

Improvement of Induction Remission Rate by Modifying the Dose of Idarubicin for Relapsed Childhood Acute Lymphoblastic Leukemia

Relapse is the major cause of treatment failure in acute lymphoblastic leukemia (ALL), yet there is no established treatment for relapsed ALL. To improve the induction remission rate, we modified the dose of idarubicin in the original Children's Cancer Group (CCG)-1884 protocol, and retrospectively compared the results. Twenty-eight patients diagnosed with relapsed ALL received induction chemotherapy according to the CCG-1884 protocol. Complete remission (CR) rate in all patients after induction chemotherapy was 57%. The idarubicin 10 mg/m²/week group showed CR rate of 74%, compared with the 22% CR rate of the idarubicin 12.5 mg/m²/week group ($p=0.010$). Remission failure due to treatment-related mortality (TRM) was 44% and 5.2% in the idarubicin 12.5 mg/m²/week and 10 mg/m²/week groups, respectively ($p=0.011$). Overall survival (OS) and 4-yr event-free survival (EFS) were 12.8% and 10.3%, respectively. OS and 4-yr EFS were higher in the idarubicin 10 mg/m²/week group (19.3% and 15.6%) than in the 12.5 mg/m²/week group (0% and 0%). In conclusion, a modified dose of idarubicin from 12.5 mg/m²/week to 10 mg/m²/week resulted in an improved CR rate in the treatment of relapsed ALL, which was due to lower TRM. However, despite improved CR rate with modified dose of idarubicin, survival rates were unsatisfactory.

Key Words : Idarubicin; Remission Induction; Recurrence; Precursor Cell Lymphoblastic Leukemia-Lymphoma

Jong Hyung Yoon, Jeong Ah Park,
Eun Kyung Kim, Hyoung Jin Kang,
Hee Young Shin, and Hyo Seop Ahn

Department of Pediatrics, Cancer Research Institute,
Seoul National University College of Medicine, Seoul,
Korea

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Address for correspondence

Hyo Seop Ahn, M.D.
Division of Hematology/Oncology, Department of
Pediatrics, Cancer Research Institute, Seoul National
University College of Medicine, 101 Daehangno,
Jongno-gu, Seoul 110-769, Korea
Tel : +82-2-2072-3625, Fax : +82-2-743-3455
E-mail : hsahn@snu.ac.kr

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INTRODUCTION

Improvements in outcome for children with acute lymphoblastic leukemia (ALL) have been dramatic. Nevertheless front-line therapy has failed in up to 25% of children with relapsed or refractory form, and their long-term prognosis is poor (1, 2). Aiming for complete remission by intensive chemotherapy is essential, in order to cure relapsed ALL and ensure the long-term survival of the patients with relapsed ALL (3, 4).

Although the schedules were diverse, many induction chemotherapy regimens for relapsed ALL have consisted of vincristine, corticosteroid, L-asparaginase, and anthracycline (1, 5-7). Idarubicin (4-demethoxydaunorubicin) was introduced as a new anthracycline which is superior to daunomycin in the treatment of acute myeloid leukemia (8-10). It has shown promise in the treatment of relapsed ALL in children because it is more effective in multidrug-resistant cell lines and has relatively low cardiotoxicity, but a high penetration rate to central nervous system (CNS), compared with daunorubicin or doxorubicin (8, 11, 12). Idarubicin has been widely used recently to treat acute myeloid leukemia or relapsed/refractory ALL, and other kinds of malignancy.

The maximum tolerated dose (MTD) of idarubicin used as a single agent to treat a childhood leukemia is between 30 and

40 mg/m² as a total dose when administered on 3 consecutive days (13). But in combination with other chemotherapeutic agents, MTD is variable according to kinds and doses of other chemotherapeutic agents in combination, and the chemotherapy schedule. The Children's Cancer Study Group (CCG) study to determine the MTD of weekly idarubicin in multidrug induction combination chemotherapy for relapsed ALL, and the study to compare the effect and toxicity of high (12.5 mg/m²) and intermediate (10 mg/m²) doses of idarubicin, determined that the optimal dose of weekly idarubicin in induction combination chemotherapy for relapsed ALL was 12.5 mg/m² according to the CCG protocol for chemotherapy of relapsed ALL (CCG-1884) (14, 15). The weekly dose of idarubicin was 12.5 mg/m² based on this induction chemotherapy protocol initially, because no study has established the optimal weekly dose of idarubicin for the treatment of relapsed ALL in Korean children. However this dose was highly toxic for many patients leading to treatment-related mortality (TRM) and a lower remission rate than that reported in a previous CCG study. Thus the weekly dose of idarubicin was reduced to 10 mg/m², and we observed a better remission rate and lower toxicity with 10 mg/m² than 12.5 mg/m². Therefore, we postulated that a weekly idarubicin dose of 12.5 mg/m² in this multidrug combination induction chemotherapy was inad-

equate and too toxic to Korean children with relapsed ALL, and that a reduced dose of idarubicin (10 mg/m²) may be optimal for them. The aim of this study was to evaluate the improvement in induction remission rate after modifying the idarubicin dose in the induction regimen for relapsed ALL (CCG-1884) retrospectively and to determine the more optimal dose of idarubicin in induction chemotherapy for relapsed ALL in Korean children.

MATERIALS AND METHODS

Patient populations

Pediatric patients who were diagnosed with relapsed ALL, and treated according to the CCG-1884 induction protocol, which consisted of prednisolone, vincristine, L-asparaginase, idarubicin as anthracycline in Seoul National University Children's Hospital were enrolled in this study between 1 January 1995 and 31 May 2005. Patients who received daunorubicin as anthracycline were excluded. Medical records of these patients were reviewed retrospectively.

Treatment progression

All patients were admitted and had a bone marrow (BM) examination before initiation of induction chemotherapy.

The original CCG-1884 protocol consisted of oral prednisolone 40 mg/m²/day for 28 days, weekly intravenous (IV) vincristine 1.5 mg/m², intramuscular L-asparaginase 6,000 IU/m² thrice weekly with a total of 9 doses, and weekly IV idarubicin on day 0, 7, 14 (Table 1). We used a modified protocol which increased the daily dose of prednisolone to 60 mg/m²/day and permitted addition of idarubicin on day 21 (Table 1). If complete blood count (CBC) on day 14 or day 21 showed absolute neutrophil count (ANC) <500/ μ L or platelet count <50,000/ μ L, IV administration of idarubicin was withdrawn. The dose of idarubicin was modified from 1 June 1999. Before 31 May 1999, the dose of weekly IV idarubicin was 12.5 mg/

m² according to CCG protocol, but after June 1999, we reduced the dose of weekly idarubicin to 10 mg/m². For CNS prophylaxis, hydrocortisone and cytosine arabinoside were injected intrathecally on days 0, 7, and 28, respectively. All patients with leukemic CNS involvement on diagnosis as relapse had intrathecal chemotherapy with hydrocortisone and cytosine arabinoside on days 0, 7, 14, 21, and 28.

If a patient had fever or other symptoms suspected treatment-related complication, such as infection or septic shock, chemotherapy was stopped and IV antibiotics and other supportive cares for complications were started.

After the completion of induction chemotherapy, the BM of all patients was examined. If patients showed complete remission on the day 28 bone marrow examination, they continued maintenance chemotherapy or stem cell transplantation as autologous a matched, sibling, or unrelated donor became available. In spite of a different weekly dose of idarubicin, all patients had the same maintenance (CCG-1884 maintenance protocol) chemotherapy before and after June 1999. Supportive care in both groups did not differ significantly.

The final outcome of treatment was divided into three categories: living without relapse, treatment failure (persistence or relapse after remission), and TRM.

Statistical analysis

Comparability of both groups (idarubicin 12.5 mg/m² and idarubicin 10 mg/m²) was examined by the Pearson chi-square homogeneity test for several available potentially important factors and presenting features. Statistical significance was defined as *p* value less than 0.05.

The duration of overall survival (OS) was defined as the period between the date of diagnosis of relapse and either the date of death or the date of the most recent follow-up. The duration of event-free survival (EFS) was defined as the period between the date of diagnosis of relapse and either the date of diagnosis of persistence of leukemia on BM examination or relapse, the date of the most recent follow-up, or the date of treatment-related death. Probabilities of OS and EFS were

Table 1. Induction chemotherapy schedule: original CCG-1884 induction (A) and modified CCG-1884 induction (B) schedule in Seoul National University Children's Hospital

(A)			(B)		
Original CCG-1884 induction chemotherapy			Modified CCG-1884 induction chemotherapy		
Prednisolone (40 mg/m ² , oral)	Days 0-27, then taper		Prednisolone (60 mg/m ² , oral)	Days 0-27, then taper	
Vincristine (1.5 mg/m ² , IV)	Days 0, 7, 14, 21		Vincristine (1.5 mg/m ² , IV)	Days 0, 7, 14, 21	
L-asparaginase (6,000 IU/m ² , IM)	Thrice weekly, total 9 doses		L-asparaginase (6,000 IU/m ² , IM)	Thrice weekly, total 9 doses	
Idarubicin (12.5 mg/m ² , IV)	Days 0, 7, 14		Idarubicin (10 or 12.5 mg/m ² , IV)	Days 0, 7, 14, 21	
CNS therapy			(if ANC \geq 500/ μ L and platelet count \geq 50,000/ μ L on day 14 and 21)		
No CNS involvement	IT Ara-C and HC	Day 0, 7, 28	CNS therapy		
CNS involvement	IT Ara-C and HC	Day 0, 7, 14, 21, 28	No CNS involvement	IT Ara-C and HC	Day 0, 7, 28
			CNS involvement	IT Ara-C and HC	Day 0, 7, 14, 21, 28

IM, intramuscular; IV, intravenous; ANC, absolute neutrophil count; IT, intrathecal; Ara-C, cytosine arabinoside; HC, hydrocortisone.

estimated using the Kaplan-Meier method and the log rank test was used to compare proportions. SPSS 12.0 software was used for the statistical analysis.

RESULTS

Patient characteristics

A total of 28 patients (17 males and 11 females) were enrolled in this study. Nine patients were in the 12.5 mg/m² idarubicin dose group (Ida 12.5 mg/m²), and 19 were in the 10 mg/m² idarubicin dose group (Ida 10 mg/m²). The median age of the patients was 8 yr 11 months (from 11 months to 18 yr). Median ages of each group were 10 yr 11 months (from 2 yr 5 months to 14 yr 7 months) in the Ida 12.5 mg/m² group and 7 yr 8 months (from 11 months to 15 yr 6 months) in the Ida 10 mg/m² group.

Numbers of relapse site in the patients at study entry were: 23 at BM only, 4 at BM and CNS, and 1 at BM and testis.

Comparisons of patient characteristics in both groups are set out in Table 2. There were no significant differences between the 2 groups with respect to white blood cell (WBC), age, gender, CD10 positivity, or duration of previous remission.

Table 2. Characteristics of patients and comparability in both groups

	Ida 12.5 mg/m ²	Ida 10 mg/m ²	<i>p</i> value
WBC at study entry			
<10,000/ μ L	5	13	0.123
10,000-49,000/ μ L	1	5	
\geq 50,000/ μ L	3	1	
Age at relapse			
<4 yr	0	2	0.066
4-9 yr	2	11	
10- yr	7	6	
Gender			
Male	5	12	0.700
Female	4	7	
Duration of previous initial remission			
<1 yr	2	5	0.406
1-3 yr	6	8	
>3 yr	1	6	
Site of relapse			
BM only	8	15	0.726
BM+CNS	1	3	
BM+testis	0	1	
CD10 positivity			
Positive	1	3	0.741
Negative	8	16	

Ida, idarubicin; WBC, white blood cell; BM, bone marrow; CNS, central nervous system.

Treatment progression

Of 9 patients on a weekly dose of idarubicin 12.5 mg/m², 5 completed induction chemotherapy and 4 died due to treatment-related sepsis or infection. Of 5 patients who had complete induction chemotherapy, 2 showed complete remission (CR) at bone marrow examination, but 3 showed persistence of leukemia. But the 2 patients with CR after induction chemotherapy had relapsed again during maintenance chemotherapy.

Of 19 patients on a weekly dose of idarubicin 10 mg/m², 18 completed induction chemotherapy, and 1 died because of treatment-related infection. Of 18 patients who completed induction chemotherapy, 4 showed persistence of leukemia and 14 had CR. Post-remission treatments in 14 patients with remission were: 9 received only maintenance chemotherapy, 1 had autologous peripheral stem cell transplantation, 2 had bone marrow transplantation (BMT) from sibling donors, 1 had BMT from an unrelated donor, and 1 patient had cord blood transplantation. Among them, only 4 patients, including 1 patient who had allogeneic BMT and 3 who received only maintenance chemotherapy, showed a continuous state of remission, and 10 had relapsed (Fig. 1).

Treatment results

CR rate in all patients after induction chemotherapy according to the modified CCG-1884 protocol was 57% (16/28). CR rates were 22% (2/9) in the Ida 12.5 mg/m² group and 74% (14/19) in the Ida 10 mg/m² group (significant at *p*=0.010). Compared with the patients who completed induction chemotherapy, the Ida 12.5 mg/m² group showed a lower CR rate (2/5, 40%) than the Ida 10 mg/m² group (14/18, 78%), but it was not statistically significant (*p*=0.104).

TRM was 44% (4/9) and 5.2% (1/19) in the Ida 12.5 mg/m² group and Ida 10 mg/m², respectively. The Ida 10 mg/m² group showed lower TRM (significant at *p*=0.011).

OS of the total patients was 12.8%, and 4-yr EFS of the total group was 10.3% (Fig. 2). OS and 4-yr EFS of the patients who had CR after induction were 26.2% and 18.2%, respectively (Fig. 3). Comparing the estimates of survival rates between the Ida 12.5 mg/m² and Ida 10 mg/m² groups, OS and 4-yr EFS in each group were both 0% in the Ida 12.5 mg/m² group, and 19.3% and 15.6% in the Ida 10 mg/m² group (Fig. 4). In the Ida 12.5 mg/m² group, no patient survived long-term as a result of relapse or treatment-related complication. There was statistical significance in OS between two groups (*p*=0.00001), but not in EFS (*p*=0.0858).

DISCUSSION

Idarubicin is an analog of daunorubicin, and an effective agent for relapsed ALL (13, 14). In the treatment of relapsed

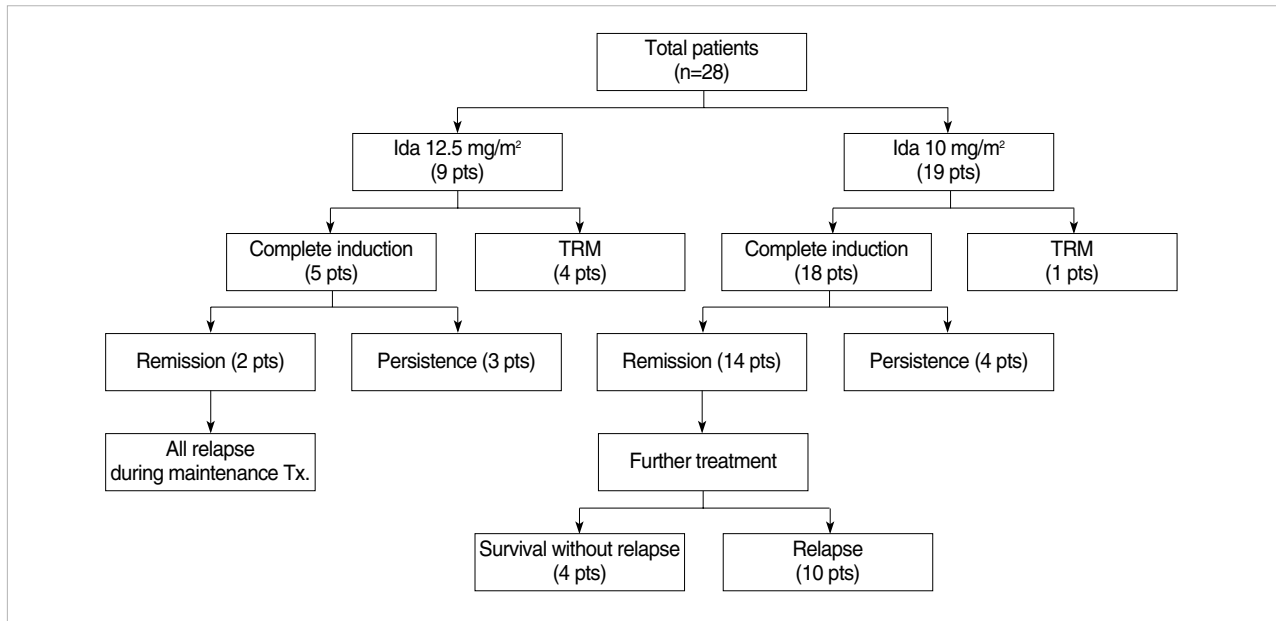


Fig. 1. Outcomes of treatment in all patients. Dose of weekly idarubicin changed from 12.5 mg/m² to 10 mg/m² in June, 1999. Ida, idarubicin; TRM, treatment-related mortality, maintenance; Tx., maintenance chemotherapy.

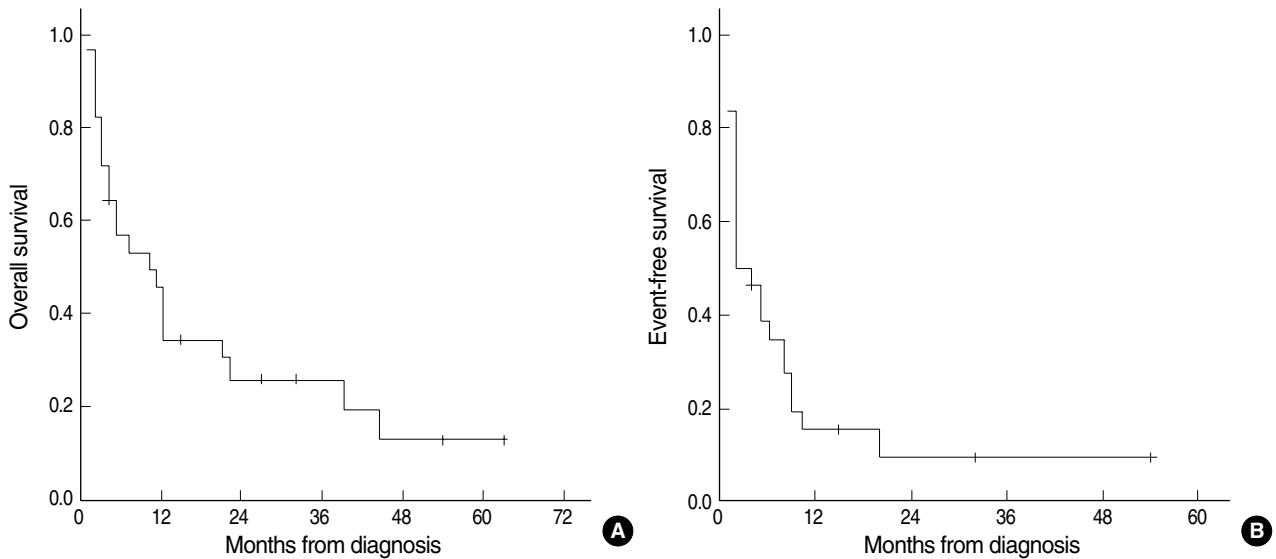


Fig. 2. Overall survival (OS, A) and event-free survival (EFS, B) in all patients, using Kaplan-Meier method. Estimates of OS and 4-yr EFS were 12.8% and 10.3%, respectively.

ALL, the prospective study of CCG by Feig *et al.* (14, 15) concluded that MTD and most effective weekly dose of idarubicin in combination induction chemotherapy (CCG-1884 induction) was 12.5 mg/m²/week. However, this dose was for Western children, and there was no study on MTD and the most effective weekly dose of idarubicin in the treatment of relapsed ALL. This study aimed to establish whether the modification of the weekly idarubicin dose improved the remission rate in Korean children who were treated according to the CCG-1884 induction chemotherapy protocol, retrospectively.

The results of this study showed that a reduced weekly idarubicin dose of 10 mg/m² resulted in a higher CR rate than that of 12.5 mg/m², due to lower TRM in the Ida 10 mg/m² group. This result is different to that of the CCG study by Feig *et al.* (15) which showed that the remission rate after CCG-1884 induction chemotherapy was higher in the weekly idarubicin 12.5 mg/m² group (19 of 26 patients, 73%) than in the lower idarubicin 10 mg/m² dose group (13 of 18 patients, 72%), without statistical significance.

In this study, the lower TRM rate is the most important

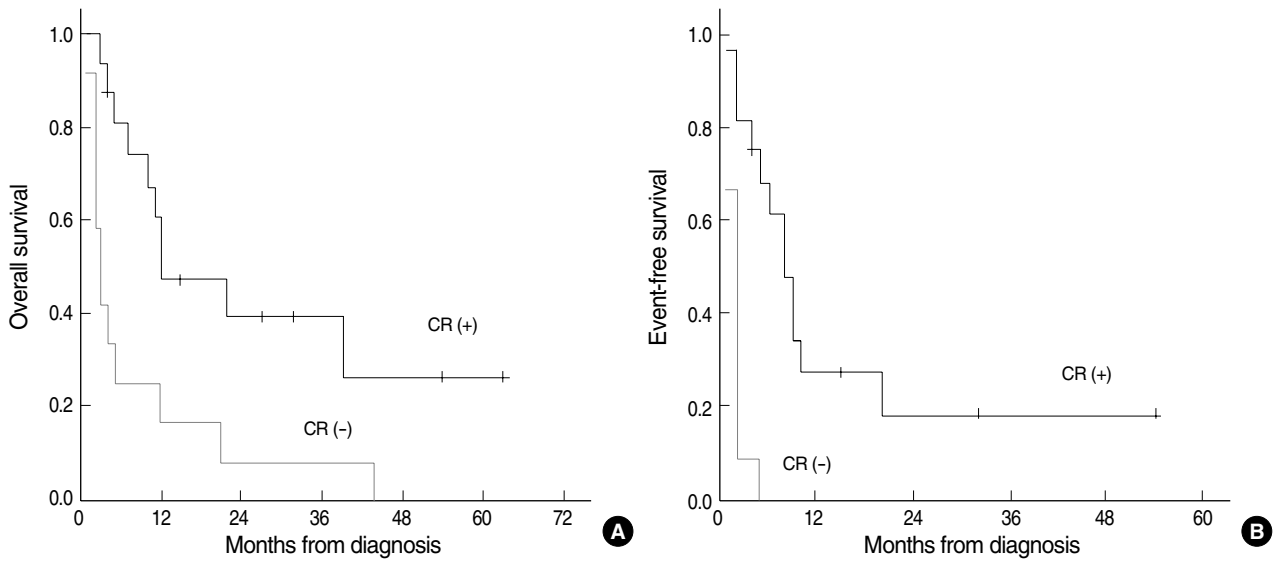


Fig. 3. Overall survivals (OS, A) and event-free survivals (EFS, B) between patients with or without complete remission (CR), using Kaplan-Meier method. Estimates of OS were 26.2% and 0% ($p=0.0045$), and 4-yr EFS were 18.2% and 0% ($p=0.000$), respectively.

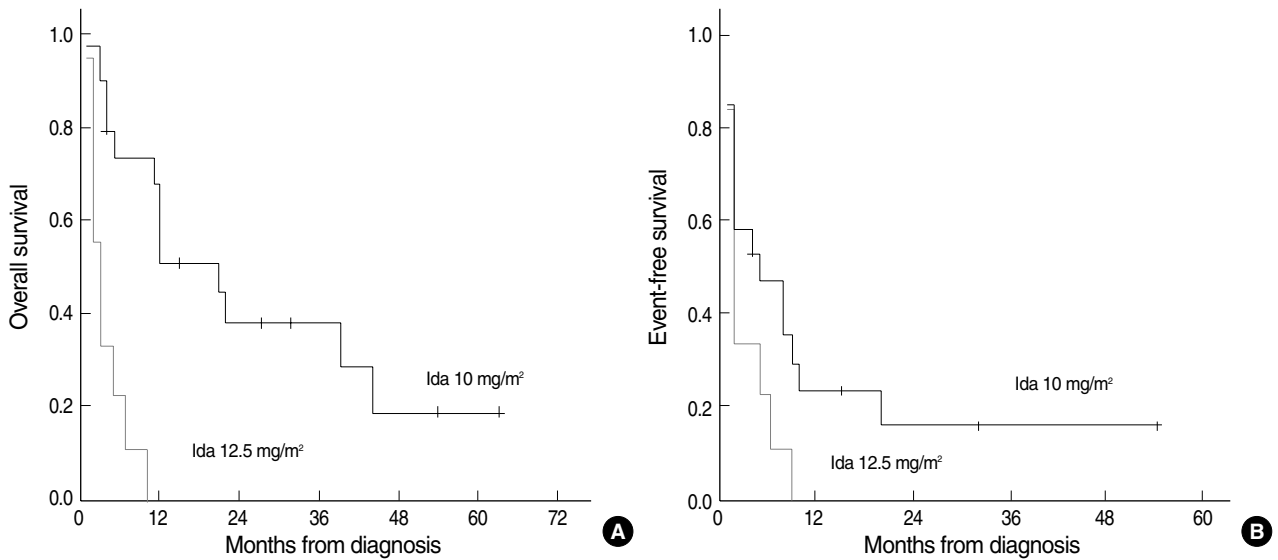


Fig. 4. Overall survivals (OS, A) and event-free survivals (EFS, B) at different dose of idarubicin in induction chemotherapy, using Kaplan-Meier method. Estimates of OS were 19.3% and 0% ($p=0.00001$), and 4-yr EFS were 15.6% and 0% ($p=0.0858$), respectively.

factor related to the improved CR rate in the Ida 10 mg/m² group. TRM rates in induction chemotherapy were 44% and 5.3% in the Ida 12.5 mg/m² group and Ida 10 mg/m² group, respectively. These results show higher TRM in the 12.5 mg/m² dose of weekly idarubicin, but a similar level of TRM in the 10 mg/m² dose, compared with the previous study by Feig et al. (15) which showed the 19% (5 of 26) and 6% (1 of 18) of TRM in the 12.5 mg/m² and Ida 10 mg/m² groups, respectively. These differences could be explained by the different level of supportive care, with no specific evidence, but can reflect the fact that Korean pediatric patients with relapsed ALL are more susceptible to the myelosuppression with high dose

idarubicin, which may indicate the importance of ethnic variation in pharmacogenetics of certain drugs. However, there is no study on pharmacogenetics or pharmacogenomics related to idarubicin metabolism or dose modification of idarubicin, although some studies exist on the relationship between specific pharmacogenetics and treatment outcomes (16-18). Further study on this topic should be investigated.

There is no consensus or study on ethnic variation of MTD of idarubicin. What is the optimal dose of weekly idarubicin in the therapy of relapsed ALL of Korean pediatric patient? There is no agreement on this point. This is the first study related to the optimal dose of idarubicin in Korea pediatric

ALL patients. No previous literature discussed whether the idarubicin dose in Western protocols for relapsed ALL is adequate for Korean pediatric patients.

Of the patients who completed induction chemotherapy, 40% and 78% of those achieved remission in the Ida 12.5 mg/m² and 10 mg/m² groups, respectively. The Ida 10 mg/m² group also showed a higher remission rate in patients who completed induction chemotherapy, but there was no statistical significance. These results differed from those of the CCG study by Feig *et al.* (15), which were 90% (19 of 21) and 76% (13 of 17) in both groups, respectively, which showed a higher remission rate in the higher idarubicin dose group. We suggest that these different results relate to the higher TRM in the high idarubicin dose (12.5 mg/m²/week) in Korean children. The weekly dose of idarubicin 10 mg/m² showed that remission rates in two studies were similar, which means that the higher dose of idarubicin 12.5 mg/m² is not only too toxic but also does not contribute to improvement in remission rate. The results of this study suggest at least that a higher 12.5 mg/m² dose of idarubicin has no advantage in both effect and safety.

The idarubicin dose in induction chemotherapy for relapsed or refractory ALL was varied according to treatment protocol. Thomson *et al.* (4) reported that idarubicin 10 mg/m² given over the initial 3 days of induction was an attempt to prevent prolonged myelosuppression seen with weekly dosing. The ALL-R87 study by Giona *et al.* (19) used the induction protocol based on daily idarubicin 5 mg/m² with continuous infusion of cytarabine 1 g/m²/day and oral prednisolone 40 mg/m²/day for 6 days consecutively. Testi *et al.* (20) reported on a single dose of idarubicin 40 mg/m² in day 6, cytarabine 3 g/m² continuous infusion over 3 hr for 6 days, prednisolone 40 mg/m² for 5 days, and subsequent G-CSF 5 µg/kg. Study for the CHP-540 protocol by Leahney *et al.* (21) showed that an induction regimen with weekly idarubicin 10 mg/m² with dexamethasone 10 mg/m² (day 0-28), weekly vincristine 1.5 mg/m² and Peg-asparaginase was an effective regimen for relapsed ALL, but was toxic. These diversities in doses and schedules of idarubicin as induction regimens for relapsed ALL suggest that the optimal dosage of this chemotherapeutic agent with more effect and less toxicity is not definite, and is determined by other factors such as other chemotherapeutic drugs in combination with idarubicin, the schedule of idarubicin, and subject patients. We suggest the ethnic difference as the another factor in the determination of the optimal dose of idarubicin.

Another important finding in this study is that a higher remission rate after a lower dose of weekly idarubicin (10 mg/m²) did not guarantee higher EFS, with statistic significance. In 14 patients with remission in the Ida 10 mg/m² group after induction chemotherapy, 10 had a relapse of leukemia during maintenance chemotherapy or after stem cell transplantation. Of a total of 16 patients with remission after modified CCG-1884 induction chemotherapy, 9 of 11 patients with

maintenance chemotherapy, 1 of 2 patients with related BMT, 1 patient with unrelated BMT, 1 patient with autologous peripheral stem cell transplantation, and 1 patient with cord blood transplantation suffered a relapse. This is consistent with a previous study by Feig *et al.* (15) which showed 15% of 3-yr EFS in patients with idarubicin (12.5 mg/m²/week or 10 mg/m²/week) in CCG-1884 induction chemotherapy. These results indicate that any present post-remission therapy resulted in a failure to achieve good long-term survival without relapse. Several reports have suggested a potential superiority for allogeneic BMT for children with ALL who achieved a second remission after relapse (19, 22-25). The CCG study by Feig *et al.* (26) reported that BMT is superior to chemotherapy in maintaining CR of relapsed childhood ALL treated according to the CCG-1884 protocol, although the EFS at 24 months was higher among the patients with maintenance chemotherapy than with transplantation (no statistical significance), if they were treated with idarubicin in induction chemotherapy. Although it is impossible to compare the result according to the post-remission therapy, because of the small number of the patient who had BMT in this study, any treatment was not associated with satisfactory long-term event-free survival. More effective and intensive post-remission therapy should be investigated.

This is the only preliminary, retrospective study of a single center for evaluation of the optimal dose of weekly idarubicin in the treatment of relapsed ALL in Korean children. For evaluation of the precise effect of a modified dose of idarubicin in induction chemotherapy for relapsed childhood ALL, a large-scale, multi-center, prospective study is now in progress in Korea (27).

In conclusion, results in this study suggest that a weekly idarubicin dose of 10 mg/m² in induction combination chemotherapy for relapsed ALL is more effective and less toxic than a dose of 12.5 mg/m² for Korean children, mainly due to low TRM. But remission for many patients after induction chemotherapy was associated with a subsequent relapse of ALL, and an unsatisfactory survival rate. A more intensive and effective post-remission treatment plan should be investigated.

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