranted.101,102

Currently, arsenic trioxide is considered the treatment of choice for patients with relapsed disease, particularly in patients exposed to ATRA within the prior 12 months. Once patients achieve a second CR, the best postremission strategy is not known. Little data exist about the duration of remission and PCR negativity with arsenic alone in patients with relapsed APL. The disease-free survival appears to be better when patients in CR after arsenic are treated with arsenic plus chemotherapy compared with arsenic alone (2 of 11 relapses versus 12 of 18 relapses; P < .01, respectively).93 Although some patients do well with maintenance arsenic trioxide with or without chemotherapy, others relapse and may be considered for either autologous bone marrow transplantation (alloBMT) or autologous stem cell transplantation (ASCT) in second CR. As initial induction, arsenic trioxide has been associated with hepatotoxicity but has been evaluated in only a limited number of patients.93 Although the number of patients is small, it appears that arsenic trioxide is as effective for treatment of refractory or relapsed APL in children as in adults with a CR rate of 81% to 100%.92,98,103,104 The role of arsenic during the induction phase of treatment for newly diagnosed patients is being studied in the current North American Intergroup trial in which patients in CR are assigned randomly or not to 2 courses of arsenic trioxide as a first consolidation cycle before 2 cycles of daunorubicin with 1 week of ATRA. Ongoing trials are under way, combining arsenic trioxide with ATRA and chemotherapy in induction in newly diagnosed patients and evaluating its role in consolidation, based on potential synergism.105,106 Preliminary studies in a small cohort of patients testing lower doses of arsenic trioxide suggest similar efficacy as the standard dose with less toxicity.107

Stem cell transplantation in APL

In a survey from the European Bone Marrow Transplant Registry, Mandelli et al108 reported 362 patients, 187 of whom had undergone ASCT and 175 alloBMT between 1979 and 1992. Most of these patients received transplants in first CR before the routine use of ATRA. The results of this retrospective study suggested that approximately 45% of patients undergoing a transplantation procedure can be cured. However, there were no data comparing the outcome of the transplantation in relation to the induction regimen, and whether initial exposure to ATRA had prognostic value. The leukemia-free survival (LFS) in patients who received transplants in first CR was 48% for ASCT and 42% for alloBMT. However, treatment-related mortality (TRM) was 19% and 42%, respectively. Patients who received transplants in second CR had an LFS of 32% for ASCT and 22% for alloBMT with a TRM of 23% and 41%, respectively. Despite the limitations of this study, the information provides some perspective. Because combined ATRA and chemotherapy is potentially curative in 75% to 80% of newly diagnosed patients, it is not justifiable to recommend alloBMT as a consolidation strategy. There are no comparative trials of patients who were maintained on long-term therapy with ATRA compared with those undergoing transplantation.

Meloni et al109 reported 15 consecutive patients with relapsed APL who underwent ASCT with unpurged marrow. Thirteen patients received anthracycline-based chemotherapy as initial treatment, and 2 were treated by combined ATRA and idarubicin. All patients received 3 cycles of consolidation therapy. The first CR duration ranged from 6 to 40 months. Second CR was achieved in all patients with oral ATRA. All but 3 patients received consolidation therapy with intravenous cytarabine at 1 g/m² on days 1 through 4 and intravenous mitoxantrone at 6 mg/m² on days 1 through 4. The median time interval from the achievement of second CR to alloBMT was approximately 2 months. In this study, 6 (40%) of 15 patients remained alive and well, and they remain in molecular remission. All 7 patients who underwent alloBMT with persistent PCR-detectable MRD in the transfused cells relapsed within 9 months after transplantation, which confirms the value of PCR positivity during remission as a predictor of relapse in APL. Only 1 of 8 patients with negative PCR relapsed, and 1 patient developed secondary leukemia. The patient with secondary leukemia, however, received a different preparative regimen. This study demonstrates that patients with negative PCR after their second CR will fare favorably with ASCT and patients with positive PCR should not routinely be offered ASCT. It is impossible to speculate, based on this study alone, what the outcome would be after alloBMT, and whether the PCR results would have the same effect. In addition, these patients were treated before the routine use of ATRA as a primary therapy, or as a therapy for relapsed disease. Sanz et al110 on behalf of the European Blood and Marrow Transplantation group have reported an OS, LFS, relapse rate, and TRM for patients in first CR undergoing alloBMT of 77%, 70%, 15%, and 20%, respectively, and for ASCT of 73%, 70%, 24%, and 12%, respectively.110 For patients in second CR, the results for alloBMT were 58%, 57%, 15%, and 33%, respectively, compared with 40%, 45%, 44%, and 25% for ASCT, respectively.

Currently, there is little role for alloBMT in first CR because the outcome with current ATRA-based strategies is excellent.111 Most patients in first relapse achieve a second CR with arsenic trioxide. However, many patients relapse after arsenic-induced second CR, and there may be a benefit for postarsenic chemotherapy.93 In second CR it is acceptable to recommend transplantation. The outcome of ASCT with molecularly negative cells is excellent, and the TRM associated with alloBMT may be obviated, but these strategies have not been directly compared. The ability to detect MRD by molecular studies provides the unique opportunity to collect minimally contaminated stem cells.

**Prognostic factors in APL**

The presenting WBC count has been the most important prognostic factor in patients treated with ATRA plus chemotherapy. Various levels of WBCs have been reported to predict for outcome, with thresholds including 10 000/μL,32,84,85 5000/μL,39 and 2000/μL.40

| Table 5. Patients with relapsed and refractory acute promyelocytic leukemia achieving complete remission after one course of arsenic trioxide therapy |
|-----------------|---|---|---|
| Study, y        | N  | No. CRs | % CR |
| Zhang et al,97 99 | 42 | 22       | 52   |
| Niu et al,98 99  | 47 | 40       | 85   |
|                 | 25 | 24       | 96   |
| Soignet et al,98 99 | 12 | 11       | 92   |
| Soignet et al,98 2001 | 40 | 35       | 85   |
Table 6. Current recommendations for treatment of acute promyelocytic leukemia for patients not participating in a clinical trial

Newly diagnosed patients

| Induction* | ATRA 45 mg/m² per day until CR + an anthracycline, either daunorubicin 50 to 60 mg/m² per day for 3 days or idarubicin 12 mg/m² per day every other day for 4 days. |
| Consolidation | One to 2 cycles of anthracycline-based chemotherapy, daunorubicin 50 to 60 mg/m² per day for 3 days to PCR negativity, or alternatively anthracyclines/anthracenedione; idarubicin 5 mg/m² per day on days 1 to 4 (first consolidation), mitoxantrone 10 mg/m² per day on days 1 to 5 (second consolidation), idarubicin 12 mg/m² on day 1 (third consolidation). High-dose cytarabine can be considered for patients who remain PCR positive after such consolidation. |
| Maintenance | ATRA 45 mg/m² daily for 15 days every 3 months + 6-MP 100 mg/m² per day + MTX 10 mg/m² per week all for 2 years for all patients. |
| Follow-up | PCR for PML-RARα every 3 to 6 months for 2 years then every 6 months for 2 years. |

Relapsed disease

Arsenic trioxide 0.15 mg/kg per day or Monday through Friday to second CR followed by ASCT with reinfusion molecularly negative peripheral blood stem cells or allogeneic transplantation considered in younger patients if a suitable donor is available. For patients relapsing late (>12 months), ATRA may be used.

MTX indicates methotrexate.

*For pediatric patients, although by an infusional schedule a dose of daunorubicin 405 mg/m² may be exceeded, the total dose should not exceed 500 mg/m².

The PETHEMA and GIMEMA groups have identified risk based on WBC and platelet counts for patients treated with ATRA plus idarubicin for induction and for ATRA plus 6-MP and methotrexate for maintenance after anthracycline-based consolidation. Patients at low risk of relapse were those with a presenting WBC count less than 10 000/µL and a platelet count of 40 000/µL or more, high-risk if the WBC count was more than 10 000/µL, and intermediate risk if the WBC count was less than 10 000/µL and platelet count less than 40 000/µL. Female sex has been shown in several trials to confer a favorable outcome compared with male sex. The long and short PML-RARα fusion transcripts have been examined for prognostic importance. Although a less favorable outcome for the short form has been reported by several groups, others have not shown a difference. Few patients with the variable form have been studied to make conclusions about its prognostic value.

Expression of CD56, which reflects the neural crest adhesion molecule believed to be involved in trafficking of leukemia cells, has also been shown to be an unfavorable prognostic factor. The importance of cytogenetic abnormalities in addition to the t(15;17) in ATRA-treated patients is not clear, but, in one study reporting the results in a small number of patients (all treated with maintenance ATRA plus low-dose chemotherapy), no apparent adverse effect was observed. Among patients treated before the availability of ATRA, such changes have been reported to confer a poor prognosis, but this observation has not been confirmed in all studies. A recent study suggested that HLA-B13 was significantly associated with relapse. Patients at high risk such as those with a presenting WBC count more than 10 000/µL and those expressing CD56 can be considered for investigational strategies that may include the anti-CD33 antibody HuM195, which has been used to treat patients in CR who remain PCR positive.

Conclusions

Historically, APL was fatal for most patients. However, the introduction of ATRA as targeted therapy for APL has dramatically improved the outcome of this disease. With contemporary therapeutic strategies, it appears that a cure rate of 70% or higher is a reasonable expectation. Chemotherapy remains critically important in the management of APL, because most patients relapse with ATRA alone. In contrast to other subgroups of AML, the mainstay of chemotherapy is with anthracyclines (Table 6). The addition of cytarabine in induction may not be necessary and adds little benefit, if any, to postremission therapy. Consolidation with anthracycline-based chemotherapy is necessary. As with other subtypes of AML, the optimal dose and required number of cycles are unknown. Also in contrast with other subtypes of AML, maintenance therapy appears to have a unique role. The addition of low doses of chemotherapy to ATRA maintenance may further improve the long-term outcome.

Although the outlook for patients with APL has remarkably improved over the past decade, more than 20% of patients presenting with APL will still die of the disease. This percentage includes some patients who relapse even after achieving apparent eradication of the PML-RARα fusion transcript after appropriate induction and consolidation therapy. Although alloBMT has no role in APL in first CR, ASCT has been prospectively studied in patients with relapsed or refractory disease who have been successfully treated with ATRA and anthracyclines. One may speculate whether such therapy, using peripheral blood–derived stem cells with associated low mortality, can further improve the long-term cure rate. However, such a prospective study would require a very large number of patients and, therefore, is unlikely to be performed. RAS remains a potentially fatal complication, although increased experience with ATRA and early intervention have significantly reduced the magnitude of this problem. The outlook has also improved for patients with relapsed APL. Arsenic trioxide is clearly very effective in this setting. However, the optimal dose, schedule, and benefits when combined with other therapies, such as ATRA, chemotherapy, or transplantation, remain to be defined. Although the last decade has seen the introduction into clinical use of numerous targeted therapies for hematologic malignancies, ATRA has most dramatically changed the clinical course of a disease from one that was highly lethal to one that now appears highly curable.

References


Acute promyelocytic leukemia: evolving therapeutic strategies

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