

Walking a Tightrope: Dosage Modifications and Treatment Outcomes of All-*Trans*-Retinoic Acid, Arsenic Trioxide, and Daunorubicin for High-Risk Acute Promyelocytic Leukemia

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PURPOSE The use of all-*trans*-retinoic acid (ATRA) and arsenic trioxide (ATO) in the treatment of low- and intermediate-risk acute promyelocytic leukemia (APL) is the standard of care. We report the combined use of ATRA, ATO, and daunorubicin (DNR) in patients newly diagnosed with high-risk APL. The primary focus was to describe the drug dosage modifications made in the real-world scenario.

METHODS In this descriptive study, we included 16 out of 28 patients with high-risk APL from two tertiary care centers in South India (Vijayawada and Trichy) between January 2015 and December 2018. A unique approach of initiating ATRA at a dose of 25 mg/m² on day 1 and escalation to 45 mg/m² after cyto-reduction with DNR and hydroxyurea was followed in all patients to avert differentiation syndrome, in the setting of hyperleukocytosis at presentation.

RESULTS All patients who survived the first 3 days of admission achieved complete remission after a median duration of 29 days. There were no deaths during induction or consolidation, and the regimen was well tolerated; two patients developed grade 3/4 peripheral neuropathy requiring treatment modification. After a median follow-up duration of 1.9 years, there were no hematologic or molecular relapses.

CONCLUSION The study sheds light on the modifications made to recommended dosages of ATRA, ATO, and DNR to optimize outcomes in high-risk APL and reaffirms the importance of ATO use in the front-line setting to achieve durable responses with minimal toxicity.

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INTRODUCTION

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML) with complete remission (CR) and long-term disease-free survival (DFS) rates of approximately 90% and 85%, respectively.¹⁻⁵ The most important challenges remaining in APL include the high incidence of early death before and during induction therapy, disparities in outcome in developing countries, and optimizing treatment in patients with high-risk disease.⁶⁻⁸

Standard induction and consolidation for low- to intermediate-risk APL involves all-*trans*-retinoic-acid (ATRA) plus arsenic trioxide (ATO).^{9,10} Adoption of the same approach in patients with high-risk APL (defined as those with an initial WBC count > 10 × 10⁹/L) has not yet shown to be superior in randomized studies.¹¹ Treatment options for high-risk APL are either ATRA plus chemotherapy or ATRA plus ATO, with the administration of hydroxyurea or one to two doses of idarubicin or gemtuzumab ozogamicin (GO), an anti-CD33 monoclonal antibody drug conjugate, as

cytoreductive strategies.^{10,12} Daunorubicin (DNR) has similar rates of primary resistance, molecular persistence of disease, and molecular and hematologic relapse rates in comparison with idarubicin and is more readily available and cost effective in developing countries.¹³

In an attempt to improve efficacy, the ALLG (Australasian Leukaemia and Lymphoma Group) APML4 trial recommended the treatment of newly diagnosed patients to therapy with a combination of ATRA and ATO with idarubicin in lower cumulative doses than those used in ATRA and idarubicin-based protocols. A significant improvement in freedom from relapse was achieved without the addition of further moderate- to high-dose chemotherapy during induction and/or consolidation.^{14,15}

The initial treatment of APL requires striking a fine balance between correction of coagulopathy and prompt recognition of treatment-related differentiation syndrome (DS). This may warrant adjustments of recommended dosages of chemotherapy, ATRA, and

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CONTEXT

Key Objective

The initial management of high-risk acute promyelocytic leukemia (APL) often involves juggling the dosages of all-*trans*-retinoic acid (ATRA), arsenic trioxide (ATO), and anthracyclines. This record review of a cohort of patients with high-risk APL at two tertiary care centers in South India elucidates these modifications to a protocol based on the APML4 trial, mandated by the clinical scenario.

Knowledge Generated

Physicians adopted a unique approach of initiating ATRA at a dose of 25 mg/m² at diagnosis and escalating to 45 mg/m² after cytoreduction. Daunorubicin, which is more readily available and cost effective, was chosen in place of idarubicin. The outcome was good for those surviving the first 3 days. After a median follow-up duration of 1.9 years, there were no hematologic or molecular relapses.

Relevance

The study reasserts the importance of ATO use in the front-line setting to achieve durable responses with minimal toxicity. The direct medical cost incurred per patient was 9,844 US dollars.

ATO. There are no published data on such dosage modifications made in the “real world” in the treatment of high-risk APL. In this study, we aimed to describe drug dosage modifications in patients with newly diagnosed high-risk APL treated with an induction regimen consisting of ATRA, ATO, and DNR and to report on the treatment outcomes and associated costs.

METHODS

Study Design

We conducted a descriptive study by reviewing case records of a cohort of patients with high-risk APL at two tertiary care centers in South India (Vijayawada and Trichy) between January 2015 and December 2018.

Management of Patients With High-Risk APL

Patients with suspected APL based on clinical and morphologic features were immediately started on ATRA at a dose of either 45 mg/m² or 25 mg/m² (in patients younger than 15 years), pending genetic confirmation of the diagnosis.¹⁶ A genetic diagnosis of APL was established by detection of the *PML-RARA* (promyelocytic leukemia/retinoic acid receptor alpha) fusion gene by means of fluorescence in situ hybridization, reverse transcriptase polymerase chain reaction (RT-PCR) assay, or demonstration of the t(15;17) translocation by means of conventional karyotyping. We considered patients with high-risk APL on the basis of Sanz score for this study.¹⁷

Treatment regimen including ATRA, ATO, and DNR is described in Figure 1. Induction included ATRA (either 45 mg/m² or 25 mg/m²) from day 1 and daily ATO at a dose of 0.15 mg/kg from day 10, until hematologic CR or for a maximum of 60 days, and one to four doses DNR at 45 or 60 mg/m²/d as a cytoreductive strategy. Marrow aspirates were obtained approximately weekly beginning 25 to 28 days after the start of treatment. Once the marrow showed < 5% blasts and no abnormal promyelocytes,

ATRA and ATO were discontinued until occurrence of CR, defined by neutrophil and platelet counts > 1 × 10⁹/L and 100 × 10⁹/L, respectively. Consolidation included ATO (0.15 mg/kg; 5 days per week, 4 weeks on, 4 weeks off) for a total of four courses and ATRA (45 mg/m² or 25 mg/m² daily, 2 weeks on, 2 weeks off) for a total of seven courses.

We followed National Cancer Institute definitions for hematologic CR and morphologic relapse.¹⁸ Time to achieve CR during induction was recorded, and we performed quantitative RT-PCR to assess molecular CR at the end of the third cycle of consolidation. Subsequent monitoring was done every 3 months during the first and second year and every 6 months during the third and fourth year. We followed all patients until April 2019.

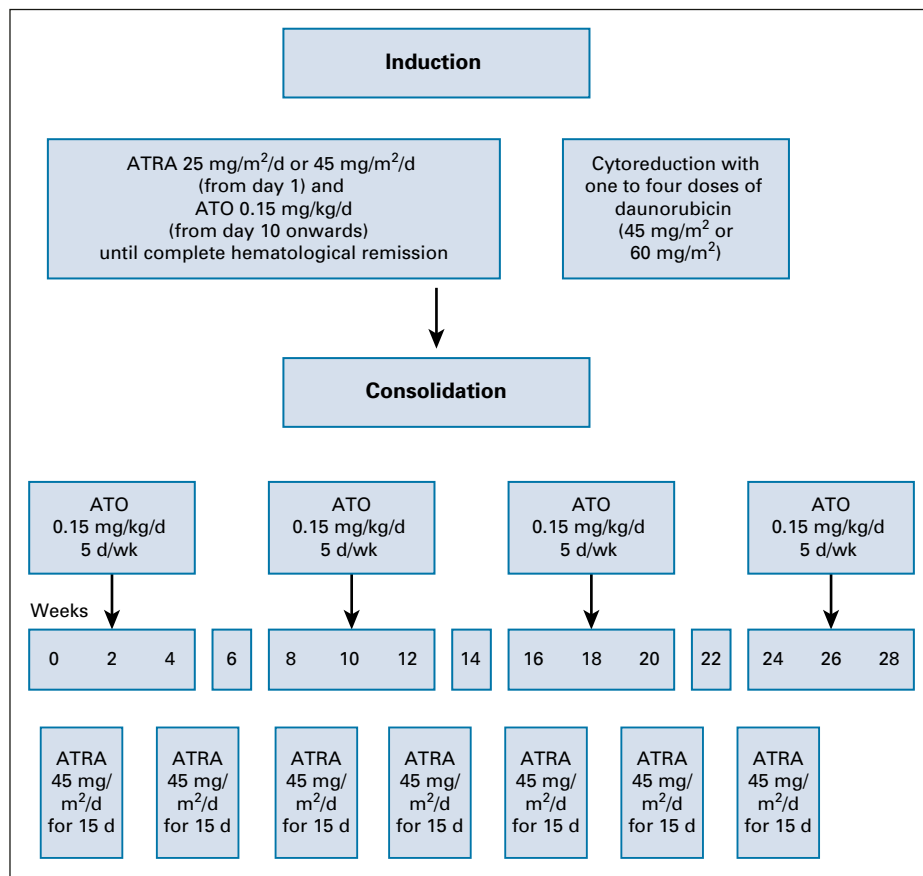
Patients either paid out of pocket or were covered under the state-funded or private health insurance plans.

Ethics approval was obtained from the Ethics Advisory Group of The Union, Paris, France (EAG number: 31/18) and Institutional Ethics Committee, Dr GVN Cancer Institute, Trichy, India (dated July 30, 2018). As the study involved review of case records, waiver for informed consent was sought and approved by the ethics committees.

Statistical Analysis

Data from the case records were entered into EpiCollect5 mobile application (Imperial College, London), and analysis was performed in STATA (version 12.1, StataCorp, College Station, TX). Continuous variables like age, duration of symptoms, and biochemical parameters were summarized as mean and standard deviation (SD) or median (interquartile range [IQR]). Dosage modifications of drugs and their toxicities were presented as frequencies and proportions. We calculated annualized direct medical costs (regimen, blood components, antibiotics and adjunct drugs, laboratory charges) and presented them as mean

FIG 1. Treatment regimen in patients with high-risk acute promyelocytic leukemia treated with all-*trans*-retinoic acid (ATRA), arsenic trioxide (ATO), and daunorubicin, between 2015 and 2018, from two private tertiary cancer centers in South India (n = 16).



(SD). Costs were discounted at 3% per annum, and dollar conversion was done at the rate of 69.58 India rupees (INR), as of March 2019.

RESULTS

A total of 50 patients were diagnosed with APL during the study period, of whom 28 (56%) patients had high-risk APL. Of 28 patients with high-risk APL, we included 16 patients for the study. Flow of patients and reasons for exclusion are described in Figure 2. The demographic and clinical characteristics of the 16 patients with high-risk APL who received ATRA, ATO, and DNR are summarized in Table 1. Median (IQR) age was 32 (19-42) years. Median (IQR) total leukocyte count at presentation was 34,650 (16,950-53,200) per μ L.

Dosage Modifications

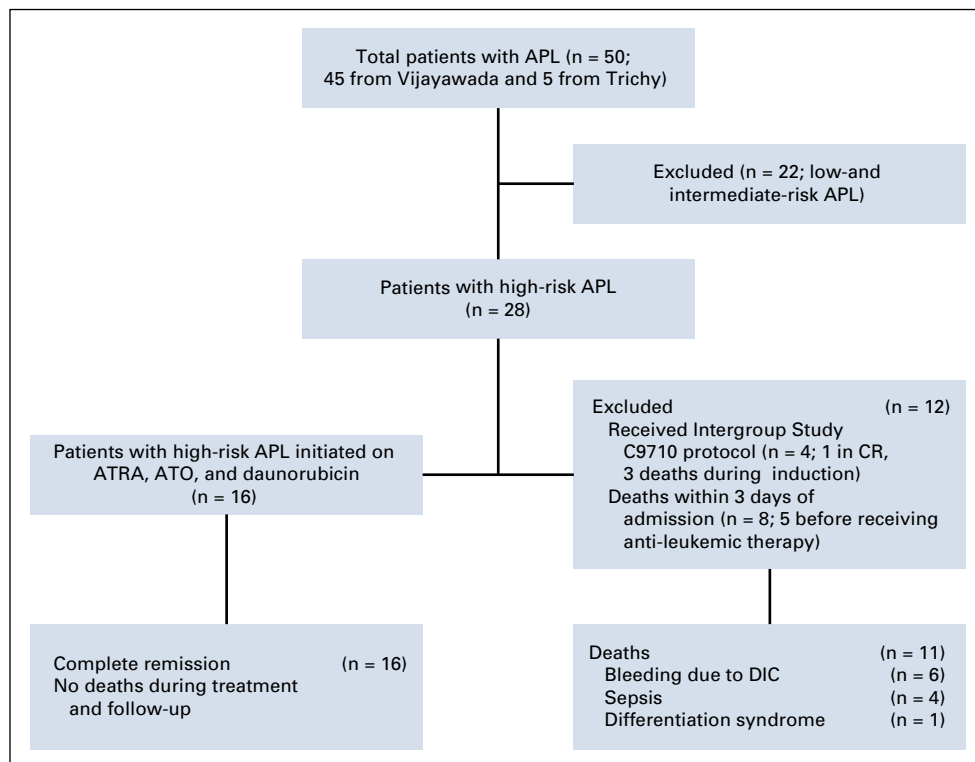
Table 2 summarizes dosage modifications of ATRA, ATO, and DNR during induction. DNR was initiated at a dose of 45 mg/m² in nine patients and 60 mg/m² in the remaining seven patients (Figure 3). Factors that influenced the initial choice of DNR dose were advanced age and severe pulmonary arterial hypertension in one patient, biochemical hepatotoxicity in one patient, and sepsis in two patients; reason for titration was not documented in five

patients. For the third dose, DNR was escalated to 60 mg/m² in two patients and de-escalated to 45 mg/m² in one patient. ATRA was initiated at a dose of 25 mg/m² in 10 patients until cytareduction was achieved and increased to 45 mg/m² thereafter. The reasons for dose reduction and brief interruption of ATRA during induction were hyperleukocytosis in five patients, DS in two patients, and benign intracranial hypertension in one patient. One patient had pyoderma during consolidation deemed to be ATRA related. Two patients had peripheral neuropathy, of whom one had severe bilateral axonal neuropathy of the common peroneal nerve. DNR and cytarabine were added to ATRA during consolidation, as a substitute to ATO in one patient who developed grade 4 peripheral neuropathy.

Outcomes

Hematologic CR was achieved in all 16 patients, and the median time to achieve CR was 29 days (range, 18-48 days). There were no deaths during induction or consolidation. After a median follow-up of 1.9 years (range, 0.5-4.3 years), all patients remained in hematologic CR. Molecular CR was documented in 13 patients after the third consolidation cycle, and all of them remained in molecular CR.

FIG 2. Flow diagram of patients with acute promyelocytic leukemia treated between 2015 and 2018, from two private tertiary cancer centers in South India (n = 50). APL, acute promyelocytic leukemia; ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; CR, complete remission; DIC, disseminated intravascular coagulation.



Adverse Events

The frequency of grade 3 and 4 adverse events during induction and consolidation phases of treatment are summarized in Table 3. One patient had prolonged QTc interval, hypokalemia, hypomagnesemia, and hypotension. The toxic effects resolved with temporary discontinuation of ATO, ATRA, or both in all cases, except those with peripheral neuropathy.

Cost Description

The direct medical costs incurred are summarized in Table 4. The mean (SD) total direct medical cost was 9,844 (1,520) US dollars per patient. Out of the two centers, one center had 85% of the patients using government plans, and 15% had private insurance or made out-of-pocket payment. The other center had only 15% of patients using government plans.

DISCUSSION

The current study confirms the safety and efficacy of a schedule including ATRA, ATO, and DNR in the treatment of patients with high-risk APL. Dosage modifications were frequent, individualized, and had no negative impact on outcomes in our study. The median age at diagnosis was 32 years and is a reflection of published literature, where most cases are diagnosed between ages 20 and 50 years.¹⁹ The median time from symptom onset to consulting a hemato-oncologist was 10 days. Delayed presentation to the hospital is a contributing factor for poorer outcomes of APL in developing countries.⁸

ATO induces both differentiation and apoptosis of APL cells in a dose-dependent manner, induces PML-RARA fusion protein degradation, is active even in patients whose leukemic cells exhibit ATRA and chemotherapy resistance, and exhibits synergism with ATRA.²⁰⁻²² Although initial studies focused on the use of ATO in the salvage setting or during consolidation, incorporating it into front-line therapy is imperative to optimize the outcomes of APL.^{10,14,23,24}

The basis of studies advocating a de-escalation or a chemotherapy-free approach is to reduce the toxicities associated with cytotoxic drugs. The introduction of GO has shown to be effective when used for this purpose.^{11,12} GO is not readily available, and the cost is prohibitive. The obvious choice in this context is DNR, and its importance cannot be overstated. An inclination to start DNR at a lower dose of 45 mg/m² in nine patients in our study was to reduce the toxicity associated with the drug. The ability to manage extreme hyperleukocytosis and DS by hydroxyurea alone was limited even when prescribed at maximal doses.

ATRA was initiated at a dose of 25 mg/m² in all patients in our study and escalated to the recommended dose of 45 mg/m² after cytoreduction. To our knowledge, such a dose-escalation method has never been documented or adopted as a strategy in other studies. This dosage modification was influenced by the degree of hyperleukocytosis at presentation and primarily focused on averting DS. DS developed in two of 16 (12%) patients.

In our study, there were eight (28%) early deaths occurring within 3 days of admission, similar to the death rates

TABLE 1. Demographic and Clinical Characteristics of Patients With High-Risk Acute Promyelocytic Leukemia Treated With All-*Trans*-Retinoic Acid, Arsenic Trioxide, and Daunorubicin Between 2015 and 2018, From Two Private Tertiary Cancer Centers in South India (n = 16)

Characteristic	Value
Age, years, median (IQR)	32(19-42)
Sex, No. (%)	
Female	10(62.5)
Male	6(37.5)
BSA, m ² , mean (SD)	1.7(0.3)
ECOG PS, No. (%)	
0-2	14(87.5)
3-4	2 (12.5)
Duration of symptoms, days,* median (IQR)	10 (4-20)
Hemoglobin, g/dL, mean (SD)	8.4 (2.2)
Total leukocyte count/ μ L, median (IQR)	34,650 (16,950-53,200)
Platelet count/ μ L, median (IQR)	24,000 (13,500-33,000)
Fibrinogen, mg/dL,* median (IQR)	112 (65-248)
Prothrombin time, seconds,* mean (SD)	18.7 (2.5)
International normalized ratio,* mean (SD)	1.5 (0.3)
APTT, seconds,* mean (SD)	31.3 (8.7)
Diagnostic modality to detect PML RARA, No. (%)	
FISH	14 (87.5)
RT-PCR	2 (12.5)

Abbreviations: APTT, activated partial thromboplastin time; BSA, body surface area calculated according to Mosteller method: BSA (m²) = (height [cm] × weight [kg])/3,600^{1/2}; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FISH, fluorescence in situ hybridization; IQR, interquartile range; PML RARA, promyelocytic leukemia/retinoic acid receptor alpha; RT-PCR, reverse transcriptase polymerase chain reaction; SD, standard deviation.

*Data missing for duration of symptoms in one patient, fibrinogen in two patients, and PT, international normalized ratio, and APTT in 10 patients.

reported in population-based studies.^{8,19} All the patients who survived the first 3 days achieved CR, and the median time to achieve hematologic CR was 29 days. Similar median duration of 30 days was reported by Abaza et al¹² using a schedule with GO.

No post-remission chemotherapy was given during consolidation. ATRA and ATO consolidation therapy was delivered on an outpatient basis and was well tolerated. Patients did not receive maintenance treatment or CNS prophylaxis. The role of maintenance in high-risk APL is controversial and has been re-examined in the ATO era. Studies based on the ATRA/chemotherapy backbone reported considerably better outcomes with maintenance treatment, whereas those that included ATO showed no such advantage.^{4,25,26}

There were no hematologic or molecular relapses in the current study after a median follow-up of 1.9 years. The possible explanation for the dramatic decrease in morphologic and molecular relapses is the synergism of ATO

TABLE 2. Dosage Modifications of All-*Trans*-Retinoic Acid, Arsenic Trioxide, and Daunorubicin During Induction Phase of Chemotherapy for Patients With High-Risk Acute Promyelocytic Leukemia Treated Between 2015 and 2018, From Two Private Tertiary Cancer Centers in South India (n = 16)

Dosage Modification	Value
Days of induction DNR given	
1, 2, 3	9 (56.1)
1, 2	2 (12.5)
2, 3	2 (12.5)
2, 3, 4	1 (6.3)
5, 6	1 (6.3)
6, 7, 18, 19	1 (6.3)
Total No. of doses of DNR	
2	5 (31.3)
3	10 (62.4)
4	1 (6.3)
Dose of ATRA initiated at diagnosis	
25 mg/m ²	10 (62.5)
45 mg/m ²	6 (37.5)
No. of days ATRA was given,* mean (SD)	25 (5)
No. of days ATO was given,* mean (SD)	18 (3.3)

NOTE. Data are presented as No. (%) unless otherwise noted.

Abbreviations: ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; DNR, daunorubicin; SD, standard deviation.

*Data missing for No. of days ATRA and ATO were given during induction for two patients.

and ATRA.²² Also, the negative effect of high-risk disease can be overcome by the use of ATO.²⁷ These results are similar to previously reported studies involving ATRA, ATO, and GO.^{11,12} The current recommendation of routine molecular monitoring during follow-up of high-risk APL needs to be revisited, especially in a resource-constrained setting.

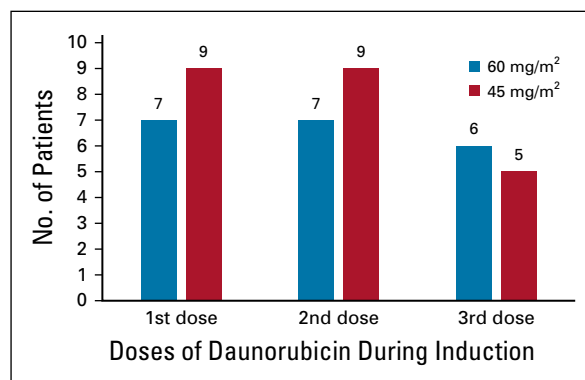


FIG 3. Dosage of daunorubicin received by patients with high-risk acute promyelocytic leukemia treated with all-*trans*-retinoic acid, arsenic trioxide, and daunorubicin, between 2015 and 2018, from two private tertiary cancer centers in South India (n = 16).

TABLE 3. Grade 3 and 4 Hematologic and Nonhematologic Toxicity of Patients With High-Risk Acute Promyelocytic Leukemia Treated With All-*Trans*-Retinoic Acid, Arsenic Trioxide, and Daunorubicin During Induction and Consolidation Phases, Between 2015 and 2018, From Two Private Tertiary Cancer Centers in South India (n = 16)

Toxicity	Induction	Consolidation
Anemia	16 (100)	2 (125)
Neutropenia	13 (813)	4 (25)
Thrombocytopenia	16 (100)	3 (188)
Neurologic	3 (188)	3 (188)
Sepsis	11 (688)	2 (126)

NOTE. Data are presented as No. (%). Grading of hematologic and nonhematologic toxicity was done as per Common Terminology Criteria for Adverse Events.

Grade 3 and 4 hematologic and nonhematological toxicities were more frequent during induction than consolidation. Although routine ECG monitoring for QTc prolongation is recommended, it was not done.¹⁰ Instead, measures were taken to maintain serum potassium levels > 4 mEq/L and serum magnesium levels > 1.8 mEq/L. One patient developed dizziness and syncope during induction but recovered.

The major limitation of our study is its retrospective design. However, APL is a rare subtype of AML, with an uneven distribution, making a prospective study with an adequately sized sample in a developing country extremely difficult. Also, the median follow-up duration was relatively short at 1.9 years. Relapses and secondary malignancies are likely to be seen with a longer period of observation. Cytogenetics study and FLT3 status were not determined for all patients. However, the negative effect of positive FLT3 status is abrogated by the use of ATO.²⁸

There are several unanswered questions in the management of high-risk APL. The most difficult hurdle to overcome is the first week, as evident in the persistently high early death rates in clinical trials and population-based studies.^{8,19} The practical challenge we face when treating patients with high-risk APL is to identify the optimal approach in patients with extreme hyperleukocytosis, major bleeding due to disseminated intravascular coagulation, sepsis, DS, poor organ reserve, advanced age, or poor performance status.

The cost effectiveness of ATRA and ATO in newly diagnosed patients with low to intermediate risk in comparison with

TABLE 4. Direct Medical Costs Associated With Management of Patients With High-Risk Acute Promyelocytic Leukemia Treated With All-*Trans*-Retinoic Acid, Arsenic Trioxide, and Daunorubicin Between 2015 and 2018, From Two Private Tertiary Cancer Centers in South India (n = 14)

Cost Head	Mean (SD) Cost in US Dollars ^a
Regimen (ATRA + ATA + DNR)	2,168 (180.1)
Blood components	2,036 (627.1)
Antibiotics and adjunct drugs	2,138 (804.1)
Laboratory	1,266 (470.4)
Miscellaneous	2,236 (285.9)
Total cost	9,844 (1,520)

NOTE. Cost information not available for two patients.

^aCosts were annualized (discounting at 3% per annum) and dollar conversion was at the rate of 69.58 India rupees as of March 2019.

patients receiving ATRA, cytarabine, and additional chemotherapy or ATRA and idarubicin was reported to be high in a study by Tallman et al.²⁹ It improved the quality-adjusted life-years (QALYs) by double and by 75% when compared with ATRA, cytarabine, and additional chemotherapy and ATRA plus idarubicin, respectively, while the total costs were only 40% and 35% more than the respective treatment groups. However, there were no cost-effective studies about ATRA, ATO, and DNR.²⁹

Our study showed that the average direct medical cost was 9,844 US dollars, translating to approximately Rs.7 lakhs in the current currency value of INR. This is a huge cost to be borne, considering the fact that it represents the sum exempting the indirect medical costs in a country where approximately 63 million people are driven to below poverty because of medical costs.³⁰ It is strongly recommended that the government should strengthen and expand its existing central and state insurance plans to reduce the health care burden. From the researchers' front, more cost-effective studies are to be conducted in India, as trial-based cost effectiveness is a valid guideline to aid the decision-making process.³¹ The results of our study show that a schedule combining ATO, ATRA, and DNR in patients with high-risk APL helps achieve good and durable responses. Drug dosage modifications based on clinical reasoning are the norm.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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No potential conflicts of interest were reported.

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