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Treatment of children with acute promyelocytic leukemia: Results of the first North American intergroup trial INT0129

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Abstract

Background—This report focuses on the children enrolled on the first North American Intergroup study of APL (INT 0129). This study was designed to compare the rates of CR, disease-free survival (DFS), overall survival (OS) and toxicity of therapy with ATRA for remission induction and/or maintenance compared to conventional chemotherapy in patients with previously untreated APL.

Procedure—Fifty-three patients who were documented to have the t(15;17) translocation were able to be evaluated for toxicity of treatment, outcome of induction, and survival.

Results—The overall CR rate was 81%. The estimated 5-year DFS from time of CR was 41% for all patients. The estimated 5-year OS for all patients from entry into the study was 69%. The 5-year DFS from time of CR for patients who were randomized to ATRA for induction or maintenance or both was 48% compared to 0% for patients who never received ATRA.(p<0.0001)

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Conclusions—The most important finding of our study is that a significant disease-free survival advantage exists for children with APL who received ATRA during induction or maintenance or both compared to children who received no ATRA. Furthermore, remissions in these children appear durable as the OS rates are stable at 10 years.

Keywords

Acute Promyelocytic Leukemia; All-trans retinoic acid; AML

Introduction

Acute promyelocytic leukemia (APL) is an uncommon form of acute myeloid leukemia (AML). (1) In the United States, APL in children has constituted only 6-10% of AML.(2-4) Molecularly, the disease is characterized by a fusion protein, PML/RAR α that results from a balanced reciprocal translocation between the PML gene on chromosome 15 and the retinoic acid receptor alpha gene on chromosome 17. (5) Morphologically, the classic APL cells are characterized by hypergranular promyelocytes and often with numerous Auer rods.(6) A severe bleeding diathesis is the clinical hallmark of APL.(7)

A major advance in the treatment of APL has been the use of all-*trans*-retinoic acid (ATRA). (8-10) ATRA differentiates leukemic promyelocytes into mature granulocytes.(11, 12) While ATRA is capable of inducing a complete remission (CR), concurrent chemotherapy and ATRA during induction have resulted in superior remission and survival rates.(13)

This report focuses on the children enrolled on the first North American Intergroup study of APL (INT 0129).(14, 15) This study was designed to compare the rates of CR, disease-free survival (DFS), overall survival (OS) and toxicity of therapy with ATRA for remission induction and/or maintenance compared to conventional chemotherapy in patients with previously untreated APL. The results of the entire cohort of adults and children who were enrolled from six cooperative groups have been previously reported.(14, 15) Since there have been few reports of children with APL treated with ATRA based therapy and very few with long follow-up,(9, 16-21) we present the detailed results of the pediatric patients who participated in this study.

Patients, materials and methods

Patients

Seventy-one patients from the Children's Cancer Group and the Pediatric Oncology Group were enrolled in the study between April 1992 and February 1995. The protocol was approved by each institution's individual IRB and informed consent was obtained from every participant or guardian. The eligibility criteria were: a diagnosis of APL based on bone marrow morphology(1), age of 0-18 years at diagnosis, no prior chemotherapy except hydroxyurea, normal hepatic and renal function, and an Eastern Cooperative Oncology Group performance status of 0 (normal activity) to 3 (in bed more than 50 percent of the time). Cytogenetics evaluation for t(15;17) was mandatory; however, the results did not affect eligibility to participate in the study. While patients without documentation of t(15;17) remained on study based on their bone marrow morphology review, these patients are not included in this report in an attempt to avoid any chance of including patients that did not have APL which would not be expected to respond to ATRA.

Eight patients were ineligible for the following reasons: French-American-British(FAB) in error (5), insurance falsification (1), age >18 (1), cancellation of registration (1). Ten

patients appeared to have APL by morphology, but lacked documentation of the t(15;17) translocation.

Fifty-three patients who were documented to have the t(15;17) translocation by conventional cytogenetics, PCR or FISH were able to be evaluated for toxicity of treatment, outcome of induction, and survival. These patients are the focus of this report. The clinical features of the patients are shown in Table I and show no significant differences in any of the clinical features of the patients randomized for induction treatment.

Study Design (Figure 1)

Induction Therapy—Patients were randomly assigned to receive either daunorubicin and cytarabine; or ATRA (Vesanoid). For patients assigned to cytotoxic chemotherapy, a second induction cycle with identical doses and schedules was given if the day 14 marrow had 50 percent or more abnormal promyelocytes or if disseminated intravascular coagulation was recurring. Patients received ATRA until complete remission, or for a maximum of 90 days. Patients who had unacceptable toxicity while taking ATRA or who did not have a complete remission after a maximum of 90 days were crossed over to the chemotherapy arm. Patients who did not have a complete remission after two cycles of chemotherapy were deemed failures and were treated at their physician's discretion off protocol. No CNS prophylaxis was given during induction or any other phase of therapy. Chemotherapy in patients < 3 years was based on milligram/kilogram.

Consolidation Therapy—Patients who had a complete remission with chemotherapy or ATRA received two cycles of consolidation therapy. The first cycle was identical to the induction chemotherapy. The second cycle included high-dose cytarabine and daunorubicin.

Maintenance Therapy—Patients in complete remission after both cycles of consolidation chemotherapy, irrespective of which induction therapy they had received, were randomly assigned either to a maintenance regimen of ATRA one year or to observation. Patients who were intolerant of induction therapy with ATRA were directly assigned to observation.

Definition of Outcome

Toxic effects were graded according to the Common Toxicity Criteria of the National Cancer Institute version 1. CR was defined as previously noted in the first study report(14) according to National Cancer Institute criteria.(22) DFS was calculated from two different starting points: time of documented CR and start of maintenance. DFS was defined as the time from one of these specified starting points to relapse, death from any cause, or censoring of the data on the patient. OS was defined as time from registration to death from any cause. Patients who were still alive at the most recent contact were censored at the time of the latest contact.

Supportive Care

Coagulopathy—Coagulopathy was treated at the physician's discretion.

Hyperleukocytosis—If the white blood count(WBC) at diagnosis for patients randomized to ATRA was more than 10,000/uL, hydroxyurea 1 gm/m² every 6 hours was given until the WBC was 10,000/uL at which time the ATRA was initiated. If the WBC count rose during therapy to > 30,000/uL, ATRA was stopped, hydroxyurea was given until the WBC was 10,000/uL, and then ATRA was resumed.

General—When Grade III or higher toxicity occurred, ATRA was withheld until the effects diminished to a Grade I level and was then resumed at 75 percent of the initial dose.

Management of Retinoic Acid Syndrome—Retinoic acid syndrome (RAS) was diagnosed in patients with unexplained fever, weight gain, respiratory distress, interstitial pulmonary infiltrates, and pleural or pericardial effusions.(14) ATRA was discontinued at the earliest signs of the syndrome, and dexamethasone was instituted for at least three days. After resolution of the symptoms, ATRA was resumed at 75 percent of the initial dose and if there was no recurrence of RAS, the initial dose was resumed.

Statistical Analysis

Descriptive statistical analysis was performed to report patient baseline and treatment characteristics. Two-sided Fisher's exact test was used for 2×2 table analysis, and a two-sided Wilcoxon-Rank-Sum test was used for two-sample comparison of continuous variables. Multiple comparisons are not adjusted in the analysis of toxicity in Table II. OS and DFS were calculated using the Kaplan-Meier method.(23) Kaplan-Meier curves were compared using log-rank tests.(24) Potential prognostic factors for OS and DFS were examined in the proportional hazards model.

Results

Induction

Complete Remission (CR)—Twenty-two of 27 patients randomized to receive ATRA alone as the induction regimen achieved CR (81%). Seventeen of 26 patients randomized to receive chemotherapy for induction achieved CR (65%; $p=0.22$). This difference did not attain a statistical significance due most likely to the small sample size. The median time to achieve CR was 55 days (range 33-95) for ATRA and 38 days (range 22-83) for chemotherapy ($p=0.02$). Examining all 53 patients, there was no significant difference in CR rate for patients with a WBC $\leq 10,000/\mu\text{L}$ (CR 83%) at diagnosis compared to a WBC $> 10,000/\mu\text{L}$ (CR 73%; $p=0.42$).

Crossover Patients—Four patients from the ATRA arm achieved a CR after crossing over to the chemotherapy arm for a cumulative CR rate in the ATRA arm of 96% (26 of 27 patients). This resulted in an overall CR rate for both arms of 81% (43 of 53 patients). The reason for crossover in these patients was ATRA toxicity. These patients received between 5 to 15 days of ATRA prior to crossover.

Induction Failures and Toxic Effects—In the ATRA group, 5 patients failed to achieve CR to ATRA alone due to: early death (ED)- 1 or toxicity- 4. In the chemotherapy group, 9 patients failed to achieve remission due to: resistant disease (RD)- 6 or ED- 3. The ED in the ATRA arm occurred on day 30 from RAS. On the chemotherapy arm, ED was secondary to intracranial hemorrhage in two cases (Days 5 and 15) and sepsis in one case (Day 16). Specific toxicities by induction regimen are listed in Table II. Notable differences in toxicity between the two induction regimens are leukopenia (26% in ATRA vs. 92% in DA, $p<0.001$) and thrombocytopenia (63% in ATRA vs. 88% in DA, $p=0.02$).

ATRA Use and Hyperleukocytosis—Of the 27 patients receiving ATRA for induction, this agent was administered for a median of 53 days (range 6 – 90 days). Of these 27 patients, sixteen received hydroxyurea prior to starting or during ATRA therapy.

Retinoic Acid Syndrome—Five out of 27 patients (19%) treated with ATRA were felt to have the RAS. One patient died during induction from RAS.

Pseudotumor Cerebri in Patients Receiving ATRA—Pseudotumor cerebri (PTC) was confirmed in three patients (11%) after central review of the clinical history, imaging studies and lumbar puncture results. Five additional patients might have had PTC based on their clinical history, but did not have complete evaluations to exclude other causes.

Consolidation Therapy

There were no deaths reported during the consolidation chemotherapy courses.

Maintenance Therapy

Of the total 53 patients, ten patients were not randomized because of resistant disease or early death. An additional seven patients were eligible for randomization, but did not register to be randomized for maintenance. Thirty-six patients were randomized for maintenance to one year of ATRA therapy (n=18) or observation only (n=18).

Disease- Free Survival (DFS)

The estimated 5-year DFS from time of CR was $41\% \pm 8\%$ for all patients. The 5-year DFS from time of CR for the ATRA and chemotherapy inductions were $49\% \pm 10\%$ and $29\% \pm 11\%$ respectively ($p = 0.16$; Figure 2). The 10-year DFS from time of CR were identical to the 5-year figures.

DFS was also calculated from the start of maintenance. Overall, the 5- year DFS from the start of maintenance was $37\% \pm 8\%$. The 5- year DFS from starting maintenance comparing ATRA maintenance to observation were $61\% \pm 11\%$ and $15\% \pm 9\%$, respectively ($p = 0.0002$; Figure 3).

DFS was also calculated for the 36 patients who underwent randomization to ATRA for maintenance versus observation. The 5-year DFS from time of CR for each of the four possible treatment combinations when considering induction and maintenance randomizations were 0% in DA/Observation, $56\% \pm 17\%$ in DA/ATRA, $24\% \pm 14\%$ in ATRA/Observation, and $67\% \pm 16\%$ in ATRA/ATRA ($p < 0.001$; Table III). The 5-year DFS from time of CR for patients who were randomized to ATRA for induction or maintenance or both was $48\% \pm 9\%$ (n=29) compared to 0% for patients who never received ATRA (n=7; $p < 0.0001$; Table III).

The 5-year DFS from time of CR for WBC at diagnosis $\leq 10,000/\mu\text{L}$ (n=35) compared to WBC $> 10,000/\mu\text{L}$ (n=8) was $51\% \pm 9\%$ and 0% respectively ($p = 0.0003$). This observation is consistent even when patients who never received ATRA are excluded from the analysis (5-yr DFS was $57\% \pm 9\%$ in WBC $\leq 10,000/\mu\text{L}$ vs 0% in WBC $> 10,000/\mu\text{L}$; $p = 0.007$). In Cox proportional hazards regression analysis, WBC is the only independent risk factor associated with poor DFS (hazard ratio: 3.5 for WBC $> 10,000/\mu\text{L}$ compared to WBC $\leq 10,000/\mu\text{L}$; $p = 0.02$). Age, induction treatment, baseline hemoglobin level and platelet count were not significant.

Overall Survival (OS)

The estimated 5-year OS for all patients from entry into the study was $69\% \pm 6\%$. The 5-year OS for the ATRA and chemotherapy induction arms were $73\% \pm 9\%$ and $65\% \pm 9\%$ respectively. The 10-year OS for the ATRA only and chemotherapy only inductions were $69\% \pm 9\%$ and $57\% \pm 10\%$ respectively ($p = 0.35$; Figure 4).

OS was also calculated for the 36 patients who underwent randomization to ATRA for maintenance versus observation. The 5-year OS for each of the four possible treatment combinations when considering induction and maintenance randomizations were $57\% \pm 19\%$

in DA/Observation, $89\% \pm 10\%$ in DA/ATRA, $73\% \pm 13\%$ in ATRA/Observation, and $78\% \pm 14\%$ in ATRA/ATRA. ($p=0.29$; Table III) The 5-year OS for patients who were randomized to ATRA for induction or maintenance or both was $79\% \pm 8\%$ ($n=29$) compared to $57\% \pm 19\%$ for patients who never received ATRA. ($n=7$; $p=0.07$; Table III)

The 5-year OS for WBC at diagnosis $\leq 10,000/\mu\text{L}$ ($n=42$) compared to WBC $> 10,000/\mu\text{L}$ ($n=11$) was $71\% \pm 7\%$ and $64\% \pm 15\%$ respectively ($p=0.46$). In Cox proportional hazards regression analysis, baseline hemoglobin level was the only factor that was associated with poor survival ($\text{HR}=1.36$; $p=0.03$) while induction treatment, age, WBC, and platelet count at diagnosis were not significant.

The overall survival and disease-free survival of the ten patients who lacked documentation of the t(15;17) translocation was not different from the 53 patients included in this analysis (see supplemental file).

Discussion

The most important finding of our study is the significant disease-free survival advantage for children with APL who received ATRA during induction or maintenance or both compared to children who received no ATRA. Furthermore, remissions in these children appear durable, as the OS rates are stable at 10 years. Relatively few series of pediatric APL patients have been published since the introduction of ATRA and only one report includes long-term follow-up at 10 years.(19) Another interesting finding is that the OS rates in our study are dramatically higher than the DFS rates. This demonstrates that the salvage rate must be high for patients who relapsed. Since some patients did not receive any ATRA (DA/Observation arm) and others had not received any ATRA since induction (ATRA/Observation arm), this could have led to ATRA being an effective component of the salvage therapy. Since we do not have complete information on the salvage regimens used in these patients, we cannot make definitive conclusions about this topic.

Our approach of using either chemotherapy or ATRA for induction resulted in lower remission and survival rates than subsequent trials that utilized both of these drugs during induction. Concurrent ATRA and chemotherapy has become the standard of care in APL. Recent pediatric APL trials utilizing this approach have demonstrated excellent CR and survival rates with a series of 107 patients from Italy resulting in a CR rate of 96%, a 10-year EFS of 76% and a 10-year OS of 89%.(19) Pediatric series from Spain and France have shown similar excellent results.(16, 20) Despite these excellent CR and survival rates, early deaths during induction continue to be problematic which was seen in 3-8% of patients of the above studies and compared similarly to our rate of 8%.

Since a large number of children with APL are cured, future efforts to examine the chronic effects of the agents used in the treatment regimens will be important. Unfortunately, the success that has been seen in APL has come, in part, from using increasing doses of anthracyclines at a cumulative daunorubicin equivalent dose range of 320 - 600 mg/m^2 (assuming an equivalence ratio of idarubicin or mitoxantrone to daunorubicin of 1:4).(19, 20, 25) While long term cardiotoxicity data in children treated for APL have not been systematically reported, there have been anecdotal reports of fatal congestive heart failure in patients treated in this dose range.(26, 27) An effort to decrease the potential cardiotoxicity of APL therapy for pediatric patients seems appropriate. This may be achieved by incorporation of newer treatment modalities such as arsenic trioxide or Gemtuzumab ozogamicin(Mylotarg), to conventional chemotherapy regimens.(28-31) The use of arsenic trioxide is also supported by the early results of the most recent North American APL

protocol which showed a survival advantage for patients randomized to receive arsenic trioxide as part of the consolidation therapy.(32)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Bennett JM, Catovsky D, Daniel MT, et al. Proposed revised criteria for the classification of acute myeloid leukemia. A report of the French-American-British Cooperative Group. *Ann Intern Med.* 1985; 103:620–625. [PubMed: 3862359]
2. Ravindranath Y, Yeager AM, Chang MN, et al. Autologous bone marrow transplantation versus intensive consolidation chemotherapy for acute myeloid leukemia in childhood. *Pediatric Oncology Group. N Engl J Med.* 1996; 334:1428–1434. [PubMed: 8618581]
3. Smith FO, Alonzo TA, Gerbing RB, et al. Long-term results of children with acute myeloid leukemia: a report of three consecutive Phase III trials by the Children's Cancer Group: CCG 251, CCG 213 and CCG 2891. *Leukemia.* 2005; 19:2054–2062. [PubMed: 16136168]
4. Ravindranath Y, Chang M, Steuber CP, et al. Pediatric Oncology Group (POG) studies of acute myeloid leukemia (AML): a review of four consecutive childhood AML trials conducted between 1981 and 2000. *Leukemia.* 2005; 19:2101–2116. [PubMed: 16136167]
5. Larson RA, Kondo K, Vardiman JW, et al. Evidence for a 15;17 translocation in every patient with acute promyelocytic leukemia. *Am J Med.* 1984; 76:827–841. [PubMed: 6586073]
6. Brunning R. Acute Myeloid Leukemia. In: Knowles, D., editor. *Neoplastic Hematology.* Second. 2001. p. 1667-1715.
7. Tallman MS, Kwaan HC. Reassessing the hemostatic disorder associated with acute promyelocytic leukemia. *Blood.* 1992; 79:543–553. [PubMed: 1732003]
8. Fenaux P, Chevret S, Guerci A, et al. Long-term follow-up confirms the benefit of all-trans retinoic acid in acute promyelocytic leukemia. *European APL group. Leukemia.* 2000; 14:1371–1377. [PubMed: 10942231]
9. Mann G, Reinhardt D, Ritter J, et al. Treatment with all-trans retinoic acid in acute promyelocytic leukemia reduces early deaths in children. *Ann Hematol.* 2001; 80:417–422. [PubMed: 11529468]
10. Burnett AK, Grimwade D, Solomon E, et al. Presenting white blood cell count and kinetics of molecular remission predict prognosis in acute promyelocytic leukemia treated with all-trans retinoic acid: result of the Randomized MRC Trial. *Blood.* 1999; 93:4131–4143. [PubMed: 10361110]
11. Chomienne C, Ballerini P, Balitrand N, et al. All-trans retinoic acid in acute promyelocytic leukemias. II. In vitro studies: structure-function relationship. *Blood.* 1990; 76:1710–1717. [PubMed: 2224120]
12. Elliott S, Taylor K, White S, et al. Proof of differentiative mode of action of all-trans retinoic acid in acute promyelocytic leukemia using X-linked clonal analysis. *Blood.* 1992; 79:1916–1919. [PubMed: 1562718]
13. Fenaux P, Castaigne S, Dombret H, et al. All-transretinoic acid followed by intensive chemotherapy gives a high complete remission rate and may prolong remissions in newly diagnosed acute promyelocytic leukemia: a pilot study on 26 cases. *Blood.* 1992; 80:2176–2181. [PubMed: 1421389]
14. Tallman MS, Andersen JW, Schiffer CA, et al. All-trans-retinoic acid in acute promyelocytic leukemia. *N Engl J Med.* 1997; 337:1021–1028. [PubMed: 9321529]
15. Tallman MS, Andersen JW, Schiffer CA, et al. All-trans retinoic acid in acute promyelocytic leukemia: long-term outcome and prognostic factor analysis from the North American Intergroup protocol. *Blood.* 2002; 100:4298–4302. [PubMed: 12393590]
16. De Botton S, Coiteux V, Chevret S, et al. Outcome of childhood acute promyelocytic leukemia with all-trans-retinoic acid and chemotherapy. *J Clin Oncol.* 2004; 22:1404–1412. [PubMed: 15084614]

17. Zubizarreta PA, Rose AB, Felice MS, et al. Childhood acute promyelocytic leukemia: no benefit of all-trans- retinoic acid administered in a short-course schedule. *Pediatr Hematol Oncol.* 2000; 17:155–162. [PubMed: 10734658]
18. Bapna A, Nair R, Tapan KS, et al. All-trans-retinoic acid (ATRA): pediatric acute promyelocytic leukemia. *Pediatr Hematol Oncol.* 1998; 15:243–248. [PubMed: 9615322]
19. Testi AM, Biondi A, Lo CF, et al. GIMEMA-AIEOPAIDA protocol for the treatment of newly diagnosed acute promyelocytic leukemia (APL) in children. *Blood.* 2005; 106:447–453. [PubMed: 15677559]
20. Ortega JJ, Madero L, Martin G, et al. Treatment with all-trans retinoic acid and anthracycline monochemotherapy for children with acute promyelocytic leukemia: a multicenter study by the PETHEMA Group. *J Clin Oncol* %20. 2005; 23:7632–7640. [PubMed: 16234524]
21. Hirota T, Fujimoto T, Katano N, et al. Treatment results of intermittent and cyclic regimen with ATRA and chemotherapy in childhood acute promyelocytic leukemia. *Children's Cancer and Leukemia Study Group. Rinsho Ketsueki.* 1997; 38:1177–1182. [PubMed: 9423334]
22. Cheson BD, Cassileth PA, Head DR, et al. Report of the National Cancer Institute-sponsored workshop on definitions of diagnosis and response in acute myeloid leukemia. *J Clin Oncol.* 1990; 8:813–819. [PubMed: 2185339]
23. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1953; 53:457–481.
24. Peto R, Peto J. Asymptotically efficient rank in variant test procedures. *J R Stat Soc A.* 1972; 2:185–206.
25. Berman E, Wiernik P, Vogler R, et al. Long-term follow-up of three randomized trials comparing idarubicin and daunorubicin as induction therapies for patients with untreated acute myeloid leukemia. *Cancer.* 1997; 80:2181–2185. [PubMed: 9395031]
26. Thomas X, Le QH, Fiere D. Anthracycline-related toxicity requiring cardiac transplantation in long-term disease-free survivors with acute promyelocytic leukemia. *Ann Hematol.* 2002; 81:504–507. [PubMed: 12373350]
27. Aldouri MA, Lopes ME, Yacoub M, et al. Cardiac transplantation for doxorubicin-induced cardiomyopathy in acute myeloid leukaemia. *Br J Haematol.* 1990; 74:541. [PubMed: 2346733]
28. Estey E, Garcia-Manero G, Ferrajoli A, et al. Use of all-trans retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia. *Blood.* 2006; 107:3469–3473. [PubMed: 16373661]
29. Estey EH, Giles FJ, Beran M, et al. Experience with gemtuzumab ozogamycin (“mylotarg”) and all-trans retinoic acid in untreated acute promyelocytic leukemia. *Blood.* 2002; 99:4222–4224. [PubMed: 12010830]
30. Shen ZX, Shi ZZ, Fang J, et al. All-trans retinoic acid/As₂O₃ combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia. *Proc Natl Acad Sci U S A.* 2004; 101:5328–5335. [PubMed: 15044693]
31. Mathews V, George B, Lakshmi KM, et al. Single-agent arsenic trioxide in the treatment of newly diagnosed acute promyelocytic leukemia: durable remissions with minimal toxicity. *Blood.* 2006; 107:2627–2632. [PubMed: 16352810]
32. Powell BL, Moser B, Stock W, et al. Effect of consolidation with arsenic trioxide (As₂O₃) on event-free survival (EFS) and overall survival (OS) among patients with newly diagnosed acute promyelocytic leukemia (APL): North American Intergroup Protocol C9710. *Journal of Clinical Oncology.* 2007; 25 abstr.

Figure 1.
Treatment Schema

Figure 2.
Disease-Free Survival from time of CR by Induction Regimen

Figure 3.
Disease-Free Survival from start of maintenance

Figure 4.
Overall Survival by Induction Regimen

TABLE I**Clinical Characteristics At Diagnosis By Induction Regimen**

	ALL	ATRA	DA	p-value
number (n) of pts.	53	27	26	
Median Age-yrs	12 (1-18)	11 (1.4-17)	12 (1.8-18)	0.47
Age $\geq$ 2 yrs	2 (4%)	1 (4%)	1 (4%)	>0.99
Sex (Male/Female) (n)	21/32	10/17	11/15	0.78
Median WBC (range)	3.1 (.5-106) $\times 10^9/L$	2.6 (.8-37.3) $\times 10^9/L$	4.2 (.5-106) $\times 10^9/L$	0.16
Median Hgb (range)	8.4 (4-11.9)	8.8 (4-10.7) g/dL	8.3 (4-11.9) g/dL	0.74
Median Platelet (range)	22 (5-223) $\times 10^9/L$	21.0 (5-166) $\times 10^9/L$	25 (5-223) $\times 10^9/L$	0.82
Bleeding Diathesis (%)	27 (51%)	12 (44%)	15 (58%)	0.41
M3 Variant (%)	1 (2%)	1 (4%)	0 (0%)	>0.99
Extramedullary Disease	0	0	0	
Race:				
White	35 (66%)	18 (67%)	17 (65%)	0.47
Hispanic	8 (15%)	3 (11%)	5 (19%)	
Afro-American	7 (13%)	4 (15%)	3 (12%)	
Asian	2 (4%)	2 (7%)	0 (0%)	
Filipino	1 (2%)	0 (0%)	1 (4%)	

DA = Daunorubicin / Cytarabine

TABLE II

Induction Toxicity (GRADE III/IV)

	ATRA (n=27)	DA (n=26)	p-value
Hemorrhage	1 (4%)	3 (12%)	0.34
Typhlitis	0	2 (8%)	0.23
Pancreatitis	1 (4%)	0	>0.99
Infection	7 (26%)	12 (46%)	0.15
Leukopenia	7 (26%)	24 (92%)	<0.001
Anemia	17 (63%)	19 (73%)	0.38
Thrombocytopenia	17 (63%)	23 (88%)	0.02
Hyperleukocytosis	5 (19%)	0	0.052
Bone Pain	3 (11%)	0	0.24
Hypertriglyceridemia	1 (4%)	0	>0.99

Table III

Survival by Treatment

	Disease-free Survival				Overall Survival			
	n	5-yr±s.e.	10 yr±s.e.	p-value	n	5-yr±s.e.	10 yr±s.e.	p-value
All patients	43	41%±8%	41%±8%		53	69%±6%	63%±7%	
By Induction Therapy								
ATRA	26	49%±10%	49%±10%	0.16	27	73%±9%	69%±9%	0.35
DA	17	29%±11%	29%±11%		26	65%±9%	57%±10%	
By Induction & Maintenance Therapy								
some ATRA	29	48%±9%	48%±9%		29	79%±8%	72%±9%	
DA/Obs	7	0%	0%		7	57%±19%	***	
DA/ATRA	9	56%±17%	56%±17%		9	89%±10%	76%±15%	
ATRA/Obs	11	24%±14%	***		11	73%±13%	62%±15%	
ATRA/ATRA	9	67%±16%	67%±16%	<0.001	9	78%±14%	78%±14%	0.29
By Maintenance Therapy from Time of Maintenance								
all	36	38%±8%	38%±8%		36	69%±8%	66%±8%	
ATRA	18	61%±11%	61%±11%	0.0002	18	83%±9%	79%±10%	0.13
Obs.	18	15%±9%	***		18	55%±12%	55%±12%	
By Baseline WBC								
WBC ≤10K	35	51%±9%	51%±9%	0.0003	42	71%±7%	65%±8%	0.46
WBC > 10K	8	0%	0%		11	64%±15%	55%±15%	

s.e.: standard error; Some ATRA: ATRA in induction or maintenance or both;

the longest follow up is between 8 and 9 years without any events to date