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All-*trans* retinoic acid significantly increases 5-year survival in patients with acute promyelocytic leukemia: long-term follow-up of the New York study

Abstract All-*trans* retinoic acid (ATRA) induces a high incidence of complete remission (CR) in patients with acute promyelocytic leukemia (APL); however, the magnitude of this agent's contribution to increased rates of cure of this disease has not yet been established. From 1990 to 1995 we used RA as remission induction therapy in 103 APL patients (73 newly diagnosed and 30 previously treated) who were retinoid-naive and were treated on the basis of initial morphology. Patients whose diagnosis was changed on the basis of the results of molecular testing ($n = 13$) were withdrawn from RA treatment and given chemotherapy alone. After achieving a CR, previously untreated patients received several cycles of consolidation chemotherapy, usually with idarubicin and cytosine arabinoside. Among individuals whose diagnosis was molecularly confirmed, 54 of 65 new patients (83%) and 25 of 30 previously treated patients (83%) achieved a CR. All induction failures in molecularly diagnosed cases were due either to early death or to premature withdrawal. Median disease-free and overall survival rates recorded for all newly diagnosed patients are currently $>40+$ and $>43+$ months, respectively. We subsequently examined a subset of 27 newly diagnosed patients treated during the first 2 years of this program whose actual median follow-up period is now >5 years. Median disease-free and overall survival rates recorded for this group are $>57+$ and $>58+$ months, respectively; 56% of these patients are alive in first remission. These results significantly exceed those achieved using chemotherapy alone in a historical control group of 80 patients consecutively treated at this center from 1975 to 1990, whose median disease-free and overall survival rates were 11 and 19 months, respectively; only 22% of these patients were alive in first remission at 5 years. Although a high proportion of previously treated patients also achieved a CR after RA treatment, median disease-free and overall survival rates noted for that group were markedly lower (i.e., 7.5 and 10.9 months, respectively). Thus, data from patients whose median follow-up period is now >5 years have confirmed earlier projections and indicate that the use of RA for remission induction yields an approximately 2.5-fold increase in the proportion of patients who have presumably been cured of this disease.

Key words All-*trans* retinoic acid · Promyelocytic leukeumia

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Introduction

Acute promyelocytic leukemia (APL) accounts for approximately 10% of the acute myeloblastic leukemias in adults [16, 21]. Until the early 1990s, conventional treatment for this disease comprised induction chemotherapy with an anthracycline plus cytosine arabinoside followed by consolidation and/or maintenance with the same or other drugs. This therapeutic strategy resulted in complete remission (CR) rates of 60–80% [8, 17, 24] and 5-year survival rates of 20–30% [1, 14, 22], although both higher [10] and lower [14] rates have also been reported.

A major advance in the management of APL was made with the use of all-*trans* retinoic acid (RA) [6, 9, 25]. Most researchers have reported high CR rates (85–95%) with this drug, and preliminary data from several centers have suggested a low risk of relapse after the use of chemother-

Table 1 Clinical characteristics and response of newly diagnosed APL patients treated with RA for remission induction

Characteristic	Number of patients
Median age (range)	48 (1–77) years
M/F	35/38
RT-PCR analysis for PML/RAR-α expression:	
Positive	65
Negative	8
Median time to CR (range)	43 (18–98) days
WBC at presentation (cells/mm^3):	
<5,000	46
≥5,000–10,000	8
≥10,000–20,000	4
≥20,000–40,000	10
≥40,000	5

apy for consolidation [25]. However, limited information regarding actual (versus projected) long-term survival rates obtained with this combined sequential treatment approach, which was first introduced into the United States in mid-1990, is available. In this paper we analyze the 5-year update from the New York series on the use of RA for treatment of APL.

Patients and methods

Patients

All patients consecutively admitted to the Memorial Sloan-Kettering Cancer Center with a morphologic diagnosis of APL from June 1990 to November 1995 were treated on the programs described below. For comparison we analyzed the outcomes of a historical control group consisting of 80 patients who were consecutively treated on chemotherapy-containing protocols at this center in the immediately preceding period (1975 to June 1990). The clinical characteristics of the control patients have previously been described [9].

Treatment

Details of the RA-containing protocols have been described elsewhere [9, 24]. In brief, RA was given in two divided doses totaling 45 mg/m^2 per day up to the time of clinical remission and for approximately another 30 days. Thereafter, consolidation chemotherapy, which generally consisted of three cycles of idarubicin and cytosine arabinoside, was given. The first cycle was equivalent to a full-dose induction course (i.e., idarubicin given at 12 mg/m^2 per day for 3 days plus cytosine arabinoside given at 200 mg/m^2 per day for 5 days). The subsequent two courses used idarubicin at 12 mg/m^2 per day for 2 days and cytosine arabinoside at 100 mg/m^2 per day for 5 days after recovery from the preceding cycle. Selected patients (after 1994) also received therapy with a recombinant humanized monoclonal antibody directed against CD33 (rHuM195) [12].

Early in the study, 12 patients experienced a large increase in peripheral blood leukocyte counts and were treated with either hydroxyurea (n = 2), low-dose cytosine arabinoside (n = 5), or leukapheresis (n = 8). However, such therapy was later abandoned when analysis showed that this approach was associated with excessive mortality [23]. Therefore, unlike those in other studies [6, 7], most patients in the New York series received no other treatment during induction.

Statistical analysis

Disease-free survival was defined as the interval from response (CR) to relapse or death, whereas survival was defined as the interval from the date of protocol entry to death. Disease-free and overall survival in both the RA group and the historical control group was estimated by Kaplan-Meier analysis. The molecular diagnosis of leukemia is an important advance that has been broadly applied only recently. Therefore, the diagnosis of patients in the historical control group was based solely on morphology. However, all patients who entered the RA programs were treated presumptively on the basis of morphology and removed later if molecular testing was negative. Therefore, the principal analysis of our results includes estimates of all patients treated on the basis of morphology at entry. To evaluate fully the results of the current treatment approach in which molecular diagnosis has become a standard of care, we performed an additional analysis of those patients whose diagnosis was molecularly confirmed.

Results

Remission incidence

Between June 1990 and November 1995, 73 newly diagnosed patients with APL were treated using RA for remission induction followed by conventional chemotherapy for consolidation. Details of most of these patients' clinical characteristics have been described elsewhere [9, 24]. Other characteristics and initial responses are detailed in Table 1.

Overall, 59 of the 73 newly diagnosed patients (81%) achieved a CR. Eight newly diagnosed and five previously treated patients ultimately proved not to have APL according to molecular criteria, and these patients were switched to chemotherapy. Among patients who were molecularly diagnosed, 54 of 65 newly diagnosed patients (83%) and 25 of 30 previously treated patients (83%) achieved a CR. The only molecularly diagnosed patients who failed to achieve a CR were ten patients who died early during induction and one patient with leukocytosis who was switched to chemotherapy alone and then achieved a CR. Five of the eight incorrectly diagnosed new patients achieved a CR with standard chemotherapy.

Survival comparison

Overall and disease-free survival rates were estimated for the newly diagnosed patients treated with RA and for the 15-year historical control group. The median follow-up in the control group is now >10 years as compared to 48+ months for all patients in the RA group. We first examined the survival of all patients treated with RA. Three analyses were conducted: the first included all patients treated [including patients who were subsequently shown to be negative for PML/RA receptor (RAR)-α expression using the reverse transcriptase-polymerase chain reaction (RT-PCR) assay]; the second examined only RT-PCR-positive patients; and the third examined only RT-PCR-positive patients treated between 1990 and 1992, whose median follow-up is >5 years.

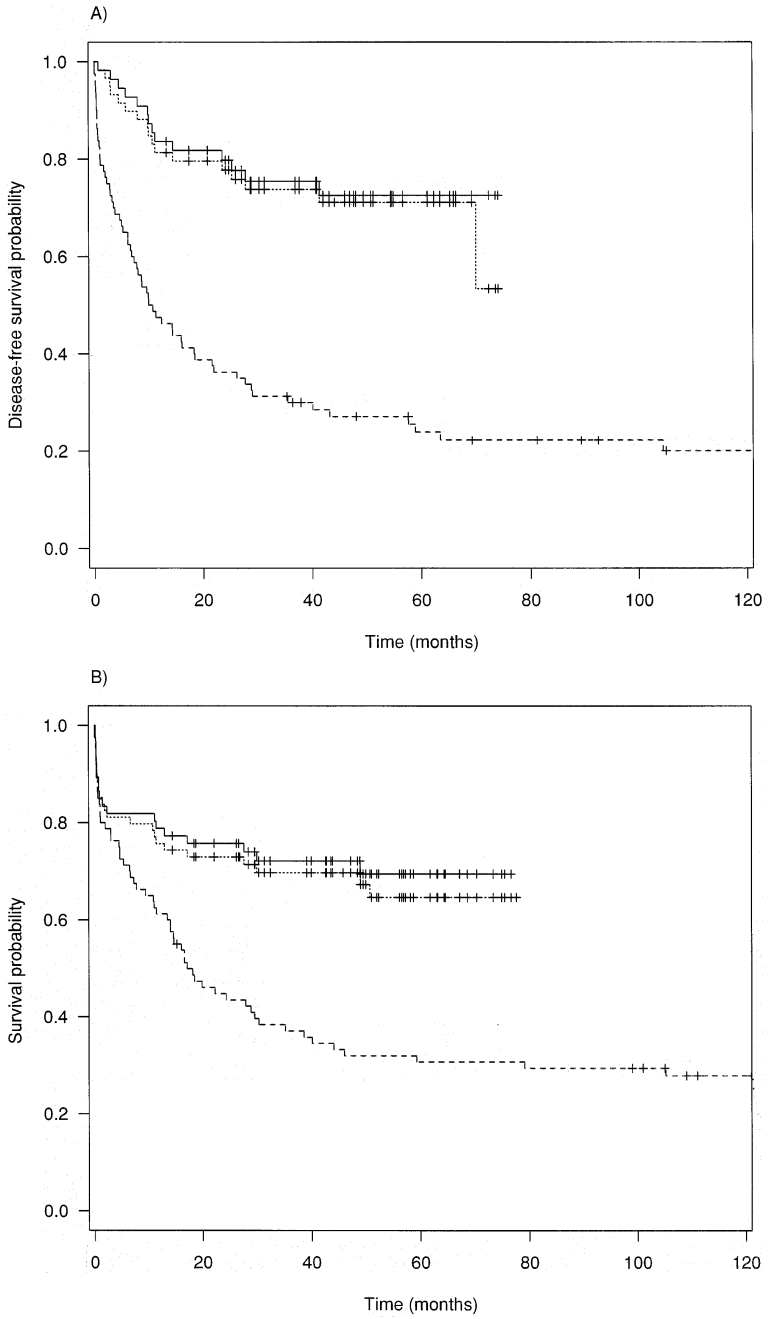

Fig. 1A, B Kaplan-Meier analysis of **A** disease-free and **B** overall survival in APL patients treated with RA for remission induction: all new patients (n = 74) diagnosed by morphology (*solid line*); newly diagnosed patients with a confirmed molecular diagnosis (n = 66; *dotted line*); and historical control patients diagnosed by morphology and treated with conventional chemotherapy (n = 80; *dashed line*)

As shown in Fig. 1, the median disease-free survival rate recorded for all patients (including those who subsequently proved to be RT-PCR-negative) is 65%. The disease-free survival rate noted for the molecularly diagnosed patients treated with the RA program is only slightly better (67%). However, as a group the eight misdiagnosed patients have fared poorly; five of them are known to have died of progressive leukemia, and one patient lost to follow-up is presumed dead. Thus, only two known patients from the misdiagnosed group are alive at 51 and 78 months after diagnosis, respectively.

The overall survival rates recorded for all newly diagnosed patients and for those with a confirmed molecular diagnosis are 68% and 71%, respectively (Fig. 1). Median disease-free and overall survival rates noted for patients treated during the initial 2 years of this program (June 1990 through May 1992, when the incidence and mortality of the "RA syndrome" [8] were higher) are 56% and 67%, respectively. By comparison, historical control patients treated solely with chemotherapy during the immediately preceding 15-year period achieved disease-free and overall survival rates of 20% and 28%, respectively. For the 30 patients who were treated with RA at the time of relapse of chemotherapy-induced CR, median disease-free and overall survival times were 7.5 and 10.9 months, respectively.

Discussion

The use of RA for induction therapy in APL patients has resulted in a high incidence of CR, and early results from a number of international groups have shown a marked increase in disease-free and overall survival rates compared to controls [25, 26]. However, due to the relatively recent introduction of this drug, only minimal long-term follow-up data exist to confirm that these early benefits have actually increased the proportion of patients who are cured of this disease. In this paper we show that the addition of RA for remission induction in APL patients has yielded an approximately 2.5-fold increase in the proportion of patients who are alive 5 years later.

The bleeding diathesis of APL is often exacerbated by the use of cytotoxic chemotherapy during induction, and this factor led to high early mortality in historical series [4, 20]. It was initially believed that the use of RA during induction would improve overall survival by decreasing early mortality from hemorrhage. Surprisingly, no study has yet shown a statistically significant reduction in early mortality with RA therapy (although a pooled analysis of these studies would probably demonstrate such a difference because all researchers have documented this trend). Unexpectedly, the increase in overall survival has resulted mainly from a markedly reduced risk of relapse. With the advent of the early use of high-dose corticosteroids to treat incipient symptoms of the RA syndrome [8], intracranial hemorrhage remains the leading cause of early mortality in patients treated with either chemotherapy or RA.

Despite the major improvement in survival documented by this and other reports, at least three important challenges remain. First, it is essential to reduce the number of patients (approximately 5–15%) who die early from hemorrhage. Second, since 25–30% of patients ultimately relapse, improved methods of detecting minimal residual disease (MRD) are required to identify those patients who are at highest risk for clinical recurrence. Third, for relapsing patients who are resistant to both retinoids and chemotherapy, alternate methods of treatment, such as bone marrow transplantation or novel antileukemic agents, need to be identified.

An important reduction in early mortality was recently reported by an Italian group using the AIDA protocol [15]: 146 of 156 (94%) newly diagnosed patients achieved a CR using a combination of RA and idarubicin for induction. A subordinate analysis of 100 patients showed that 61% were in molecular remission (using standard RT-PCR methods [17]) after induction therapy alone, whereas 97% had achieved molecular remission after 2 or 3 courses of consolidation therapy. In an assay with similar sensitivity, only 17% of the patients (8 of 46) in our series were found to be molecularly negative after induction therapy with RA alone; however, 92% were negative after completing 3 cycles of consolidation chemotherapy [13]. In both studies, persistently negative tests were associated with long-term remission. Most patients who were persistently positive, or those patients who converted from negative to positive, ultimately experienced a clinical relapse. These patients are therefore candidates for additional treatment during clinical remission.

The standard RT-PCR test presently used to assess MRD detects approximately 1 PML/RARα-positive cell per 10^4 normal cells [13, 17]. This level of sensitivity is substantially lower than that commonly cited for the assay of BCR/ABL used in chronic myelocytic leukemia (i.e., 1 in 10^6) [11]. In our series, approximately 25% of patients in clinical remission with at least one negative RT-PCR assay suffered a sustained clinical relapse [13]. We have recently reported on several technical improvements that may greatly increase the sensitivity of this assay: using a "hot start" technique; increasing the number of cycles during the PCR step; and using interferon to up-regulate the expression of PML/RAR-α prior to amplification [18].

Finally, recent reports suggest that APL may be exquisitely sensitive to the actions of various arsenicals [2, 3]. In a recent study, 15 of 16 patients with relapsed, resistant APL were induced into CR with As_2O_3 [3]; As_2O_3 appeared to down-regulate Bcl-2 expression and induce apoptosis. Similar in vitro findings have recently been reported by our group using melarsoprol, an organic arsenical [19] that is currently undergoing clinical study.

Conclusions

The use of RA for remission induction of APL has significantly decreased morbidity [5] and produced a major increase in overall survival and cure rates. The optimal management of this disease will include refinements that decrease both early mortality due to hemorrhage and the risk of late relapse.

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