

CLINICAL UPDATE

Updates on study findings in essential therapeutic areas of hematology and oncology

Is Cytarabine Required in the Treatment of Acute Promyelocytic Leukemia? Updated Experience and Review of the Literature

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Acute promyelocytic leukemia (APL) is a specific type of acute myeloid leukemia (AML) characterized by its morphology (M3 or M3v in the French-American-British classification); t(15;17) translocation, leading to *PML/RAR α* fusion gene; and a nonspecific coagulopathy, combining disseminated intravascular coagulopathy, fibrinolysis, and nonspecific proteolysis.¹⁻⁴ Before the advent of all-*trans*-retinoic acid (ATRA), APL was treated exclusively by conventional chemotherapy using anthracyclines with or without cytarabine (ara-C). With this chemotherapy and intensive platelet support during induction treatment, complete remission (CR) rates of 70–80% were obtained, and about 40% of the patients who achieved CR were cured of their disease with consolidation chemotherapy.⁵⁻⁷

ATRA can differentiate APL blasts *in vitro* and *in vivo*. With ATRA treatment, about 90% of newly diagnosed or relapsed APL patients can obtain CR, through differentiation of APL blasts into mature granulocytes.⁸⁻¹⁰ However, in some cases, ATRA also leads to major blood hyperleukocytosis and potentially fatal ATRA syndrome.^{11,12} Furthermore, almost all patients relapse unless they receive consolidation chemotherapy. This has led clinical groups to combine ATRA and classic anthracycline–ara-C chemotherapy in the treatment of newly diagnosed APL in order to reduce the incidence and severity of ATRA syndrome and the incidence of relapse. Many recent trials, including two randomized trials (the European APL 91 trial and a US intergroup trial), have clearly shown that ATRA followed by anthracycline–ara-C chemotherapy can reduce the incidence of relapse to about 30% as well as slightly increase the CR rate.¹³⁻¹⁴ In a subsequent trial (APL 93), it was found that early addition of chemotherapy to ATRA during induction treat-

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ment rather than after CR achievement, and maintenance therapy with continuous chemotherapy and intermittent ATRA, could further reduce the incidence of relapse.¹⁵ Other groups have confirmed the role of maintenance treatment in reducing the incidence of relapse.¹⁴ It therefore appears possible, with ATRA and anthracycline-based chemotherapy followed by maintenance treatment, to achieve CR in approximately 90% of newly diagnosed APL patients, with a relapse rate of 10–15%. Table 1 summarizes patient outcome in the main APL trials published since the advent of ATRA.

With current therapeutic approaches, however, approximately 10% of the patients will not achieve CR and 10–15% will relapse.^{13–15} Failure to achieve CR with current treatment approaches is almost exclusively due to early death during induction treatment. Causes of death are predominantly bleeding, ATRA syndrome, and, less often, infection. Early deaths predominate in elderly patients and patients with high white blood cell (WBC) counts.¹⁶ The main pretreatment factor associated with a higher risk of relapse is high WBC count at diagnosis. Therefore, a predictive model for relapse risk based on patient leukocyte and platelet counts at diagnosis was established: low-risk patients had a WBC count less than 10,000 cells/ μ L and a platelet count greater than 40,000 cells/ μ L; intermediate-risk patients had a WBC count less than 10,000 cells/ μ L and a platelet count less than 40,000 cells/ μ L; and high-risk patients had a WBC count greater than 10,000 cells/ μ L.¹⁶ This predictive model for relapse risk has been validated in patients receiving ATRA plus idarubicin (IDA)-like protocols.

Failure in APL may also result from the toxicity of treatment regimens used after the achievement of CR. In the APL 93 trial, 4–5% of the patients died in CR due to complications of the consolidation treatment phase, mainly from infection during chemotherapy-induced aplasia.¹⁵ The incidence of this complication was 10% in patients older than 60 years.¹⁶ Further improvement in the outcome of APL would require reduction of mortality in CR, especially through reduction of the intensity of consolidation chemotherapy by avoiding ara-C.

Avoiding Ara-C May Reduce Toxicity Without Increasing the Relapse Rate

Before the ATRA era, a few nonrandomized studies suggested that chemotherapy with an anthracycline alone, provided it was given at relatively high doses, conferred similar results as anthracycline–ara-C regimens.^{6,17} In 2002, the Italian GIMEMA group published results of a trial that randomized patients to receive IDA alone or IDA plus ara-C as induction treatment.¹⁸ The cumulative dose of anthracycline was higher in patients treated with IDA

alone (60 mg/m²) than in those treated with IDA–ara-C (48 mg/m²). Overall, 76% of patients receiving IDA alone and 67 patients receiving IDA–ara-C achieved hematologic CR (P =NS). The 8-year event-free survival rate was significantly better for the patients treated with IDA alone (35% vs 23%), partially due to a higher incidence of hemorrhagic deaths observed during induction treatment in the IDA–ara-C arm compared to those observed in the IDA-alone arm. This randomized trial, designed before the advent of ATRA, suggested that ara-C could be avoided in the treatment of APL when high cumulative doses of an anthracycline were used.¹⁸ Other retrospective analyses published before the ATRA era also suggested a benefit for high-dose anthracyclines in APL.^{6,19}

Since the advent of ATRA, relatively few studies using ATRA and chemotherapy with an anthracycline alone have been reported. A group at the University of Texas M. D. Anderson Cancer Center published results of 43 newly diagnosed APL patients who received an induction course combining ATRA 45 mg/m²/day and IDA 12 mg/m² for 4 days followed by two consolidation courses with IDA 12 mg/m² for 3 days and 2-year maintenance treatment including reinductions with IDA 12 mg/m² for 2 days.²⁰ Historical comparison was made with patients treated with doxorubicin, daunorubicin, or amosacrine without ATRA. The CR rate was similar in the two groups but disease-free survival was significantly better in the ATRA-IDA group. This nonrandomized trial suggested that omission of ara-C from the treatment of newly diagnosed APL, allowing delivery of a higher anthracycline dose in combination with ATRA, could result in high antileukemic efficacy.

The Spanish PETHEMA group, however, reported the largest experience of ATRA with anthracycline-alone chemotherapy in APL patients in two successive trials.²¹ The induction regimen consisted of ATRA and IDA (12 mg/m²/d \times 4). Between 1996 and 1999 (LPA 96 study), all patients in CR received three monthly consolidation courses (IDA 5 mg/m²/d \times 4; mitoxantrone 10 mg/m²/d \times 5; IDA 12 mg/m²/d \times 1) and a 2-year maintenance treatment combining ATRA and chemotherapy consisting of low-dose mercaptopurine plus methotrexate. From 1999 (LPA 99 study), intermediate- and high-risk patients received reinforced chemotherapy with increased doses of IDA and ATRA during the consolidation course. Overall, 384 of 426 patients achieved hematologic CR (90%). All but 2 of the patients who achieved CR received consolidation therapy and only four deaths from infection occurred during consolidation courses. The 3-year cumulative incidence of relapse for patients in the LPA 96 and LPA 99 studies was 17.2% and 7.5%, respectively (P =.008), suggesting that escalating the dose of anthracyclines and/or the addition of ATRA during

Table 1. Outcome of Patients in Main APL Trials

	Publication Year	N	Treatment	CR, %	Relapse, %	OS, %	DFS, %
APL 93 ¹⁵	1993	576	Induction: ATRA + CT vs ATRA followed by CT Maintenance or not	ATRA + CT: 96 ATRA→CT: 93	<i>Induction</i> ATRA + CT: 19 ATRA→CT: 22 (<i>P</i> =.04) <i>Maintenance</i> No CT vs CT: 37 vs 21 (<i>P</i> =.0001) No ATRA vs ATRA: 34 vs 21 (<i>P</i> =.0001)	ATRA + CT: 84 ATRA→CT: 77 (<i>P</i> =NS)	-
Japan Adult Leukemia Study Group ²⁷	1995	110	ATRA + CT with ara-C	89	-	-	-
MD Anderson ²⁰	1997	43	IDA without ara-C	77	-	-	1-year: 67
US Intergroup Trial ¹⁴	1999	346	Induction: CT vs ATRA Maintenance or not	CT: 69 ATRA: 72 (<i>P</i> =NS)	<i>Induction</i> CT: 58 ATRA: 29 (<i>P</i> <.001) <i>Maintenance</i> No maintenance: 48 Maintenance: 31 (<i>P</i> <.01)	<i>Induction</i> CT: 50 ATRA: 71 <i>P</i> <.001	<i>Induction</i> CT: 32 ATRA: 67
MRC Trial ²⁸	1999	239	Short ATRA vs extended ATRA	87 vs 70 (<i>P</i> <.001)	20 vs 36 (<i>P</i> =.04)	80 vs 57 (<i>P</i> =.009)	72 vs 59 (<i>P</i> =.07)
PETHEMA 96 ^{26,29}	1999	181	IDA without ara-C	90	CIR 3-year: 17.2	3-year: 78	3-year: 81
German AML Cooperative Group ³⁰	2000	51	Double induction strategy including high-dose ara-C	92	Relapse free: 96	88	88
PETHEMA LPA 99 ²¹	2004	251	Risk-adapted treatment without ara-C	90	High risk: 21	3-year: 85	Low risk: 93 Int risk: 97 High risk: 77
GIMEMA AIDA 2000 ²⁵	2004	298	Risk-adapted treatment with ara-C in high risk	94	CIR: 5	-	90

ara-C = cytarabine; ATRA = all-*trans*-retinoic acid; CIR = cumulative incidence of relapse; CR = complete remission; CT = chemotherapy; DFS = disease-free survival; IDA = idarubicin; OS = overall survival.

consolidation courses reduce the incidence of relapse.²¹ Those studies showed that ATRA with anthracycline monochemotherapy for induction and consolidation, followed by maintenance therapy, has a high antileukemic efficacy with moderate toxicity, even in elderly patients. Results appeared similar to those of the best arm of the APL 93 trial but with less toxicity and only a 2–3% rate of death in CR, including in elderly patients. Furthermore, consolidation chemotherapy with an anthracycline alone could be administered in outpatients and was associated with low morbidity and no mortality.

Is This Finding Confirmed in a Randomized Trial?

Although both the LPA 96 and LPA 99 trials included large numbers of patients, they were nonrandomized studies.²¹ In order to confirm the results of the PETHEMA group in a randomized trial, the APL 2000 trial, conducted by the European APL group, randomized patients 60 years or younger with WBC counts below 10,000 cells/ μ L to the best treatment regimen of the APL 93 trial, which was ATRA with early introduction of anthracycline–ara-C chemotherapy (ara-C group), followed by two consolidation anthracycline–ara-C courses and maintenance combining continuous chemotherapy and intermittent ATRA, or to the same regimen, but without ara-C (non–ara-C group).²² Patients over 60 years of age and patients with initial WBC counts over 10,000 cells/ μ L were not randomized but received risk-adapted treatment, with higher doses of ara-C and central nervous system (CNS) prophylaxis in patients with WBC counts over 10,000 cells/ μ L. Overall, 328 of 340 (96.4%) patients achieved CR. The CR rates in the ara-C and non–ara-C groups were similar (99% and 94%, respectively; $P=$.066); however, the 2-year cumulative incidence of relapse (CIR) was 4.7% versus 15.9% ($P=$.011), the event-free survival (EFS) was 93.3% versus 77.15% ($P=$.0016), and overall survival was 97.9% versus 89.6% ($P=$.0066), respectively. In patients 60 years or under with WBC counts over 10,000 cells/ μ L, the CR, 2-year CIR, EFS, and overall survival rates were 97.3%, 2.9%, 89%, and 91.9%, respectively. The results led to early discontinuation of accrual in the non–ara-C group.

Thus, in patients with WBC counts below 10,000 cells/ μ L (ie, at low risk of relapse), an anthracycline alone for chemotherapy instead of the classic anthracycline–ara-C combination may lead to an increased risk of relapse. Reasons for discrepancies between our results and those of the PETHEMA group studies, apart from the fact that our study was randomized, are unclear. The higher cumulative dose of anthracycline administered in the Spanish studies may have had an effect. Another reason may be a superiority of IDA over daunorubicin in

APL. In AML in general, several randomized studies have suggested the superiority of IDA over daunorubicin.^{23–24} The Italian GIMEMA group also suggested that IDA alone was very effective in APL.²⁵ Thus, substituting IDA for daunorubicin during induction and consolidation treatment could improve long-term results in APL. Finally, using ATRA during consolidation courses, as in the LPA 99 trial, may have a positive effect on the risk of relapse.

Toward a Risk-adapted Treatment

We performed a joint analysis of patients less than 65 years of age included in the PETHEMA, LPA 99, and APL 2000 studies to assess the role of ara-C. As previously mentioned, in LPA 99, patients received ATRA and IDA alone for induction, followed by three consolidation anthracycline courses and maintenance for 2 years. High-risk patients also received ATRA during consolidation courses and a higher cumulative dose of IDA (100 mg/ m^2) without ara-C. In APL 2000, we restricted the analysis to treatment groups that received ara-C: patients with low or intermediate risk received induction with ATRA and daunorubicin (60 mg/ $m^2/d \times 3$) plus ara-C (200 mg/ $m^2/d \times 7$) followed by consolidation with a similar course and a final course of daunorubicin (45 mg/ $m^2/d \times 3$) plus ara-C (1 g/ $m^2/12h \times 8$) and the same maintenance as in LPA 99. High-risk patients received the same treatment but with intrathecal CNS prophylaxis and, in patients younger than 60 years, ara-C (2 g/ $m^2/12h \times 8$) during the last course. Comparisons between LPA 99 and APL 2000 were adjusted for age, gender, and WBC and platelet counts. In low- and intermediate-risk patients, the CR, 2-year CIR, EFS, and overall survival rates were not significantly different in the LPA 99 and APL 2000 trials. In high-risk patients, the CR rate was significantly better in those included in the APL 2000 trial, and the CIR was significantly lower than in patients treated in LPA 99. This analysis suggests that in patients with WBC counts below 10,000 cells/ μ L, the current PETHEMA approach is not associated with more relapses than a classic regimen of ATRA plus daunorubicin plus ara-C while being clearly less myelosuppressive. On the other hand, in patients with high WBC counts, APL 2000 yielded better EFS and overall survival and a strong trend for fewer relapses (including relapses involving the CNS), suggesting a beneficial role for ara-C, possibly at high doses, in this subset of patients.

Those findings were also supported by the Italian GIMEMA group, which made a historical comparison in APL patients with WBC counts over 10,000 cells/ μ L in two cohorts treated with ATRA combined with IDA and mitoxantrone (Novantrone, Sereno/OSI), with or with-

out ara-C. A significantly higher CIR was observed in the cohort treated without ara-C (29% vs 2%).

Conclusion

Published results suggest that ATRA combined with a high cumulative dose of IDA without ara-C (the PETHEMA approach) confers excellent results with limited toxicity in patients with low- or intermediate-risk APL (ie, WBC count <10,000 cells/ μ L). Those good results, however, probably require application of the full treatment approach: high-dose anthracycline, perhaps IDA instead of daunorubicin, combined maintenance treatment, and possibly ATRA during consolidation courses.

Any substantial change in this approach (eg, daunorubicin instead of IDA) may perhaps lead to an increased relapse risk. The PETHEMA approach may, however, be insufficient in patients at higher risk of relapse, mainly those with a WBC count over 10,000 cells/ μ L. Addition of ara-C (or other drugs such as arsenic derivatives) to ATRA and anthracycline therapy appears to be required in those patients to ensure optimal cure rates.

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