

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 trans-

plantation 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)

© 2002 by The American Society of Hematology

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 rubidzone 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

From the Division of Hematology and Oncology, Robert H. Lurie Comprehensive Cancer Center, Northwestern University Medical School, Chicago, IL; Children's Hospital of Oakland, CA; and the Department of Hematology and Bone Marrow Transplantation, Technion Israel Institute of Technology, Rambam Medical Center, Haifa, Israel.

Submitted July 20, 2001; accepted September 30, 2001.

Reprints: Martin S. Tallman, Division of Hematology and Oncology, Robert H. Lurie Comprehensive Cancer Center, 676 N St Clair St, Suite 850, Chicago, IL 60611; e-mail: m-tallman@northwestern.edu.

© 2002 by The American Society of Hematology

Table 1. Anthracycline monotherapy in acute promyelocytic leukemia

Study, y	Anthracycline	No. of patients	Complete remission (%)
Bernard et al, ⁴ 1973	Daunorubicin	34	55
Collins, ⁵ 1978	Daunorubicin	7	71
Marty et al, ⁶ 1984	Daunorubicin	83	64
Petti et al, ⁷ 1987	Daunorubicin	30	67
Sanz et al, ⁸ 1988	Daunorubicin	34	68
Avvisati et al, ⁹ 1990	Idarubicin	27	81
Avvisati, ¹⁰ 1999	Idarubicin	131	76
Fenaux et al, ¹⁶ 1991	Daunorubicin	35	88

central nervous system penetration, daunorubicin and idarubicin appear equally effective. It appears that what may be critical is the dose of anthracycline.¹¹

Combining ATRA with chemotherapy

Although early phase II trials showed a high CR rate with ATRA alone, the remission durations were short.¹⁸⁻²¹ 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).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.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 ($< 5000/\mu\text{L}$). 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^{25,26} to approximately 10% with concurrent chemotherapy and ATRA (Table 3).^{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 ($< 10\,000/\mu\text{L}$).

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/m²) cytarabine in consolidation.²⁹⁻³¹ The North American Intergroup study administered one cycle of daunorubicin 45 mg/m² per day for 3 days and standard-dose cytarabine 100 mg/m² per day for 7 days as a first consolidation course followed by high-dose cytarabine 2 g/m² twice daily for 4 days with 2 days of daunorubi-

cin 45 mg/m² per day for 2 days.²⁹ Patients in the Medical Research Trial younger than 60 years received consolidation with cytarabine 1 g/m² twice daily on days 1 to 3.³⁰ The German AML Cooperative Group administered intensified double induction therapy including high-dose cytarabine with ATRA to newly diagnosed patients.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.^{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.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 anthracycline, although, as in all subtypes of AML, there are no prospective data establishing the number of courses of intensive postremission consolidation.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.^{30,34-37}

Role of maintenance therapy

Before the introduction of ATRA, several studies suggested a role for maintenance chemotherapy in patients with APL.^{6,38,39} Two large prospective randomized trials now suggest that maintenance therapy with ATRA is useful (Table 4).^{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.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%.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/m² per day plus methotrexate 50 mg/m² per week, or the combination of ATRA and 6-MP/methotrexate as above.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

Study, y	Anthracycline	No. of patients	Complete remission (%)
Estey et al, ¹² 1997	Idarubicin	43	77
Avvisati, ⁴² 1998	Idarubicin	480	93
Sanz et al, ¹⁴ 1999	Idarubicin	123	89

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

Study, y	N	Induction	Incidence (%)	Mortality (%) of patients with RAS	Mortality (%) of all treated patients due to RAS
Fenaux et al, ²⁸ 1999	413	ATRA ± Chemo	15	8	1
Frankel et al, ⁴¹ 1994	78	ATRA	27	29	8
Tallman et al, ²⁹ 1997	172	ATRA	26	5	1
Asou et al, ³² 1998	196	ATRA ± Chemo	6	9	0.5
Firkin et al, ⁴⁴ 1999	87	ATRA + Steroids	16	21	3
Avvisati, ⁴² 1998	480	ATRA + Chemo	9	4	0.4
Sanz et al, ¹⁴ 1999	123	ATRA + Chemo	6	17	0.8

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.¹¹

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.⁴¹ Among patients induced into remission with ATRA alone, the incidence is approximately 25% (Table 3).^{25,26,41} The mortality rate of 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,²⁶⁻²⁹ although the presence of microgranular variant (M3v) morphology was protective in one study.²⁶ An additional 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%.¹³ As experience with concurrent ATRA plus idarubicin accumulated, the incidence of the syndrome decreased to approximately 4%.^{15,42} 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%.³² An overall incidence of 15% was reported by the European APL group with a mortality rate of 8%.²⁸ 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.²⁶ 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/ μ L). 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%.^{43,44} 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.⁴⁵

It has been suggested that development of the syndrome may be associated with an increased incidence of extramedullary relapse.⁴⁶ 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.⁴⁷⁻⁵¹ This incidence may be related to modulation of adhesion molecules by ATRA.⁵²

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.^{53,54} It is now clear that approximately 95% of patients are molecularly negative after intensive consolidation chemotherapy.^{15,30} However, a negative PCR test does not guarantee the absence of relapse.³⁰

Overall, there is general agreement that a positive promyelocytic-retinoic acid receptor- α (PML/RAR α) test after consolidation reliably predicts subsequent hematologic relapse, whereas repeatedly negative results are associated with long-term survival in most patients.⁵⁵ Diverio et al³⁷ reported a prospective study in which 163

Table 4. Maintenance therapy in acute promyelocytic leukemia

Study, y	N	Maintenance	Relapse rate (%)
Sanz et al, ¹⁴ 1999	123	ATRA + CT	5
Fenaux et al, ²⁸ 1999	63	ATRA	20
	64	ATRA + CT	9
	63	CT	22
	67	Observation	32
Tallman et al, ²⁹ 1997	94	ATRA	32
	105	Observation	57

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.³⁷ 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,⁵⁶ 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.⁵⁷ It is currently accepted that the persistence of a negative PCR is associated with long-term survival.⁵⁸ 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 2 to 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.^{59,60}

Should children with APL be treated differently than adults?

APL constitutes 6.2% to 8.7% of AML in children in the United States^{61,62} and up to 31% in some areas of Italy.⁶³ Why 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.⁵⁵ 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.⁶³⁻⁶⁸

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%⁶⁸⁻⁷¹ and long-term EFS of 64% to 76%.⁶⁹⁻⁷²

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.⁷³ An alternative approach might be the use of a relatively newly developed liposomal ATRA compound.⁷⁴⁻⁷⁶ 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.^{77,78} 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.⁷⁹ It is speculated that the difference may be attributable to poorly understood enhanced end-organ sensitivity to ATRA in younger pediatric patients.⁷⁹

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.⁸⁰⁻⁸² 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,⁸³ 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.^{24,28,30,32,84-87} Age appears to be an important prognostic factor for both achievement of CR^{14,32} as well as EFS^{14,28,32} and, in one study, early death and overall survival.²⁸ 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.¹⁴ 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 ($P = .01$) than among patients aged 65 years or younger presenting with a WBC count less than 5000/ μ L or among all patients presenting with a WBC count more than 5000/ μ L. 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,⁷⁴⁻⁷⁶ arsenic trioxide, or anti-CD33 antibody-based approaches should be explored.^{88,89}

Current role of arsenic trioxide in APL

Investigators from China reported that arsenic trioxide induces CR in patients with relapsed and refractory APL (Table 5).⁹⁰⁻⁹³ Preclinical studies suggested that arsenic has several mechanisms of action, including apoptosis and leukemic cell differentiation.⁹⁴⁻⁹⁷

Soignet et al⁹⁸ 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

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, ⁹¹ 1996	42	22	52
Niu et al, ⁹³ 1999	47	40	85
	25	24	96
Soignet et al, ⁹⁸ 1998	12	11	92
Soignet et al, ⁹⁹ 2001	40	35	85

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/RAR α fusion transcript later becoming negative.⁹⁸ 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 allogeneic 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 6mg/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/ μ L,^{32,84,85} 5000/ μ L,³⁰ and 2000/ μ L.⁴⁰

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-RAR α 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.⁸⁶ Patients at low risk of relapse were those with a presenting WBC count less than 10 000/ μ L and a platelet count of 40 000/ μ L or more, high-risk if the WBC count was more than 10 000/ μ L, and intermediate risk if the WBC count was less than 10 000/ μ L and platelet count less than 40 000/ μ L. Female sex has been shown in several trials to confer a favorable outcome compared with male sex.^{40,84} The long and short PML-RAR α fusion transcripts have been examined for prognostic importance. Although a less favorable outcome for the short form has been reported by several groups,^{25,112} others have not shown a difference.^{84,113,114} Few patients with the variable form have been studied to make conclusions about its prognostic value.¹¹⁵ 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.^{116,117} 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.¹⁴ 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.^{118,119} A recent study suggested that HLA-B13 was significantly associated with relapse.¹²⁰ Patients at high risk such as those with a presenting WBC count more than 10 000/ μ L 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.¹²¹

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-RAR α 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

1. Paietta E, Andersen J, Racevskis J, et al. Significantly lower P-glycoprotein expression in acute promyelocytic leukemia than in other types of acute myeloid leukemia: immunological, molecular and functional analyses. *Leukemia*. 1994;8:968-973.
2. Michieli M, Damiani D, Ermacora A, et al. P-glycoprotein (PGP), lung resistance-related protein (LRP) and multidrug resistance-associated protein (MRP) expression in acute promyelocytic leukaemia. *Br J Haematol*. 2000;108:703-709.
3. Takeshita A, Shinjo K, Naito K, et al. Role of P-glycoprotein in all-trans retinoic acid (ATRA) resistance in acute promyelocytic leukaemia cells: analysis of intracellular concentration of ATRA. *Br J Haematol*. 2000;108:90-92.

4. Bernard J, Weil M, Boiron M, Jacquillat C, Flandrin G, Gemon MF. Acute promyelocytic leukemia: results of treatment by daunorubicin. *Blood*. 1973;41:489-496.
5. Collins AJ, Bloomfield CD, Peterson BA, McKenna RW, Edson JR. Acute promyelocytic leukemia: management of the coagulopathy during daunorubicin-prednisone remission induction. *Arch Intern Med*. 1978;138:1677-1680.
6. Marty M, Ganem G, Fischer J, et al. Acute promyelocytic leukemia: retrospective study of 119 patients treated with daunorubicin. *Nouv Rev Fr Hematol*. 1984;26:371-387.
7. Petti MC, Avvisati G, Amadori S, et al. Acute promyelocytic leukemia: clinical aspects and results of treatment in 62 patients. *Haematologica*. 1987;72:151-155.
8. Sanz MA, Jarque I, Martin G, et al. Acute promyelocytic leukemia: therapy results and prognostic factors. *Cancer*. 1988;61:7-13.
9. Avvisati G, Mandelli F, Petti MC, et al. Idarubicin (4-demethoxydaunorubicin) as single agent for remission induction of previously untreated acute promyelocytic leukemia: a pilot study of the Italian cooperative group GIMEMA. *Eur J Haematol*. 1990;44:257-260.
10. Avvisati G. Event-free survival (EFS) duration in newly diagnosed acute promyelocytic leukemia (APL) is favorably influenced by induction treatment with idarubicin alone: final results of the GIMEMA randomized study (LAP389) comparing idarubicin+Ara-C in newly diagnosed APL [abstract]. *Blood*. 1999;94:2259a.
11. Head D, Kopecky KJ, Weick J, et al. Effect of aggressive daunomycin therapy on survival in acute promyelocytic leukemia. *Blood*. 1995;86:1717-1728.
12. Estey E, Thall PF, Pierce S, Kantarjian H, Keating M. Treatment of newly diagnosed acute promyelocytic leukemia without cytarabine. *J Clin Oncol*. 1997;15:483-490.
13. Avvisati G, Lo Coco F, Diverio D, et al. AIDA (all-trans retinoic acid + idarubicin) in newly diagnosed acute promyelocytic leukemia: a Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) pilot study. *Blood*. 1996;88:1390-1398.
14. Sanz MA, Martin G, Rayon C, et al. A modified AIDA protocol with anthracycline-based consolidation results in high antileukemic efficacy and reduced toxicity in newly diagnosed PML/RAR-alpha-positive acute promyelocytic leukemia. *Blood*. 1999;94:3015-3021.
15. Mandelli F, Diverio D, Avvisati G, et al. Molecular remission in PML/RAR alpha-positive acute promyelocytic leukemia by combined all-trans retinoic acid and idarubicin (AIDA) therapy. Gruppo Italiano-Malattie Ematologiche Maligne dell'Adulto and Associazione Italiana di Ematologia ed Oncologia Pediatrica Cooperative Groups. *Blood*. 1997;90:1014-1021.
16. Fenaux P, Tertan G, Castaigne S, et al. A randomized trial of amsacrine and rubidazole in 39 patients with acute promyelocytic leukemia. *J Clin Oncol*. 1991;9:1556-1561.
17. Berman E, Little C, Kher U, et al. Prognostic analysis of patients with acute promyelocytic leukemia [abstract]. *Blood*. 1991;78:43a.
18. Huang ME, Ye YC, Chen SR, et al. Use of all-trans retinoic acid in the treatment of APL. *Blood*. 1988;72:567-572.
19. Chen ZX, Xue YQ, Zhang R, et al. A clinical and experimental study on all-trans retinoic acid-treated acute promyelocytic leukemia patients. *Blood*. 1991;78:1413-1419.
20. Castaigne S, Chomienne C, Daniel MT, et al. All-trans retinoic acid as a differentiation therapy for acute promyelocytic leukemia. I. Clinical results. *Blood*. 1990;76:1704-1709.
21. Castaigne S, Chomienne C, Daniel MT, et al. Retinoic acids in the treatment of acute promyelocytic leukemia. *Nouv Rev Fr Hematol*. 1990;32:36-38.
22. Warrell RP Jr, Frankel SR, Miller WH Jr, et al. Differentiation therapy of acute promyelocytic leukemia with tretinoin (all-trans-retinoic acid). *N Engl J Med*. 1991;324:1385-1393.
23. Fenaux P, Castaigne S, Dombret H, et al. All-trans-retinoic acid followed by intensive chemotherapy gives a high complete remission rate and may prolong remissions in newly diagnosed acute promyelocytic leukemia: a pilot study on 26 cases. *Blood*. 1992;80:2176-2181.
24. Fenaux P, Le Deley MC, Castaigne S, et al. Effect of all-trans-retinoic acid in newly diagnosed acute promyelocytic leukemia: results of a multicenter randomized trial. European APL 91 Group. *Blood*. 1993;82:3241-3249.
25. Vahdat L, Maslak P, Miller WH, et al. Early mortality and the retinoic acid syndrome in acute promyelocytic leukemia: impact of leukocytosis, low-dose chemotherapy, PMN/RAR-alpha isoform, and CD13 expression in patients treated with all-trans retinoic acid. *Blood*. 1994;84:3843-3849.
26. Tallman MS, Andersen JW, Schiffer CA, et al. Clinical description of 44 patients with acute promyelocytic leukemia who developed the retinoic acid syndrome. *Blood*. 2000;95:90-95.
27. De Botton S, Dombret H, Sanz M, et al. Incidence, clinical features, and outcome of all-trans-retinoic acid syndrome in 413 cases of newly diagnosed acute promyelocytic leukemia. The European APL Group. *Blood*. 1998;92:2712-2718.
28. Fenaux P, Chastang C, Chevret S, et al. A randomized comparison of all-trans-retinoic acid (ATRA) followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. The European APL Group. *Blood*. 1999;94:1192-1200.
29. Tallman MS, Andersen JW, Schiffer CA, et al. All-trans-retinoic acid in acute promyelocytic leukemia. *N Engl J Med*. 1997;337:1021-1028.
30. Burnett AK, Grimwade D, Solomon E, Wheatley K, Goldstone AH. Presenting white blood cell count and kinetics of molecular remission predict prognosis in acute promyelocytic leukemia treated with all-trans retinoic acid: result of the Randomized MRC Trial. *Blood*. 1999;93:4131-4143.
31. Lengfelder E, Reichert A, Schoch C, et al. Double induction strategy including high-dose cytarabine in combination with all-trans retinoic acid: effects in patients with newly diagnosed acute promyelocytic leukemia. *Leukemia*. 2000;14:1362-1370.
32. Asou N, Adachi K, Tamura J, et al. Analysis of prognostic factors in newly diagnosed acute promyelocytic leukemia treated with all-trans retinoic acid and chemotherapy. Japan Adult Leukemia Study Group. *J Clin Oncol*. 1998;16:78-85.
33. Rowe JM. Uncertainties in the standard care of acute myelogenous leukemia. *Leukemia*. 2001;15:677-679.
34. Lo Coco F, Avvisati G, Diverio D, et al. Molecular evaluation of response to all-trans-retinoic acid therapy in patients with acute promyelocytic leukemia. *Blood*. 1991;77:1657-1659.
35. Grimwade D, Howe K, Langabeer S, Burnett A, Goldstone A, Solomon E. Minimal residual disease detection in acute promyelocytic leukemia by reverse-transcriptase PCR: evaluation of PML-RAR alpha and RAR alpha-PML assessment in patients who ultimately relapse. *Leukemia*. 1996;10:61-66.
36. Miller WH Jr, Kakizuka A, Frankel SR, et al. Reverse transcription polymerase chain reaction for the rearranged retinoic acid receptor alpha clarifies diagnosis and detects minimal residual disease in acute promyelocytic leukemia. *Proc Natl Acad Sci U S A*. 1992;89:2694-2698.
37. Diverio D, Rossi V, Avvisati G, et al. Early detection of relapse by prospective reverse transcriptase-polymerase chain reaction analysis of the PML/RAR-alpha fusion gene in patients with acute promyelocytic leukemia enrolled in the GIMEMA-AIEOP multicenter "AIDA" trial. GIMEMA-AIEOP Multicenter "AIDA" Trial. *Blood*. 1998;92:784-789.
38. Kantarjian HM, Keating MJ, Walters RS, et al. Role of maintenance chemotherapy in acute promyelocytic leukemia. *Cancer*. 1987;59:1258-1263.
39. Fenaux P, Pollet JP, Vanderbossche-Simon L, et al. Treatment of acute promyelocytic leukemia: a report of 70 cases. *Leuk Lymphoma*. 1991;4:239-248.
40. Tallman MS, Andersen JW, Schiffer CA, et al. All-trans retinoic acid in acute promyelocytic leukemia: long-term outcome results and prognostic factor analysis from Intergrup protocol 0129 [abstract]. *Blood*. 1999;94:3086a.
41. Frankel SR, Eardley A, Heller G, et al. All-trans retinoic acid for acute promyelocytic leukemia: results of the New York Study. *Ann Intern Med*. 1994;120:278-286.
42. Avvisati G. AIDA Protocol: the Italian way of treating APL [abstract]. *Br J Haematol*. 1998;102:593a.
43. Wiley JS, Firkin FC. Reduction of pulmonary toxicity by prednisolone prophylaxis during all-trans retinoic acid treatment of acute promyelocytic leukemia. Australian Leukaemia Study Group. *Leukemia*. 1995;9:774-778.
44. Firkin FC, Mathews JP, Bradstock KF, Wiley JS. A phase II study of all-trans retinoic acid (ATRA) with prednisone prophylaxis in the treatment of acute promyelocytic leukemia (APL) [abstract]. *Proc Am Soc Clin Oncol*. 1999;94:4225a.
45. de Ridder MC, van der Plas AJ, Erpelinck-Verschueren CA, Löwenberg B, Jansen JH. Dexamethasone does not counteract the response of acute promyelocytic leukaemia cells to all-trans retinoic acid. *Br J Haematol*. 1999;106:107-110.
46. Ko BS, Tang JL, Chen YC, et al. Extramedullary relapse after all-trans retinoic acid treatment in acute promyelocytic leukemia—the occurrence of retinoic acid syndrome is a risk factor. *Leukemia*. 1999;13:1406-1408.
47. Weiss MA, Warrell RP Jr. Two cases of extramedullary acute promyelocytic leukemia: cytogenetics, molecular biology, and phenotypic and clinical studies. *Cancer*. 1994;74:1882-1886.
48. Wiernik PH, DeBellis R, Muxi P, Dutcher JP. Extramedullary acute promyelocytic leukemia. *Cancer*. 1996;78:2510-2514.
49. Liso V, Specchia G, Pogliano EM, et al. Extramedullary involvement in patients with acute promyelocytic leukemia: a report of seven cases. *Cancer*. 1998;83:1522-1528.
50. Evans GD, Grimwade DJ. Extramedullary disease in acute promyelocytic leukemia. *Leukemia Lymph*. 1999;33:219-229.
51. de Botton S, Chevret S, Thomas X, et al. Incidence and outcome of central nervous system (CNS) relapses in acute promyelocytic leukemia (APL) treated with all-trans retinoic acid (ATRA) and chemotherapy (CT) [abstract]. *Blood*. 1999;94:1319.
52. Brown DC, Tsuji H, Larson RS. All-trans retinoic acid regulates adhesion mechanism and transmigration of the acute promyelocytic leukemia cell line NB-4 under physiologic flow. *Br J Haematol*. 1999;107:86-98.
53. Ikeda K, Sasaki K, Tasaka T, et al. Reverse transcription-polymerase chain reaction for PML-RAR alpha fusion transcripts in acute promyelocytic leukemia and its application to minimal residual leukemia detection. *Leukemia*. 1993;7:544-548.
54. Fukutani H, Naoe T, Ohno R, et al. Prognostic significance of the RT-PCR assay of PML-RARA transcripts in acute promyelocytic leukemia. The

- Leukemia Study Group of the Ministry of Health and Welfare (Kouseisho). *Leukemia*. 1995;9:588-593.
55. Douer D, Preston-Martin S, Chang E, et al. High frequency of acute promyelocytic leukemia among Latinos with acute myeloid leukemia. *Blood*. 1996;87:308-313.
 56. Lo Coco F, Diverio D, Avvisati G, et al. Therapy of molecular relapse in acute promyelocytic leukemia. *Blood*. 1999;94:2225-2229.
 57. Hoffman R, Haddad N, Sahar D, Rosenbaum H, Brenner B, Rowe JM. High-dose cytarabine therapy induces a molecular remission in APL patients who failed to achieve a complete response following treatment with ATRA and anthracyclines [abstract]. *Blood*. 1998;92:2517.
 58. Lo Coco F, Diverio D, Falini B, Biondi A, Nervi C, Pellicci PG. Genetic diagnosis and molecular monitoring in the management of acute promyelocytic leukemia. *Blood*. 1999;94:12-22.
 59. Cassinat B, Zassadowski F, Balitrand N, et al. Quantitation of minimal residual disease in acute promyelocytic leukemia patients with t(15;17) translocation using real-time RT-PCR. *Leukemia*. 2000;14:324-328.
 60. Tobal K, Moore H, Macheta M, Yin Liu JA. Monitoring minimal residual disease and predicting relapse in APL by quantitating PML-RAR α transcripts with a sensitive competitive RT-PCR method. *Leukemia*. 2001;15:1060-1065.
 61. Steuber CP, Civin C, Krischer J, et al. A comparison of induction and maintenance therapy for acute nonlymphocytic leukemia in childhood: results of a Pediatric Oncology Group study. *J Clin Oncol*. 1991;9:247-258.
 62. Argyle JC, Benjamin DR, Lampkin B, Hammond D. Acute nonlymphocytic leukemias of childhood: inter-observer variability and problems in the use of the FAB classification. *Cancer*. 1989;63:295-301.
 63. Biondi A, Rovelli A, Cantu-Rajoldi A, et al. Acute promyelocytic leukemia in children: experience of the Italian Pediatric Hematology and Oncology Group (AIEOP). *Leukemia*. 1994;8:1264-1268.
 64. Carter M, Kalwinsky DK, Dahl GV, Santana VM, Mason CA, Schell MJ. Childhood acute promyelocytic leukemia: a rare variant of nonmyeloid leukemia with distinctive clinical and biologic features. *Leukemia*. 1989;3:298-302.
 65. Engelhard D, Yatziv S, Rachmilewitz E, Polliack A. Acute promyelocytic leukemia in childhood. *Acta Haematol*. 1979;62:282-284.
 66. Chan KW, Steinherz PG, Miller DR. Acute promyelocytic leukemia in children. *Med Pediatr Oncol*. 1981;9:5-15.
 67. Rovelli A, Biondi A, Cantu-Rajoldi A, et al. Microgranular variant of acute promyelocytic leukemia in children. *J Clin Oncol*. 1992;10:1413-1418.
 68. Shimizu H, Nakadate H, Taga T, et al. Clinical characteristics and treatment results of acute promyelocytic leukemia in children. Children's Cancer and Leukemia Study Group. *Rinsho Ketsu*—Jpn J Clin Hematol. 1993;34:989-996.
 69. Hirota T, Fujimoto T, Katano N, et al. Treatment results of intermittent and cyclic regimen with ATRA and chemotherapy in childhood acute promyelocytic leukemia. Children's Cancer and Leukemia Study Group. *Rinsho Ketsu*—Jpn J Clin Hematol. 1997;38:1177-1182.
 70. Bapna A, Nair R, Tapan KS, et al. All-trans-retinoic acid (ATRA): pediatric acute promyelocytic leukemia. *Pediatr Hematol Oncol*. 1998;15:243-248.
 71. Mann G, Reinhard D, Ritter J, et al. Treatment with all-trans retinoic acid in acute promyelocytic leukemia reduces early deaths in children. *Ann Hematol*. 2001;80:417-422.
 72. Guglielmi C, Martelli M, Diverio D, et al. Immunophenotype of adult and childhood acute promyelocytic leukaemia: correlation with morphology, type of PML gene break-point and clinical outcome: a cooperative Italian study on 196 cases. *Br J Haematol*. 1998;102:1035-1041.
 73. Bargetzi MJ, Tichelli A, Gratwohl A, Speck B. Oral all-trans-retinoic acid administration in intubated patients with acute promyelocytic leukemia. *Schweiz Med Wochenschr*. 1996;126:1944-1945.
 74. Estey EH, Giles FJ, Kantarjian H, et al. Molecular remissions induced by liposomal-encapsulated all-trans retinoic acid in newly diagnosed acute promyelocytic leukemia. *Blood*. 1999;94:2230-2235.
 75. Douer D, Estey E, Santillana S, et al. Treatment of newly diagnosed and relapsed acute promyelocytic leukemia with intravenous liposomal all-trans retinoic acid. *Blood*. 2001;97:73-80.
 76. Estey E, Koller C, Cortes J, et al. Treatment of newly-diagnosed acute promyelocytic leukemia with liposomal all-trans retinoic acid. *Leukemia Lymphoma*. 2001;42:309-316.
 77. Smith MA, Adamson PC, Balis FM, et al. Phase I and pharmacokinetic evaluation of all-trans-retinoic acid in pediatric patients with cancer. *J Clin Oncol*. 1992;10:1666-1673.
 78. Mahmoud HH, Hurwitz CA, Roberts WM, Santana VM, Ribeiro RC, Krance RA. Tretinoin toxicity in children with acute promyelocytic leukemia. *Lancet*. 1993;342:1394-1395.
 79. Adamson PC. Clinical and pharmacokinetic studies of all-trans-retinoic acid in pediatric patients with cancer. *Leukemia*. 1994;8(suppl 3):S22-S25.
 80. Silber JH, Jakacki RI, Larsen RL, Goldwein JW, Barber G. Increased risk of cardiac dysfunction after anthracyclines in girls. *Med Pediatr Oncol*. 1993;21:477-479.
 81. Godoy LY, Fukushige J, Igarashi H, Matsuzaki A, Ueda K. Anthracycline-induced cardiotoxicity in children with malignancies. *Acta Paediatr Jpn*. 1997;39:188-193.
 82. Krischer JP, Epstein S, Cuthbertson DD, Goorin AM, Epstein ML, Lipshultz SE. Clinical cardiotoxicity following anthracycline treatment for childhood cancer: the Pediatric Oncology Group experience. *J Clin Oncol*. 1997;15:1544-1552.
 83. Legha SS, Benjamin RS, Mackay B, et al. Reduction of doxorubicin cardiotoxicity by prolonged continuous intravenous infusion. *Ann Intern Med*. 1982;96:133-139.
 84. Chou WC, Tang JL, Yao M, et al. Clinical and biological characteristics of acute promyelocytic leukemia in Taiwan: a high relapse rate in patients with high initial and peak white blood cell counts during all-trans retinoic acid treatment. *Leukemia*. 1997;11:921-928.
 85. Ohno R, Asou N, Kanamaru A, Miyawaki S, Ohtake S, Tomonaga M. The JALSG APL92 Study for newly diagnosed acute promyelocytic leukemia (APL): analysis of prognostic factors to increase cure rate in the next study [abstract]. *Blood*. 1999;94:2262a.
 86. Sanz M, LoCoco F, Martin G, et al. Definition of relapse risk and role of nonanthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study of the PETHMA and GIMEMA Cooperative groups. *Blood*. 2000;96:1247-1253.
 87. Latagliata R, Avvisati G, Lo Coco F. The role of all-trans-retinoic acid (ATRA) treatment in newly-diagnosed acute promyelocytic leukemia patients aged > 60 years. *Ann Oncol*. 1997;8:1273-1275.
 88. Jurcic JG, Caron PC, Miller WH Jr, et al. Sequential targeted therapy for relapsed acute promyelocytic leukemia with all-trans retinoic acid and anti-CD33 monoclonal antibody M195. *Leukemia*. 1995;9:244-248.
 89. Jurcic JG, DeBlasio T, Dumont L, Yao TJ, Scheinberg DA. Molecular remission induction with retinoic acid and anti-CD33 monoclonal antibody HuM195 in acute promyelocytic leukemia. *Clin Cancer Res*. 2000;6:372-380.
 90. Sun H, Ma L, Hu X, Zhang T. Treatment of acute promyelocytic leukemia by Ailing-1 therapy with use of syndrome differentiation of traditional Chinese medicine. *Chin J Comb Trad Chin Med West Med*. 1992;12:170-172.
 91. Zhang P, Wang S, Hu X. Arsenic trioxide treated 72 cases of acute promyelocytic leukemia. *Chin J Hematol*. 1996;17:58-62.
 92. Shen Z, Chen G, Ni J. Use of arsenic trioxide in the treatment of APL, clinical efficacy and pharmacokinetics in relapsed patients. *Blood*. 1997;89:3354-3360.
 93. Niu C, Yan H, Yu T, et al. Studies on treatment of acute promyelocytic leukemia with arsenic trioxide: remission induction, follow-up, and molecular monitoring in 11 newly diagnosed and 47 relapsed acute promyelocytic leukemia patients. *Blood*. 1999;94:3315-3324.
 94. Chen GQ, Zhu J, Shi XG, et al. In vitro studies on cellular and molecular mechanisms of arsenic trioxide (As₂O₃) in the treatment of acute promyelocytic leukemia: As₂O₃ induces NB4 cell apoptosis with downregulation of Bcl-2 expression and modulation of PML-RAR alpha/PML proteins. *Blood*. 1996;88:1052-1061.
 95. Shao W, Fanelli M, Ferrara FF, et al. Arsenic trioxide as an inducer of apoptosis and loss of PML/RAR alpha protein in acute promyelocytic leukemia cells. *J Natl Cancer Inst*. 1998;90:124-133.
 96. Chen GQ, Shi XG, Tang W, et al. Use of arsenic trioxide (As₂O₃) in the treatment of acute promyelocytic leukemia (APL): I. As₂O₃ exerts dose-dependent dual effects on APL cells. *Blood*. 1997;89:3345-3353.
 97. Jing Y, Dai J, Chalmers-Redman RM, et al. Arsenic trioxide selectively induces acute promyelocytic leukemia cell apoptosis via a hydrogen peroxide-dependent pathway. *Blood*. 1999;94:2102-2111.
 98. Soignet SL, Maslak P, Wang ZG, et al. Complete remission after treatment of acute promyelocytic leukemia with arsenic trioxide. *N Engl J Med*. 1998;339:1341-1348.
 99. Soignet SL, Frankel SR, Douer D, et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. *J Clin Oncol*. 2001;19:3852-3860.
 100. Camacho LH, Soignet SL, Chaneil S, et al. Leukocytosis and the retinoic acid syndrome in patients with acute promyelocytic leukemia treated with arsenic trioxide. *J Clin Oncol*. 2000;18:2620-2625.
 101. Unnikrishnan D, Dutcher JP, Varshneya N, et al. Torsades de pointes in 3 patients with leukemia treated with arsenic trioxide. *Blood*. 2001;97:1514-1516.
 102. Westervelt P, Brown RA, Adkins DR, et al. Sudden death among patients with acute promyelocytic leukemia treated with arsenic trioxide. *Blood*. 2001;98:266-271.
 103. Bergstrom S, Gillan E, Quinn J, Altman A. Arsenic trioxide in the treatment of a patient with multiply recurrent, ATRA-resistant promyelocytic leukemia: a case report. *J Pediatr Hematol Oncol*. 1998;20:545-547.
 104. Jun M, Minghua J, Liying C, et al. Clinical observation on arsenic trioxide in the treatment of relapsed acute promyelocytic leukemia [abstract]. *Blood*. 1998;92:404a.
 105. Jing Y, Wang R, Xai L, et al. Combined effects of all-trans retinoic acid and arsenic trioxide in acute promyelocytic leukemia cells in vitro and in vivo. *Blood*. 2001;97:264-269.
 106. Dombret H, Rousselot P, Hermine O, et al. Treatment of relapsing acute promyelocytic leukemia (APL) with arsenic trioxide (As₂O₃) $\pm$ all-trans retinoic acid (ATRA): The French As98 Study [abstract]. *Blood*. 2000;96:3578a.
 107. Shen Y, Shen ZX, Yan H, et al. Studies on the clinical efficacy and pharmacokinetics of low-dose arsenic trioxide in the treatment of relapsed acute promyelocytic leukemia: a comparison with conventional dosage. *Leukemia*. 2001;15:735-741.

108. Mandelli F, Labopin M, Granena A, et al. European survey of bone marrow transplantation in acute promyelocytic leukemia (M3). Working Party on Acute Leukemia of the European Cooperative Group for Bone Marrow Transplantation (EMBT). *Bone Marrow Transplant*. 1994;14:293-298.
109. Meloni G, Diverio D, Vignetti M, et al. Autologous bone marrow transplantation for acute promyelocytic leukemia in second remission: prognostic relevance of pretransplant minimal residual disease assessment by reverse-transcription polymerase chain reaction of the PML/RAR alpha fusion gene. *Blood*. 1997;90:1321-1325.
110. Sanz MA, Arcese W, de la Rubia J, et al. Stem cell transplantation (SCT) for acute promyelocytic leukemia (APL) in the ATRA era: a survey of the European Blood and Marrow Transplantation Group (EBMT) [abstract]. *Blood*. 2000;96:2246.
111. Nabhan C, Mehta J, Tallman MS. The role of stem cell transplantation in acute promyelocytic leukemia. *Bone Marrow Transplant*. 2001;28:219-226.
112. Albitar M, Chang KS, Pierce S, Kantarjian H, Estey E. The short form of PML-RAR-alpha fusion transcript is associated with poor survival. *Leuk Res*. 1999;23:89-92.
113. Fukutani H, Naoe T, Ohno R, et al. Isoforms of PML-retinoic acid receptor alpha fused transcripts affect neither clinical features of acute promyelocytic leukemia nor prognosis after treatment with all-trans retinoic acid. The Leukemia Study Group of the Ministry of Health and Welfare (Kohseisho). *Leukemia*. 1995;9:1478-1482.
114. Gallagher RE, Willman CL, Slack JL, et al. Association of PML-RAR alpha fusion mRNA type with pretreatment hematologic characteristics but not treatment outcome in acute promyelocytic leukemia: an intergroup molecular study. *Blood*. 1997;90:1656-1663.
115. Slack JL, Willman CL, Andersen JW, et al. Molecular analysis and clinical outcome of adult APL patients with the type V PML-RAR-alpha isoform: results from intergroup protocol 0129. *Blood*. 2000;95:398-403.
116. Murray CK, Estey E, Paietta E, et al. CD56 expression in acute promyelocytic leukemia: a possible indicator of poor treatment outcome? *J Clin Oncol*. 1999;17:293-297.
117. Ferrara F, Morabito F, Martino B, et al. CD56 expression is an indicator of poor clinical outcome in patients with acute promyelocytic leukemia treated with simultaneous all-trans-retinoic acid and chemotherapy. *J Clin Oncol*. 2000;18:1295-1300.
118. Hiorns LR, Swansbury GJ, Mehta J, et al. Additional chromosome abnormalities confer worse prognosis in acute promyelocytic leukaemia. *Br J Haematol*. 1997;96:314-321.
119. Slack JL, Arthur DC, Lawrence D, et al. Secondary cytogenetic changes in acute promyelocytic leukemia—prognostic importance in patients treated with chemotherapy alone and association with the intron 3 breakpoint of the PML gene: a Cancer and Leukemia Group B study. *J Clin Oncol*. 1997;15:1786-1795.
120. Bolognesi E, Cimino G, Diverio D, et al. HLA class I in acute promyelocytic leukemia (APL): possible correlation with clinical outcome. *Leukemia*. 2000;14:393-398.
121. Jurcic JG, Caron PC, Miller WH Jr, et al. Sequential targeted therapy for relapsed acute promyelocytic leukemia with all-trans retinoic acid and anti-CD33 monoclonal antibodies M195. *Leukemia*. 1995;2:244-248.