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Outcome of Therapy-Related Acute Promyelocytic Leukemia With or Without Arsenic Trioxide as a Component of Frontline Therapy

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Abstract

BACKGROUND—Patients with therapy-related acute promyelocytic leukemia (t-APL) have been commonly exposed to topoisomerase inhibitors and may potentially benefit from induction regimens omitting anthracyclines.

METHODS—Retrospective analysis of the outcomes of 29 patients with t-APL who were either treated with arsenic trioxide (ATO) and all-*trans*-retinoic acid (ATRA) or with standard ATRA plus anthracycline-based chemotherapy was performed.

RESULTS—Prior therapy included chemotherapy alone, radiation alone, or a combination of the 2 in 19%, 33%, and 47% of patients, respectively. The combination of ATO and ATRA (n = 19) for induction resulted in a similar remission rate compared with ATRA plus chemotherapy (n = 10) (89% vs 70%; P = .35). The median overall survival for the patients treated with ATRA plus ATO was not reached compared with that for patients treated with ATRA plus chemotherapy (161 weeks; P =.79).

CONCLUSIONS—In this cohort of t-APL patients, outcomes with ATO and ATRA appeared to be comparable to anthracycline-containing induction regimens. This combination may be preferable in t-APL patients to avoid any risk of anthracycline-induced toxicities.

Keywords

therapy-related acute promyelocytic leukemia; arsenic trioxide; outcome; all-*trans*-retinoic acid

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CONFLICT OF INTEREST DISCLOSURES

Dr. Ravandi has been a member of advisory boards and has received honoraria from Cephalon.

Although the majority of patients with acute promyelocytic leukemia (APL) have de novo disease with no clear underlying etiology, an increasing number of cases have been linked to prior exposure to chemotherapy, in particular to topoisomerase II inhibitors.[1,2] Recent work has demonstrated specific hot spots in the breakpoint region of the *PML* and *RARA* genes, underscoring the causative role of topoisomerase II inhibitors in the etiology of these leukemias.[3–5] In addition to topoisomerase II inhibitors, many other classes of cytotoxic agents (such as alkylating agents and nucleoside analogues), as well as radiotherapy alone, have been linked to therapy-related acute myeloid leukemias in general[6–13] and therapy-related APL (t-APL) in particular.[1] Many of these studies did not specify all the cytogenetic subtypes of the patients with therapy-related acute myeloid leukemias.

Treatment with regimens containing all-*trans*-retinoic acid (ATRA) has revolutionized outcomes in APL.[14] More recently, arsenic trioxide (ATO), either alone or in combination with ATRA, was shown to be effective and less toxic than chemotherapy as frontline therapy for APL.[15–17] Previous reports have established outcomes of patients with t-APL,[1,2,18] comparing them with de novo APL. However, to the best of our knowledge, none included patients who were treated with ATO as a part of their initial therapy.

The objective of the current study was to characterize clinical parameters and treatment outcomes of 29 patients with t-APL at the study institution, 19 of whom were treated with a frontline ATO-containing regimen.

MATERIALS AND METHODS

Informed consent in accordance with the Declaration of Helsinki and institutional approval were obtained. The database of the Department of Leukemia at The University of Texas M. D. Anderson Cancer Center (MDACC) was searched to identify patients with a diagnosis of APL (total n = 301) from 1980 through 2008. Among these, 35 patients carried a previous diagnosis of a malignancy other than APL, 1 patient had been treated previously for multiple sclerosis (total t-APL; n = 36). Seven patients, treated between 1980 and 1990, had not received ATRA and therefore were excluded from our analysis. Therefore, a total of 29 patients with t-APL, treated between 1992 and 2008, were included in our analysis. Clinical parameters, bone marrow studies, and prior chemotherapy exposure were retrieved by chart review (F.D.) and confirmed by another coauthor (S.P.). Complete response (CR) was defined as normalization of peripheral blood counts and bone marrow findings. Overall survival was measured as the time from diagnosis of APL to the time of death or last follow-up.

Routine workup included bone marrow morphology, cytogenetics, fluorescence in situ hybridization for t(15;17), and reverse transcriptase-polymerase chain reaction (RT-PCR) for both short and long forms of the *PML-RARA* fusion transcript. Two patients with normal cytogenetics were diagnosed based on bone marrow morphology and RT-PCR.

The chi-square test was used to describe differences of clinical values among groups. Overall survival was calculated by the Kaplan-Meier method and log-rank test.

RESULTS

Patients

Twenty-nine patients who had received prior chemotherapy and/or radiotherapy developed t-APL between 1992 and 2008. Table 1 shows the patient characteristics. The median age of the patients was 54 years (range, 35–81 years) and 14 (48%) were female. The median white blood cell count (WBC) at the time of presentation was 1.6 × 1000/μL (range, 0.6–162.5× 1000/μL). As a comparison, the median age at presentation in 265 patients with de novo APL treated at our institution in the same time interval was 42 years (range, 13–80 years; *P* <.001), and 49% were female (*P* value was not significant) with a median WBC of 3.5 ×1000/μL (range, 0.2–195 × 1000/μL; *P* value not significant.).

Prior Malignancies

The most common primary cancer was breast cancer (9 of 29 patients), followed by prostate cancer (5 of 29 patients), and lymphoma (4 of 29 patients). Six patients had been previously treated with chemotherapy only, 10 with radiotherapy only, and 13 had received both treatment modalities. Thirteen of 29 patients had prior exposure to topoisomerase II inhibitors (10 patients with anthracyclines, 1 with etoposide, and 3 with mitoxantrone; 2 patients had received 2 different topoisomerase II inhibitors). The exact prior chemotherapy was not documented for 1 patient with breast cancer.

The median interval from primary disorder to the diagnosis of t-APL was 3.5 years (range, 1–19 years). The incidence of t-APL has increased with advancing decades (9% of all patients with APL diagnosed between 1992 and 1999 vs 16% of patients diagnosed between 2000 and 2008; *P* = .027). This trend confirms previous reports,[1,19] possibly explained by the more widespread use of topoisomerase II inhibitors, mainly for the treatment of breast cancer.

Molecular Studies

Cytogenetics data were available for 28 of 29 patients (Table 1). Cytogenetic abnormalities in addition to t(15;17) occurred in 13 of 29 patients (45%) and most frequently involved chromosome 8 (4 of 29 patients; 14%). The presence of additional cytogenetic abnormalities was not associated with a worse outcome. Among 25 patients with available RT-PCR data, detection of the short *PML-RARA* isoform (14 of 25 patients; 56%) was associated with a trend toward shorter survival compared with the long isoform (11 of 25 patients; 44%) (161 weeks vs 344 weeks; *P* = .29).

Prognostic Factors

A WBC >10,000/μL was associated with fewer CRs and worse survival. The CR rate in 10 patients with a WBC >10,000/μL was 60% (6 of 10 patients), with a median survival of 5 weeks (range, 0–282 weeks) versus 95% (18 of 19 patients) and a median survival of 117 weeks (range, 4–650 weeks) for 19 patients with a WBC <10,000/μL. Four of 10 patients with a WBC >10,000/μL failed to achieve a CR, and all had died within 2 weeks of the initiation of induction therapy for t-APL.

Response to Therapy and Survival

The detailed doses and schedules for the drugs used for t-APL induction regimens are shown in Table 2. Postremission therapy was varied depending on the regimen, and the details have been published previously.[16,20,21] The combination of ATO and ATRA (n = 19) for induction resulted in a CR rate comparable to that of ATRA plus chemotherapy (n = 10) (89% vs 70%; *P* = .35). The median overall survival for the patients treated with ATRA plus ATO was not reached compared with that for patients treated with ATRA plus chemotherapy (161 weeks; *P*=.79) (Fig. 1). The difference in the median survival was not significantly different between the 2 groups and likely was a result of a shorter follow-up interval in the ATRA plus ATO group. The median follow-up for all patients (both alive and dead) in the ATRA plus chemotherapy cohort was 51 months (range, 1–117 months), whereas the median follow-up time for all patients in the ATRA plus ATO cohort was 18 months (range, 1–65 months). The median ages for patients treated with ATRA plus ATO and ATRA plus chemotherapy were 53 years and 56.5 years, respectively (*P* value not significant). The percentage of patients with a presenting WBC >10,000/μL was 37% (7 of 19 patients) in patients treated with ATRA plus ATO versus 30% (3 of 10 patients) in patients treated with ATRA plus chemotherapy.

At the time of last analysis (December 2009), 7 of 19 patients in the ATRA plus ATO group and 7 of 10 patients in the ATRA plus chemotherapy group had died. The cause of death was due to leukemia in 4 of 7 patients in the ATRA plus ATO group and 5 of 7 patients in the ATRA plus chemotherapy group. There was no difference in early mortality noted between the 2 cohorts, because in each group, 2 patients died within 4 weeks of the initiation of induction therapy for t-APL.

We also compared the outcome of the patients with t-APL with a cohort of patients with de novo APL who were treated at our institution during the same time interval. As expected, the de novo APL cohort had a significantly younger age at the time of diagnosis (median age, 42 years; range, 13–80 years [*P* < .0001 vs t-APL]). Otherwise, clinical parameters and outcomes were similar to t-APL patients: the median presenting WBC was 3500/μL (range, 200–195,000 μL [*P* = .106 vs t-APL]) and the 3-year survival rate was 65% (*P* = .175 vs t-APL). In the de novo APL cohort, 80 of 85 patients (94%) who were treated with ATRA plus ATO (*P* = .099 vs t-APL) and 26 of 110 patients (76%) treated with ATRA plus chemotherapy achieved a CR.

DISCUSSION

The long-term effects of anthracycline-containing chemotherapy include myelodysplastic syndromes (MDS) and cardiac dysfunction. Therefore, it is plausible that front-line treatment of patients with t-APL previously exposed to anthracyclines, with regimens that omit chemotherapy, particularly topoisomerase II inhibitors, might be beneficial. To our knowledge, this is the first study examining the outcome of patients with t-APL who were treated with ATRA and ATO. In our experience, ATO and ATRA appear to produce results comparable to anthracycline-containing regimens. Although not statistically significant due to the relatively small number of patients, the combination of ATO plus ATRA was found to be associated with a similar response rate and overall survival compared with ATRA plus

chemotherapy. In addition to the risk of MDS and cardiotoxicity, there are patient-related reasons why such a regimen would be desirable in patients with t-APL. Pulsoni et al reported a significantly higher proportion of t-APL patients with poor performance status (Eastern Cooperative Oncology Group score >2) when compared with de novo APL patients.[19] Furthermore, their higher median age makes these patients more susceptible to chemotherapy-induced adverse events and organ toxicities. The higher median age as well as worse performance status in t-APL patients compared with de novo APL patients might have contributed to the inferior outcomes in our cohort of t-APL patients compared with de novo APL patients treated during the same time interval. In addition, consistent with the referral pattern to a major cancer center, it is possible that there was a bias toward poorer prognosis patients treated at our center compared with patients treated at other centers.

There are several limitations to the current study. The small number of patients diagnosed with t-APL during the time span included in the study, the lack of randomization, and the retrospective nature of the analysis make the results susceptible to uncontrolled biases that might influence the validity of our conclusions. However, the most important prognostic factor (WBC >10,000/μL) remained valid. It would be ideal to determine the exact causes of death of the patients on study. However, the majority of patients died outside of our institution with no detailed record of the cause of death available, making it difficult to determine the influence of the toxicities of the 2 strategies on the long-term outcome. Finally, supportive care has improved over the past 3 decades, possibly accounting for differences in survival among our patients. Nevertheless, a higher percentage of patients treated with ATRA and ATO achieved a CR, an endpoint that should not be as significantly influenced by supportive care.

In summary, the current study presents our single-institution experience of what to the best of our knowledge is the largest series of patients with t-APL treated with a frontline regimen with no chemotherapy reported to date. Although we cannot draw definitive conclusions because of the limited sample size, the combination of ATO plus ATRA appears not to be inferior and therefore might be preferable in patients with t-APL to reduce the possible risk of anthracycline-induced cardiomyopathy or MDS. Although ideally, given the low incidence of t-APL, prospective randomized trials are required to confirm our observation, it will be a difficult task to accrue enough patients for such a trial. Thus, although lacking controlled randomized trials data, we might need to resort to observational studies such as this one, despite its limitations, to gain insight into possible treatment options for patients with t-APL.

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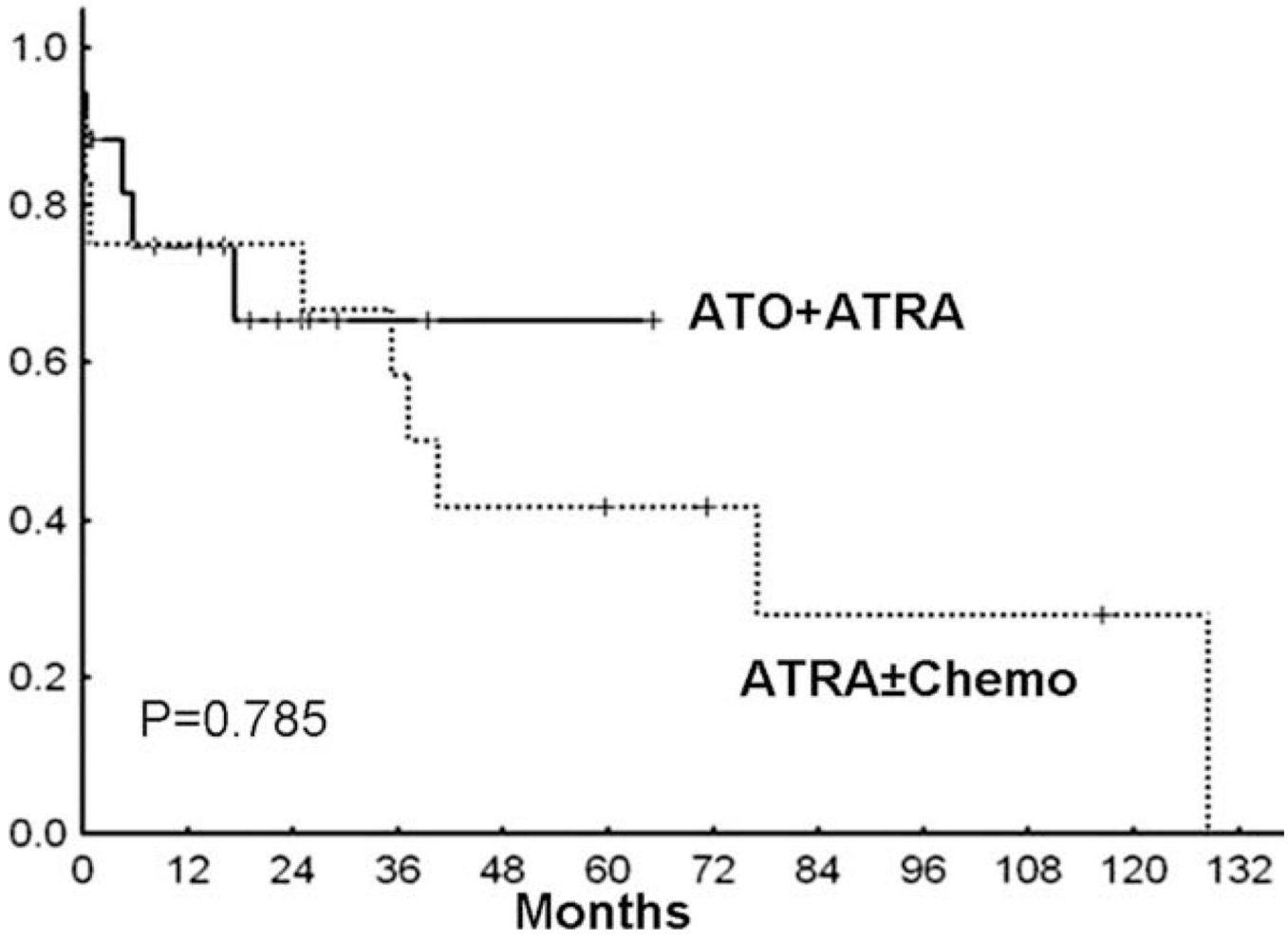

Figure 1.

Overall survival in patients with therapy-related acute promyelocytic leukemia (t-APL) who were treated with arsenic trioxide (ATO) plus all-*trans*-retinoic acid (ATRA) as a frontline regimen compared with patients treated with ATRA plus anthracycline-containing regimens is shown. The bold line indicates ATO plus ATRA (n = 19); dotted line, ATRA plus chemotherapy (Chemo) (n = 10). The median survival was not reached in the group of patients treated with ATO plus ATRA but was 161 weeks in the group of patients treated with ATRA plus chemotherapy (*P* = .79).

Table 1

Patient Characteristics[a]

Gender	Age, Years	Year of Diagnosis	WBC, ×1000/μL	Cytogenetics	RT-PCR Isoform	Primary Malignancy	Prior Chemotherapy	Prior XRT	Frontline Regimen for APL	Response to Induction	Status	Remission Duration, Weeks
ATRA ± Idarubicin ± GO												
Man	37	1994	17.2	46,XY,t(15;17),del(16)	NA	Testis	A+CIS+BLEO	No	IDA+ATRA	Fail	Dead	0
Man	60	1999	2	46,XY,t(15;17)	Short	NHL	CHOP+FND	Yes	IDA+ATRA	CR	Dead	57
Man	63	1992	11	46,XY, t(15;17)	Neither	Prostate	None	Yes	IDA+ATRA	CR	Died in CR	552
Woman	46	1992	1.2	46XX,t(15;17)	Long	Cervix	None	Yes	IDA+ATRA	CR	Alive	304
Woman	59	1996	0.6	46,XX,t(15;17), 46,XX,t(2;4)	Neither	NHL	CHOP+ESHAP	Yes	IDA+ATRA	CR	Alive	500
Man	75	1996	3	46,XY,del(7),t(15;17)	Short	Prostate	None	Yes	IDA+ATRA	Fail	Dead	0
Man	65	1999	0.7	46,XY,t(15;17)	Long	HNSCC	CIS	Yes	IDA+ATRA	CR	Dead	118
Man	35	2001	0.8	46,XY,t(15;17)	Long	NHL	CHOP	Yes	GO+ATRA	CR	Alive	255
Woman	54	2001	1	45,XX,t(15;17),−21	Short	Breast	A+C+TAX	Yes	GO+ATRA	CR	Died in CR	172
Woman	48	2001	30.6	47,XX,+8,t(15;17)	Neither	Breast	None	Yes	GO+IDA+ATRA	Fail	Dead	0
ATO + ATRA ± GO												
Woman	45	2003	9.9	46,XX,t(15;17)	Short	Breast	Capecitabine	Yes	ATO+ATRA	CRp	Died in CR	14
Man	47	2006	1.6	46,XY,t(15;17)	Long	Prostate	A	Yes	ATO+ATRA	CR	Died in CR	21
Woman	63	2002	12.7	46,XX,t(8;14),t(15;17), der(18),t(8;18)	Short	Breast	Not recorded for breast cancer	Yes	ATO+ATRA+GO	CR	Alive	277
						Arthritis	MTX for arthritis					
Man	72	2004	1.2	46,XY,inv(2),t(15;17)	Long	NHL	CHOP+RITUX+F	No	ATO+ATRA	CR	Died in CR	71
Man	60	2005	0.9	46,XY,t(15;17)	Long	HNSCC	None	Yes	ATO+ATRA	CR	Alive	104
Man	81	2004	1.5	CG not done (FISH 60.5%)	Short	Stomach	5-FU	Yes	ATO+ATRA	CR	Alive	167
Woman	56	2004	11.5	47,XX,t(15;17),+mar	Short	Breast	Not recorded	Yes	ATO+ATRA+GO	Fail	Dead	0
Woman	46	2004	0.8	46,XX,del(12),t(15;17)	Long	SLL	Flu+FND+RITUX	No	ATO+ATRA	CR	Alive	120
Woman	65	2006	1.4	47,XX,+8,t(15;17)	Short	Breast	None	Yes	ATO+ATRA	CR	Alive	65
Man	66	2005	162.5	46,XY,inv(9),t(15;17)	Short	Prostate	None	Yes	ATO+ATRA+GO	Fail	Dead	0
Woman	42	2005	24.7	46,XX,t(15;17)	Long	Breast	A+C+TAX	No	ATO+ATRA+GO	CR	Alive	107
						MDS/AML	Ara-C+IDA					
Man	47	2005	0.6	46,XY,del(9),inv(9),t(15;17)	Short	Seminoma	None	Yes	ATO+ATRA	CR	Alive	93
Woman	36	2006	1.5	46,XX	Short	MS	FND	No	ATO+ATRA	CR	Alive	73

Gender	Age, Years	Year of Diagnosis	WBC, ×1000/μL	Cytogenetics	RT-PCR Isoform	Primary Malignancy	Prior Chemotherapy	Prior XRT	Frontline Regimen for APL	Response to Induction	Status	Remission Duration, Weeks
Woman	53	2008	65.3	46,XX	Short	Breast	5-FU+E+C+TAX	Yes	ATO+ATRA+GO	CR	Alive	54
Woman	52	2008	46.3	46,XX,t(15;17)	Long	Breast	A+C+DOC+TAX	Yes	ATO+ATRA+GO	CR	Alive	32
Man	46	2007	68.5	46,XY,t(15;17)	Short	Testis	BEP	No	ATO+ATRA+GO	CR	Alive	0
Man	77	2008	0.7	46,XY,add(8),t(15;17)	Long	Prostate	None	Yes	ATO+ATRA	CR	Alive	0
Woman	53	2001	2.6	47,XX,t(15;17),del(20),+mar	Short	Cervix	None	Yes	ATO+ATRA+GO	CR	Dead	69
Man	60	1999	0.5	46,XY,t(15;17)	Long	MFH	A+I	Yes	ATO+ATRA	CR	Dead	34

WBC indicates white blood cell count; RT-PCR, reverse transcriptase-polymerase chain reaction; XRT, radiotherapy; APL, acute promyelocytic leukemia; ATRA, all-*trans*-retinoic acid; GO, gemtuzumab ozogamicin; t, translocation; del, deletion; NA, not applicable; A: Adriamycin (doxorubicin); CIS, cisplatin; BLEO, bleomycin; IDA, idarubicin; NHL, non-Hodgkin lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; FND, fludarabine, mitoxantrone, and dexamethasone; CR, complete response; ESHAP, etoposide, methylprednisolone, high-dose cytarabine, and cisplatin; HNSCC, head and neck squamous cell carcinoma; C, cyclophosphamide; TAX, paclitaxel; ATO, arsenic trioxide; CRp, pathologic complete response; MTX, methotrexate; RITUX, rituximab; F, FND (mitoxantrone); CG, cytogenetics; FISH, fluorescence in situ hybridization; 5-FU, 5-fluorouracil; SLL, small lymphocytic lymphoma; Flu, fludarabine; MDS/AML, myelodysplastic syndrome/acute myelogenous leukemia; Ara-C, cytarabine; MS, multiple sclerosis; E, epirubicin; DOC, docetaxel; BEP, bleomycin, etoposide, and cisplatin; MFH, malignant fibrous histiocytoma; I, ifosfamide.

[a]Two patients with negative cytogenetics were diagnosed before RT-PCR was introduced into clinical practice, and therefore the diagnosis of t-APL was based on morphology only.

Table 2

Drug Doses and Schedules in t-APL Induction Regimens[a]

Drug	Dose	Schedule	Route
		ATRA + **ATO** ± **GO**[16]	
ATRA	(45 mg/m^2)	Starting on D 1, once daily	PO
ATO	(0.15 mg/kg)	Starting D 1 or D 10 once daily until CR	iv
GO	(9 mg/m^2)	D 1 for WBC >10,000/μL	iv
		ATRA + **IDA** ± **GO**[21]	
ATRA	(45 mg/m^2)	Starting D 1 once daily	PO
IDA	(12 mg/m^2)	D 1–4	iv
GO	(9 mg/m^2)	D1	iv
		ATRA + **GO**[20]	
ATRA	(45 mg/m^2)	Starting D 1 once daily	PO
GO	(9 mg/m^2)	D1	iv

t-APL indicates therapy-related acute promyelocytic leukemia; ATRA, all-*trans*-retinoic acid; ATO, arsenic trioxide; GO, gemtuzumab ozogamicin; PO, orally; CR, complete response; iv, intravenously; WBC, white blood cell count; IDA, idarubicin.

[a] GO was added to the regimen for patients with a WBC >10,000/μL.