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ORIGINAL ARTICLE

Improved treatment results for childhood acute myeloid leukemia in Taiwan

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To improve treatment results for children with *de novo* acute myeloid leukemia (AML), we introduced a novel protocol, Taiwan Pediatric Oncology Group-AML-97A, for AML other than acute promyelocytic leukemia (APL), for which modified conventional protocols were used. From January 1, 1997, to December 31, 2002, 141 children younger than 17 years old with *de novo* AML were enrolled. In total, 117 patients with non-APL AML were treated with induction therapy of idarubicin and cytarabine (Ara-C), postremission therapy with high-dose Ara-C – containing regimens for four monthly courses, and moderate-dose therapy with idarubicin and Ara-C for four monthly courses. The first 19 patients with APL were treated with all-*trans* retinoic acid, idarubicin and Ara-C, with the remaining five patients receiving all-*trans* retinoic acid and idarubicin, followed by maintenance therapy for 2 years. Stem cell transplantation was performed in 29 patients in first remission with a similar outcome as chemotherapy alone. The remission rate in the AML-97A study was 90%, the 5-year survival 51±5.3% (s.e.) and the 5-year event-free survival 50±4.8%; for APL, these were 100%, 86±7.0, and 75±9.8%. For the whole group, the 5-year survival was 57±4.7% and the 5-year event-free survival 54±4.4%. The AML-97A regimen was well tolerated.
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Introduction

Several treatment components have contributed to the recent improvement in treatment for *de novo* childhood acute myeloid leukemia (AML). A combination of cytarabine (Ara-C) and anthracycline remains the most frequently used remission induction therapy. Mitoxantrone has shown to be an active agent against AML.[1] The addition of etoposide to some regimens has also improved the treatment of AML.[2] Another crucial development is the introduction of high-dose Ara-C (HDAra-C) in either the postremission or induction phase of therapy, for both adults[3,4] and children[5] with AML. The beneficial effect of HDAra-C during postremission therapy was first demonstrated by the Cancer and Leukemia Group B,[4] while Hiddemann *et al*.[6] reported the effectiveness of HDAra-C in combination with mixtoxantrone (HAM) in adults with refractory AML. Other innovations contributing to an improved outcome in AML were described in numerous recent reports.[7–15] Besides agents that increase the antileukemic efficacy of modern AML treatments, advances in molecular biology have led to the recognition of prognostically and therapeutically relevant subtypes of AML, while improved supportive care, consisting of more effective antimicrobials (especially the antifungal agents), blood component therapy, hematopoietic stem cell transplantation, and antiemetics, has prevented excessive toxic deaths due to intensive chemotherapy.

Here we report the improved results of recent Taiwan Pediatric Oncology Group (TPOG) protocols for children and adolescents with *de novo* AML, which incorporated many of the treatment components deemed to be important in other successful studies.

Patients and methods

Eligibility

Studies TPOG AML-97A, TPOG APL-97, and TPOG-APL-2001 enrolled children under 18 years of age with newly diagnosed *de novo* AML, after written informed consent from the guardians. While patients with Down's syndrome or systemic disease with chloroma were included, those with secondary AML or myelodysplastic syndrome were excluded. In our nationwide TPOG studies from January 1, 1997, to December 31, 2002, all patients with APL were enrolled in the TPOG-APL-97 study and then the TPOG-APL-2001 study. AML patients without APL were treated with either the TPOG-97A study according to the participating institutions, or the TPOG-97B study; the latter study was modified from MRC AML10[9] and will be reported separately. Hematopoietic stem cell transplantation, when feasible, was performed in 29 patients. The study results were censored on December 31, 2004.

Diagnosis and classification

The initial diagnosis of AML, including the subtyping, was established according to the French–American–British (FAB) classification.[16–18] Diagnosis of the M0 and M7 subtypes was confirmed by immunologic methods.[17,18] The karyotypes were

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interpreted according to the International System for Human Cytogenetics Nomenclature.[19] Common fusion transcripts were detected by reverse transcriptase (RT) PCR assays, followed by Southern blot analysis as described previously.[20] The diagnosis and classification of each case were also evaluated according to the new classification system of the World Health Organization.[21]

Treatment

TPOG-AML-97A protocol. The TPOG-AML-97A protocol consisted of induction therapy with idarubicin (9 mg/m^2/day × 3) and Ara-C (100 mg/m^2/day × 7) every 3 weeks. If a remission could not be induced after two courses, second-line treatment including mitoxantrone (8 mg/m^2/day × 5) and etoposide (100 mg/m^2/day × 5) every 4 weeks was given. Cranial irradiation was not used for either prophylaxis or treatment of central nervous system leukemia (CNSL) at diagnosis. Instead, intrathecal methotrexate (IT MTX) was administered to all patients (including those with APL) on day 1 of each course. The doses were 6, 8, 10, 12, and 15 mg for patients aged <1, 1–2, 2–3, 3–9, and >9 years, respectively. Once complete remission was achieved, postremission therapy was begun, consisting of four monthly courses of Ara-C (1 g/m^2/12 h on days 1–4) and etoposide (100 mg/m^2/day × 5) alternating with Ara-C (1 g/m^2/12 h on days 1–4) and mitoxantrone (10 mg/m^2/day on days 2–5) if absolute neutrophils exceeded 1.5×10^9/l and platelets 100×10^9/l. Four monthly courses of idarubicin (9 mg/m^2/day × 1) and Ara-C (200 mg/m^2/day × 5) followed. IT MTX was administered on day 1 of the four courses at the dose schedule described above. The median duration of treatment was 10 months.

TPOG-APL-97 protocol. All-*trans* retinoic acid (ATRA, 30 mg/m^2/day) was started on day 1. Idarubicin and Ara-C (administered as described for TPOG-AML-97A) were given if the leukocyte count exceeded 5×10^9/l before treatment, 6×10^9/l on day 5, 10×10^9/l on day10, or 15×10^9/l on day 15 of induction therapy. The postremission therapy consisted of six monthly courses of idarubicin and Ara-C (as described above). IT MTX was administered on day 1 of each course at the same dose schedule described above. In all, 19 patients were enrolled.

TPOG-APL-2001 protocol. This treatment plan was modified from the PETHEMA LPA 96 protocol,[22] and was activated in 2001. It started with ATRA (25 mg/m^2/day) and idarubicin (9 mg/m^2/day × 3). After remission induction, consolidation therapy with three monthly courses of idarubicin (9 mg/m^2/day × 3) was instigated. IT MTX was given on day 1 of each idarubicin course at a dose schedule described before. This phase of therapy was followed by 2 years of maintenance therapy comprising 6-mercaptopurine (90 mg/m^2/day PO), MTX (15 mg/m^2/week PO), and ATRA (25 mg/m^2/day × 15 every 3 months). Five patients were enrolled.

Hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation, including allogeneic bone marrow transplantation, allogeneic peripheral blood stem cell transplantation, autologous bone marrow transplantation, or autologous peripheral blood stem cell transplantation, when feasible, was performed during first remission.

Supportive care

Granulocyte-colony-stimulating factor (G-CSF, 200 μg/m^2/day SC) was administered each day during marrow aplasia induced by induction chemotherapy and prophylactically over 36–48 h after the end of each HDAra-C-containing course. Bactrim (trimethoprim-sulfamethoxazole) for prophylaxis of *Pneumocystis carinii* pneumonitis was given 3 days a week beginning 2 weeks after the initiation of induction therapy and continuing to 6 months after the completion of chemotherapy. The strategy in preventing and treating infectious complications applied the same principles as used in BFM group.[23] Rasburicase,[24] a recombinant urate oxidase, has been available for effective prevention and treatment of leukemia lysis syndrome for the recent 2 years.

Statistical methods

The primary end points of this study were overall survival (OS), event-free survival (EFS), and disease-free survival (DFS). OS was measured from the start of treatment to death from any causes, and EFS from the start of treatment to first progression, relapse or death from any cause. Patients not achieving a first remission were assigned an EFS of zero. DFS extended from the time of transplantation to the time of failure. Patients who did not fail were censored at the time of their last follow-up. Survival curves were estimated by the Kaplan–Meier method. Prognostic factor analysis was performed by univariate analysis using the two-sided log-rank test, and multivariate analysis using the Cox regression model. A statistically significant difference was classified as a P-value <0.05. Survival rates were represented as the mean percent ($\pm$s.e.) probability estimates.

Results

A total of 243 children were enrolled in the TPOG-AML studies, of whom 12 girls and 12 boys had APL and 219 non-APL AML. In the latter group, 117 patients (56 girls, 61 boys) were enrolled in study TPOG-AML-97A and 102 in study TPOG-AML-97B (not included in this report). Overall, the ages of the patients ranged from 0 to 17 years old, with 32 patients older than 13 years. In this subgroup, 17 patients were older than 15 years. In all, 68 of the patients were girls and 73 were boys. In the study TPOG-AML-97A, 61 patients presented with a leukocyte count $<20 \times 10^9$/l, 56 had counts 20–100×10^9/l, while 21 had counts $\geqslant 100 \times 10^9$/l. In the TPOG-APL studies, there were 23 patients with a leukocyte count $<50 \times 10^9$/l, and only one patient in APL-97 had a count $>50 \times 10^9$/l. The distribution of phenotype is reported in Table 1. The most frequent subtypes in decreasing order were M2, M3, M5, M1, and M4. Genetic classification showed after the t(15;17)/*PML-RARα*, the leading abnormalities were t(8;21)/*AML1-ETO, MLL* rearrangements, and inv(16)/*CBFβ-MYH11*. Three patients had Down's syndrome. Two patients had monosomy 7, and five patients had complex chromosomal abnormalities. In all, 56 patients had a normal karyotype or other cytogenetic changes.

In TPOG-AML-97A, 90% attained complete remission, compared with 100% of those with APL. The remission rate was 91% overall. Of 29 patients who underwent hematopoietic stem cell transplantation in first remission, 17 had allogeneic bone marrow donor and six an allogeneic peripheral blood stem cell donor. Other procedures used were two autologous bone marrow and four autologous peripheral blood stem cells. In the AML-97A study, 31 patients relapsed: 26 in the bone marrow, two in the isolated CNS, two in both bone marrow and CNS, and one in bone marrow and breast. All three relapses in APL

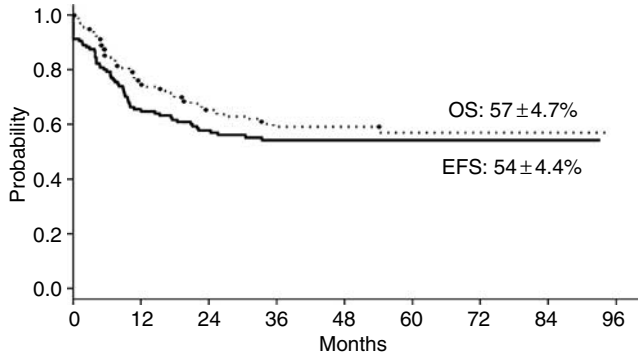

Figure 1 5-year event-free survival (EFS) and overall survival (OS) rates for all 141 patients with AML.

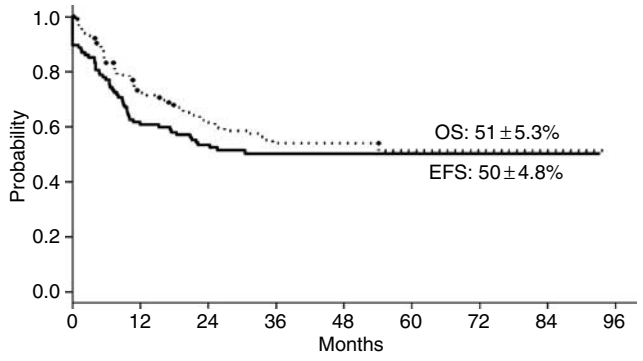

Figure 2 5-year event-free survival (EFS) and overall survival (OS) rates for 117 children with non-APL, treated with AML-97A protocol.

patients were in the bone marrow: two in APL-97 and one in APL-2001. In all, 56 patients in 97A have died, 30 with refractory or relapsed leukemia, 25 of infection, and one of hemorrhage. Four patients in APL-97 study died, three of infection, one of leukemia, and none of hemorrhage.

Figure 1 shows the EFS and OS rates for all 141 patients regardless of disease subtype. The 5-year EFS estimate was $54\pm4.4\%$, with a 5-year OS of $57\pm4.7\%$. One patient relapsed very late, at 25 months after the initiation of treatment, and died 29 months later. The 117 patients enrolled in TPOG-AML-97A had a 5-year EFS rate of $50\pm4.8\%$, and a 5-year OS of $51\pm5.3\%$ (Figure 2). Overall, the 5-year OS and EFS rates for patients with APL were 86 ± 7.6 and $75\pm9.8\%$, respectively. The DFS rate for patients undergoing hematopoietic stem cell transplantation were $60\pm9.5\%$, compared with $68\pm5.4\%$ for those receiving chemotherapy alone ($P=0.63$). Table 1 shows the distribution of patients and their survival by FAB subtype. Outcome was clearly better among patients with an M2, M3 or M6 subtype, and clearly worse among those with an M7 or M0 subtype. Of the genetic features examined (Table 1), trisomy 21, t(15;17)/*PML-RARα*, inv(16)/*CBFβ-MYH11*, t(8;21)/*AML1-ETO*, and t(9;11)/*MLL-AF9* were associated with a better outcome, while *MLL* rearrangements other than t(9;11)/*MLL-AF9* conferred a poor prognosis. The 56 patients with a normal karyotype or other cytogenetic changes had a 5-year OS rate of 48%. Table 2 lists the complications that were encountered during these studies. Sepsis, other infections, and febrile neutropenia were common, especially in study AML-97A. Notably, there were no episodes of cardiotoxicity of the three studies. None of the treatments produced excessive toxicity.

Among the factors analyzed, only high leukocyte count $\geqslant100\times10^9$/l and poor early response (attaining complete

Table 1 Patient characteristics and treatment outcome

Category	*No. of patients*	*5-years EFS (s.e.)*	P-*value*	*5-years OS (s.e.)*	P-*value*
Overall	138	54 (4.4)		57 (4.7)	
Gender			0.683		0.988
Male	71	56 (6.2)		58 (6.2)	
Female	67	52 (6.2)		55 (7.0)	
Age			0.418		0.197
<2 years	29	54 (9.4)		54 (9.4)	
2–9 years	61	61 (6.6)		68 (6.3)	
10–14 years	34	47 (8.9)		51 (9.2)	
15–17 years	14	38 (14.8)		42 (13.4)	
WBC(10^9/l)			**0.011**		**0.003**
<20	61	53 (6.8)		58 (7.2)	
20–100	56	63 (6.5)		66 (6.6)	
⩾100	21	30 (10.3)		30 (10.3)	
FAB			0.194		0.076
M0	8	29 (17.3)		29 (17.1)	
M1	14	52 (14.6)		48 (15.7)	
M2	43	54 (7.6)		59 (7.7)	
M3	23	75 (9.8)		86 (7.6)	
M4	13	40 (15.6)		51 (14.7)	
M5	21	51 (11.1)		51 (11.1)	
M6	6	83 (15.2)		83 (15.2)	
M7	10	33 (15.7)		22 (17.8)	
Genetic			0.470		0.322
inv(16)	4	50 (4.9)		75 (9.2)	
t(15;17)	21	67 (11.2)		79 (9.2)	
t(8;21)	19	63 (11.2)		67 (11.2)	
t(9;11)	2	100		100	
Other MLL	7	29 (17.1)		29 (8.9)	
Trisomy 21	3	100		100	
Monosomy 7	2	50 (35.4)		50 (35.4)	
Complex	5	60 (21.9)		60 (22.0)	
Normal and others	56	48 (7.1)		48 (7.9)	
Cycle[a]			0.001		0.002
1	42	75 (7.0)		80 (6.3)	
>1	96	45 (5.3)		47 (5.7)	
CNSL			0.710		0.821
Absent	122	55 (4.7)		57 (5.1)	
Present	16	46 (13.1)		52 (13.2)	
APL					
APL97	18	75 (11.0)		81 (9.7)	
APL2001	5	67 (27.2)		100	
Overall	23	75 (9.8)		86 (7.6)	

[a]To achieve complete remission.

Table 2 Complications in studies TPOG-97A and TPOG-APL

Complication	*No. of episodes*			
	97A (n=117)	*APL-97 (n=19)*	*APL-2001 (n=5)*	*Total (n=141)*
Sepsis	152	15	2	169
Other infection	481	62	19	562
Febrile neutropenia	386	47	11	444
Hemorrhage	41	15	4	60
Cardiotoxicity	0	0	0	0

remission after two or more courses of therapy) were associated with poor OS and EFS (Table 1).

Discussion

The 5-year EFS of 54 ± 4.4% achieved in studies TPOG-AML-97A, TPOG-APL-97, and TPOG-APL-2001 were at least comparable to the 31–54% attained in studies conducted in other developed countries during the same era,[25–37] and the treatment was well tolerated. However, like in the Dutch Childhood Oncology Group experience, a more effective, but less toxic, therapy and better supportive care guidelines for childhood AML are still needed.[38] For remission induction, the use of idarubicin with Ara-C on a '3 + 7' schedule was based on a report from Cancer and Leukemia Group B, which demonstrated that this regimen is better than a '2 + 5' regimen.[39] Idarubicin was selected for remission induction therapy because of its superiority over daunorubicin in treatment. In study AML-BFM93, induction with idarubicin was more effective than daunorubicin in reducing the blast cells in bone marrow on day 15.[10] Moreover, meta-analysis of results from randomized trials comparing idarubicin, mitoxantrone, and daunorubicin revealed a statistically significant improvement in remission rate with idarubicin, and a trend toward a better rate with mitoxantrone compared to daunorubicin (Wheatley K. *Blood*, 1995;**86**:43; abstract). When combined with Ara-C (100 mg/m^2/day × 7), idarubicin was more effective than daunorubicin in remission induction.[40,41] A 9 mg/m^2/day schedule of idarubicin was selected because of prior experience in Taiwan, indicating that higher doses of idarubicin resulted in unacceptable morbidity and mortality in pediatric patients.

Ara-C at 100 mg/m^2/day × 7, rather than 200 mg/m^2/day × 7 or HDAra-C, was chosen for induction therapy because increases in Ara-C doses have not consistently resulted in a higher remission rate, but have contributed to increased toxicity, particularly in older patients.[42] For example, randomized studies in adults with AML found no significant differences in the induction rate at doses raising from 100 to 200 mg/m^2.[43] Further dose increases, by even 20–30 times (i.e., to 3 g/m^2 every 12 h for 8–12 doses), have not significantly improved the remission rates.[44,45]

Cardiotoxicity due to intensive chemotherapy is of great concern in the treatment of AML patients. Idarubicin, for example, has a reduced cardiotoxic index by comparing with either daunorubicin or doxorubicin.[46,47] In animal studies, the therapeutic index related to chronic cardiotoxicity favors idarubicin over daunorubicin by a factor of about 3.[46] In a retrospective study, a cumulative dose of idarubicin at 150 mg/m^2 was estimated to be safe, while 290 mg/m^2 was considered probably safe.[48] The therapeutic index of idarubicin versus doxorubicin with regard to chronic cardiotoxicity is estimated to be 1.8–1.9. In study TPOG-AML-97A, patients generally received a cumulative dose of idarubicin 63 mg/m^2 and mitoxantrone dose of 80 mg/m^2, which is equivalent to a dose of 340 mg/m^2 of doxorubicin. The lack of cardiotoxicity in the current TPOG studies supports these calculations of a 'safe' cumulative dose.

A third or fourth drug was not added to our induction regimen because the benefits of this modification are uncertain. Some trials have demonstrated an increased remission duration with the addition of etoposide to the '3 + 7' regimen.[2] However, another study by the Cancer and Leukemia Group B did not observe an increased remission rate or duration of remission with the addition of 6-thioguanine to '3 + 7'.[49] Since the combination of mitoxantrone and etoposide in refractory AML is both effective and well tolerated,[50] we reserved this regimen for second-line induction therapy.

Some studies have achieved dose intensification, in part, by extending the period of induction therapy as a part of consecutive daily treatments. This practice has resulted in a trend toward slightly higher remission induction rates.[9] An alternative strategy is based on the concept that leukemic blasts could be effectively recruited into S phase of the cell cycle by following the initial course of chemotherapy with a 6- to 8-day gap before reinstitution of therapy. This type of timed, sequential, or intensively timed therapy originated from work on leukemic cell cycle kinetic studies.[51] For example, the CCG 2891 trial tested a 'standard' versus 'intensive' timing induction using the five-drug dexamethasone, Ara-C, thioguanine, etoposide, and rubidomycin (DCTER) regimen.[8,52] Standard timing specified that the second course of chemotherapy be delivered after bone marrow recovery, usually at about 30 days unless residual leukemia was present on day 14, in which case therapy was instigated at that time. Intensively timed induction therapy specified the second course of DCTER on days 10–13, regardless of bone marrow status. Complete remission rate for the standard and intensive timing arms were not significantly different, 74 and 78%, respectively.[8,53] However, induction mortality was appreciably greater with the intensively timed induction, although there were few cases of refractory leukemia. Recently, the addition of cladribine to daunorubicin and Ara-C was reported to increase the remission induction rate in adults with AML.[53]

During postremission treatment, the effect of dose scheduling and dose intensification was demonstrated in the Children's Cancer Group 213P study. Two courses of HDAra-C and asparaginase administered at a 7-day interval resulted in superior survival rates compared with arms administered at a 28-day interval.[5] Furthermore, in the Children's Cancer Group study 2861 patients receiving intensive-timing induction chemotherapy (second cycle 10 days after the first cycle) had a significantly better DFS than did patients receiving standard-timing induction therapy (second cycle 14 days or more after the first cycle, depending on bone marrow status).[52] In postremission therapy, however, several studies in adults have strongly suggested that increasing the intensity of immediate postremission therapy, especially with HDAra-C, results in a lower relapse rate, with relapse occurring later than in patients receiving less intense maintenance therapy.[54] This was especially true for patients with favorable cytogenetics, for example, t(8;21) or inv(16).[55]

HDAra-C cannot increase the remission rate because primary refractoriness to conventional-dose Ara-C does not arise until the residual leukemic infiltrate has decreased to fewer than 10^6 cells,[56] and the probability that subpopulations of cells will become resistant to Ara-C increases with time.[56] Thus, it seems more reasonable to use HDAra-C for postremission treatment rather than remission induction.[57] In consolidation therapy, HDAra-C has a beneficial effect on long-term outcome that may be similar to the results achieved with bone marrow transplantation.[57] In adult patients younger than 60 years, induction therapy with mitoxantrone and Ara-C, in randomized doses of 1 or 3 g/m^2/dose, resulted in similar remission rates, although CNS toxicity was more frequent in the Ara-C 3 g/m^2 group than in the 1 g/m^2 group (79 versus 28%, $P < 0.10$).[58] This finding promotes the rationale for the use of the Ara-C 1 g/m^2/dose rather than 3 g/m^2 in the present study.

These results show remarkable improvement over a previous TPOG AML study (1990–1996), in which the 5-year OS was

only 21%, and compare favorably with outcomes during the same era reported from successful treatment centers worldwide.[25–37] The challenge now is to extend the benefits of contemporary AML therapy to larger numbers of patients in developing countries, where fewer than 10% children with acute leukemia are receiving protocol-based therapy.[59]

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