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Real-Life Experience of a Brief Arsenic Trioxide-Based Consolidation Chemotherapy in the Management of Acute Promyelocytic Leukemia: Favorable Outcomes With Limited Anthracycline Exposure and Shorter Consolidation Therapy

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Abstract

Arsenic trioxide (ATO)-based consolidation chemotherapy can be effective in patients with high-risk acute promyelocytic leukemia (APL) and might reduce anthracycline-related toxicity. We report a retrospective analysis of 63 patients with APL given 1 cycle of ATO-based consolidation chemotherapy. The 5-year overall survival, event-free survival, and leukemia-free survival was 93%, 89%, and 92%, respectively.

Background—Anthracyclines have activity against acute promyelocytic leukemia (APL) but can cause cardiac toxicity and secondary malignancy. The all-trans retinoic acid (ATRA)-arsenic trioxide (ATO) combination is an effective noncytotoxic approach for APL. However, its efficacy against high-risk APL (white blood cell count > 10,000/ μ L) has not been documented. Also, it requires 8 months to complete therapy.

Patients and Methods—We report a retrospective analysis of 63 patients with APL given one cycle of ATO-based consolidation chemotherapy.

Results—The 5-year overall survival, event-free survival, and leukemia-free survival was 93% (95% confidence interval [CI], 82%–97%), 89% (95% CI, 77%–95%), and 92% (95% CI, 80%–97%), respectively.

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Disclosure

The authors have stated that they have no conflicts of interest.

The results of our study were presented in part at American Society of Hematology Meeting, New Orleans, 2013.

Conclusion—These data have confirmed that an abbreviated ATO-based chemotherapy regimen is an effective consolidation therapy for APL, including high-risk APL, and can be completed within 4 months.

Keywords

All-trans retinoic acid; Anthracyclines; APL; ATO; Promyelocytic leukemia-retinoic acid receptor α

Introduction

Although anthracyclines have significant activity and a proven role in the management of acute promyelocytic leukemia (APL),^{1,2} their use has been associated with significant cardiac toxicity^{3,4} and an increased risk of secondary malignancy.^{5–7} Because the outcomes of patients with APL have improved considerably during the past few decades, the focus has shifted to minimizing cytotoxic chemotherapy exposure without compromising the outcomes. The combination of all-trans retinoic acid (ATRA) plus arsenic trioxide (ATO) has been shown to be an active and less toxic regimen for APL. However, the most experience with this regimen has largely been limited to patients with low- to intermediate-risk disease (white blood cell [WBC] count < 10,000/ μ L).⁸ Moreover, this ATRA-ATO based regimen requires 8 months of ongoing daily hospital- or clinic-based therapy to complete.

We previously reported that a single cycle of ATO-based consolidation chemotherapy is effective in the primary management of APL and significantly minimizes anthracycline exposure.⁹ In the original report by Gore et al,⁹ the data from 45 patients were analyzed, and the disease-free survival and overall survival rate was 88.7% and 88%, respectively. Two institutions, Johns Hopkins University (JHU), Baltimore, Maryland, and Northside Hospital (NSH), Atlanta, Georgia, subsequently adopted this treatment approach as a standard consolidation regimen for patients with newly diagnosed APL. We report the outcomes for 63 patients with APL treated using this consolidation therapy at both institutions through August 2012.

Patients and Methods

Patients

All patients with APL who received timed-sequential ATO-based consolidation therapy at JHU (Baltimore, MD) and NSH (Atlanta, GA) were identified and screened. We included the patients who had been enrolled in the original trial⁹ at either institution and those who had been treated subsequently. We excluded those patients who had been diagnosed after August 1, 2012 to allow for adequate follow-up. The patients had confirmation of the pathognomonic promyelocytic leukemia-retinoic acid receptor α gene rearrangement by cytogenetic, fluorescence in situ hybridization, and/or molecular studies. The institutional review boards at both institutions approved the study protocol.

Treatment Protocol

The treatment schema has been previously described and is outlined in Figure 1.

Induction—The induction therapy consisted of ATRA 45 mg/m²/d administered in 2 divided doses orally for 60 days and daunorubicin 60 mg/m² intravenously (I.V.) on days 4, 6, and 8. Patients whose presenting WBC count was > 20,000/μL received hydroxyurea 1500 mg orally (p.o.) every 6 hours and dexamethasone 10 mg I.V. every 12 hours to maintain a WBC count < 20,000/μL and prevent differentiation syndrome until daunorubicin was administered. Hydroxyurea and dexamethasone were also added for patients presenting with a lower WBC count if the count had increased to 20,000/μL before day 14. ATRA was continued for 60 days, regardless of WBC count recovery, unless the drug was not tolerated. Remission was assessed between days 60 and 67 by bone marrow biopsy.

Consolidation Therapy—Consolidation consisted of 1 course of therapy that included continuous infusion cytarabine 667 mg/m²/d on days 1 to 3, daunorubicin 60 mg/m²/d I.V. on days 1 to 3, and ATO 0.15 mg/kg I.V. given for 5 d/wk for 30 doses beginning on day 8. The original study protocol required a second module of consolidation if the patient had not achieved complete remission (CR) after induction; however, no patients in the original study or our cohort required or received this second module.

An echocardiogram was obtained for all patients before consolidation. If the left ventricular ejection fraction (LVEF) was 35% to 45%, the daunorubicin dose was reduced to 30 mg/m²/d. If the LVEF was < 35%, a cardiology consultation was obtained, and the consolidation therapy outlined in Figure 1 was delayed or omitted.

An electrocardiogram was obtained twice weekly and as needed during ATO administration. Symptomatic or asymptomatic corrected QT interval (QTc) prolongation was managed by careful monitoring, correction of electrolytes, and/or withholding ATO. Medications that prolong the QTc interval were avoided, especially in patients with a prolonged QTc.

Maintenance Therapy—The patients received 2 years of risk-adapted maintenance therapy. All patients received ATRA 22.5 mg/m² p.o. twice daily for 15 days every 3 months for 8 cycles. High-risk patients whose WBC count was > 10,000/μL on presentation also received 6-mercaptopurine (6-MP) 90 mg/m²/d p.o. and methotrexate 15 mg/m²/wk p.o. The ATRA regimen was not dose-modified, but 6-MP and methotrexate were both modified for hepatic transaminase elevation (> 300 IU) or a decrease in the absolute neutrophil count < 1500/μL.

The patients' disease status after CR was monitored using monthly reverse transcription-polymerase chain reaction (RT-PCR) testing of peripheral blood and RT-PCR testing of bone marrow samples every 6 months.

Statistical Analysis

Descriptive statistics were calculated to summarize the baseline characteristics and were stratified by risk category. The patient characteristics are presented as the median and range for continuous variables and as the count and percentage for categorical variables.

Comparisons of the characteristics between the risk categories were done using the Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables. Overall survival (OS) was defined as the interval from diagnosis to death, event-free survival (EFS) was defined as the interval from diagnosis until relapse or death, and leukemia-free survival (LFS) was defined as the interval from remission to relapse or death. Only the survival data for patients with CR were used to estimate the LFS. The survival probabilities were estimated using the Kaplan-Meier method. The 95% confidence intervals (CIs) were calculated using the log-log transformation. The log-rank test was conducted to compare the survival outcomes between the two institutions and between the high- and low-risk patients. All statistical tests were 2-sided, and $P < .05$ was considered statistically significant for all comparisons.

Results

A total of 84 patients received timed-sequential ATO-based consolidation (Figure 2). Of the 84 patients, 15 had been diagnosed after August 1, 2012 and were therefore excluded to allow for an adequate follow-up period. As of August 31, 2013, none of the 15 excluded patients had developed a relapse. Also, 6 patients' treatment deviated from the outlined consolidation and were excluded from analysis. Of these 6 patients, 1 received ATO-only consolidation and maintenance¹⁰ because of a severe adverse reaction to ATRA. One received ATO-only consolidation¹⁰ because of recent surgery but received maintenance therapy as planned. One patient received ATRA-ATO 28-week consolidation¹¹ owing to a recommendation by a cardiologist because of the patient's extensive cardiac history. One patient's therapy was changed to an ATO plus daunorubicin-based consolidation regimen² owing to insurance coverage but subsequently received maintenance therapy. One patient declined additional treatment after induction; and one elected to forego consolidation therapy because of a difficult recovery from the induction therapy. All 6 off-study patients were in CR at data censoring.

A total of 63 patients were included in our analysis. The demographic characteristics are included in Table 1. Nineteen patients on the original study by Gore et al⁹ were included in the present analysis. The median age at diagnosis was 50 years (range, 20–73 years). Of the 63 patients, 32 were women (51%) 31 were men (49%). The JHU treated 37 patients (59%) and the NSH treated 26 patients (41%). Of the 63 patients, 43 (68%) were low risk and 20 (32%) were high risk. Two patients died during induction: 1 patient was high risk and died of APL differentiation syndrome and 1 was low risk and died of intracranial hemorrhage.

All 61 patients surviving induction achieved CR. The median duration from diagnosis to CR was 62 days. All patients completed the ATO-based consolidation therapy, except for 1 patient who elected to stop therapy after 8 of the 30 planned ATO doses because of side effects. That patient remained in remission at data censoring.

All but 2 patients subsequently received maintenance therapy: 1 was lost to follow-up and 1 refused maintenance. Two patients died during maintenance therapy but were in CR (both with low-risk disease; 1 died of graft failure in a cardiac transplant recipient and 1 died of recurrent metastatic breast cancer).

As of August 31, 2013, the median follow-up duration for the survivors was 52 months (range, 14 to 115 months). Of the 56 remaining patients, 38 had completed maintenance therapy and 18 were still receiving it. Two patients developed a relapse. One initially reported patient developed central nervous system relapse 2.4 years into remission and was in their second CR after an autologous transplant at the last follow-up point. The other patient developed a relapse 6 months into maintenance therapy and was in their second CR after an autologous transplant at the last follow-up point.

The results of the survival analysis are shown in Figure 3. The 5-year survival outcomes were OS, 93% (95% CI, 82%–97%); EFS, 89% (95% CI, 77%–95%); and LFS, 92% (95% CI, 80%–97%). The survival outcomes did not differ between the 2 institutions ($P = .719$ for OS, $P = .191$ for EFS, and $P = .685$ for LFS).

We also analyzed survival by considering specifically the high-risk patient population ($n = 20$). The 5-year survival outcomes for the high-risk patients were 95% (95% CI, 70%–99%) for OS, 89% (95% CI, 61%–97%) for EFS, and 93% (95% CI, 61%–99%) for LFS. No difference was found in the outcomes between the patients with high-versus low-risk APL, with a hazard ratio (high- to low-risk APL) of 0.71 (95% CI, 0.07–6.85; $P = .768$) for OS, 1.03 (95% CI, 0.19–5.61; $P = .977$) for EFS, and 0.68 (95% CI, 0.07–6.58; $P = .742$) for LFS.

We also performed a sensitivity analysis based on the intent-to-treat principle that included the 6 patients who had not followed the treatment protocol. The 5-year OS, EFS, and LFS for this expanded cohort (69 patients) was 94% (95% CI, 83%–98%), 90% (95% CI, 79%–95%), and 93% (95% CI, 82%–97%), respectively. These estimates are very close to the estimated survival rates for the on-protocol cohort.

Discussion

APL is more sensitive to chemotherapy and differentiating drugs than other forms of acute myeloid leukemia. Because high cure rates have been obtained with current therapy, recent studies have focused on limiting the toxicity while preserving the efficacy. We previously evaluated an approach using a single cycle of timed-sequential chemotherapy as consolidation therapy for patients receiving ATRA-daunorubicin induction to limit anthracycline exposure and improve the patients' quality of life by shortening the duration of intensive treatment.¹² Timed-sequential therapy refers to the delivery of additional therapy relatively close to the first therapy without considering the status of the bone marrow to target the stem cells while they are in cycle and more sensitive to chemotherapy.¹³ ATO was incorporated into the consolidation cycle to further limit the chemotherapy exposure.⁹ The findings of the present report have confirmed the activity of a single cycle of ATO-based consolidation therapy in a larger patient cohort with a longer follow-up period.

From our results, a single cycle of ATO-based consolidation is an effective strategy in the primary treatment of APL. The outcomes after this concise approach were comparable to those with strategies using multiple cycles of consolidation therapy containing ATO with or

without chemotherapy.^{2,8,14,15} The presented data have also confirmed the outcomes of the original clinical trial that reported an OS of $88\% \pm 5\%$, EFS of $76\% \pm 7\%$, and LFS of $88.7\% \pm 6\%$.⁹

Our approach limits anthracycline exposure compared with most modern treatment paradigms,^{2,16,17} with comparable efficacy. The Australasian Leukaemia and Lymphoma Group recently presented similar data on reducing anthracycline exposure, with good results, using ATRA, ATO, and 4 doses of idarubicin for induction. Consolidation therapy consisted of 2 cycles of ATRA and ATO, and a 2-year maintenance regimen similar to that of our present protocol.¹⁸

Most recently published treatment regimens have included multiple cycles of consolidation therapy, frequently containing anthracyclines with or without ATRA, ATO, or cytarabine.^{2,14,15} The most active arm of the C9710 study conducted by the North American Leukemia Intergroup, for example, included 4 cycles of consolidation for a total intensive treatment period (induction plus consolidation) of approximately 24 weeks.² The Italian Group's approach entailed 28 weeks of consolidation therapy alone, not including induction,⁸ compared with 14 total weeks using our approach. We included 2 years of maintenance therapy; however, during this treatment phase, most patients will be able to resume normal activities and full employment. The requirement for maintenance therapy after ATO-based consolidation therapy is currently unknown, especially for those with low- to intermediate-risk APL. Recent data have suggested that maintenance therapy in this setting might be eliminated.^{1,19,20}

A landmark report published by the Italian Group demonstrated the efficacy of differentiating therapy alone in the treatment of patients with low- to intermediate-risk APL.⁸ Their regimen, although completely eliminating the risk of anthracycline-induced cardiomyopathy, requires approximately 5 months longer to complete than ours, and its efficacy in high-risk patients is unknown. High-risk patients constitute 32% of our patient population. Our results in high-risk patients, with a 5-year LFS and OS of 93% and 95%, respectively, compared favorably with the LFS and OS of approximately 70% to 80% reported in most studies.^{13,17,21}

Conclusion

The results of our study have shown that standard anthracycline plus ATRA induction therapy followed by a single cycle of ATO-based time-sequential consolidation therapy is an active, abbreviated regimen against APL. This approach can be considered for patients with high-risk APL and for patients unable or unwilling to comply with longer treatment strategies.

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Clinical Practice Points

- Anthracyclines have significant activity and a proven role in the management of APL, but their use has been associated with significant cardiac toxicity and an increased risk of secondary malignancy. The focus has shifted to minimizing anthracycline exposure.
- The ATRA-ATO combination is an effective noncytotoxic approach for APL, but its efficacy in high-risk APL (WBC count 10,000/ μ L) has not been documented.
- Our results have shown that treatment with a single cycle of ATO-based consolidation therapy results in outcomes comparative to those of other recently published regimens, with comparative outcomes in the high-risk patient population.
- Using ATO-based consolidation, intensive therapy (induction plus consolidation) can be completed within approximately 14 weeks in contrast to the 24 to 28 weeks required for other anthracycline-based regimens or the ATRA-ATO regimen.
- ATO-based consolidation is an efficacious treatment option for patients with APL, including those with high-risk disease and those unwilling or unable to comply with longer treatment strategies.

Figure 1. Treatment Schema

Abbreviations: ATO = arsenic trioxide; ATRA = all-trans retinoic acid; BID = twice daily; IV = intravenous; PO = oral; QD = daily; RT-PCR = reverse transcription-polymerase chain reaction; WBC = white blood cell (count).

Figure 2. Flow Chart of Cohort

Abbreviations: APL = acute promyelocytic leukemia; CR = complete remission.

Figure 3. Survival Analysis

Abbreviations: EFS = event-free survival; High risk = white blood cell count > 10,000/ μ L on presentation; LFS = leukemia-free survival; Low risk = white blood cell count $\leq$ 10,000/ μ L on presentation; OS = overall survival.

Table 1

Demographics and Baseline Characteristics

Characteristic	All (n = 63)	High Risk (n = 20; 32%)	Low Risk ^a (n = 43; 68%)	P Value (High vs. Low Risk)
Age (years)				.232
Median	50	47	52	
Range	20–73	20–70	21–73	
Sex (n)				1.000
Male	31 (49)	10 (50)	21 (49)	
Female	32 (51)	10 (50)	22 (51)	
Treatment location (n)				1.000
JHU	37 (59)	12 (60)	25 (58)	
NSH	26 (41)	8 (40)	18 (42)	

Data in parentheses are percentages.

Abbreviations: JHU = Johns Hopkins University; NSH = Northside Hospital.

^a A low-risk level was defined as a white blood cell count < 10,000/ μ L on presentation.