VOLUME 46 · NUMBER 2 · June 2011

KJH

THE KOREAN JOURNAL OF HEMATOLOGY

ORIGINAL ARTICLE

Treatment outcomes in children with Burkitt lymphoma and L3 acute lymphoblastic leukemia treated using the lymphoma malignancy B protocol at a single institution

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p-ISSN 1738-7949 / e-ISSN 2092-9129
DOI: 10.5045/kjh.2011.46.2.96
Korean J Hematol 2011;46:96-102.

Received on February 11, 2011
Revised on March 26, 2011
Accepted on May 17, 2011

*This study was supported by a grant from the National R&D Program for Cancer Control, Ministry for Health, Welfare and Family affairs, Republic of Korea (0520290).

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Background
We compared the outcomes of patients with Burkitt lymphoma and French-American-British (FAB) L3 acute lymphoblastic leukemia treated using Lymphoma Malignancy B (LMB) or other treatment protocols.

Methods
Thirty-eight patients diagnosed between July 1996 and December 2007 were treated using LMB 96, and 22 patients diagnosed between January 1991 and May 1998 (defined as the early period) were treated using the D-COMP or CCG-106B protocols. We retrospectively reviewed their medical records and analyzed cumulative survival according to the treatment period by using Kaplan-Meier analysis.

Results
There were no intergroup differences in the distribution of age, disease stage, or risk group. The median follow-up period of the 33 live patients in the LMB group was 72 months (range, 36-170 months). Overall survival (OS) and event-free survival (EFS) of patients treated using LMB 96 were 86.8%±5.5% and 81.6%±6.3%, respectively, whereas OS and EFS of patients treated in the early period were 72.7%±9.6% and 68.2%±9.9%, respectively. In the LMB 96 group, OS of cases showing non-complete response (N=8) was 62.5%±17.1%, and OS of relapsed or primary refractory cases (N=6) was 33.3%±19.3%. Central nervous system (CNS) disease, high lactate dehydrogenase levels at diagnosis, and treatment response were significant prognostic factors.

Conclusion
Survival outcome has drastically improved over the last 2 decades with short-term, dose-intensive chemotherapy. However, CNS involvement or poor response to chemotherapy was worse prognostic factors; therefore, future studies addressing this therapeutic challenge are warranted.

Key Words Burkitt lymphoma, L3 lymphocytic leukemia, Treatment outcome, Prognosis

INTRODUCTION

Burkitt lymphoma (BL) originates from B lymphocytes that have characteristic surface immunoglobulin markers due to translocation of the *myc* gene [1, 2]. French-American-British (FAB) L3 acute lymphoblastic leukemia (L3 ALL) is considered to be in the same disease category. BL is well-known to have a rapid growth rate. It frequently spreads systemically prior to the time of diagnosis; thus, 70% to 80% of patients are in the advanced stages of disease. In addition, early death due to tumor lysis syndrome is frequent, owing to the high turnover rate of these tumor cells. However, survival outcome has drastically improved over the last 2 decades following the Lymphoma Malignancy B (LMB) study by the French Society of Pediatric Oncology

(SFOP). In the LMB 81 study, 9 drugs were used for 1 year, but acute toxic death was still an area of concern [3]. A subsequent study, LMB 84, concluded that poor responders (tumor response <20% at day 7) have a poor outcome [4]. Even in patients with central nervous system (CNS) involvement, which is known to result in a poorer survival outcome, event-free survival (EFS) of over 70% could be achieved by dose escalation of methotrexate (8 g/m^2) and addition of cytarabine (cytosine arabinoside; Ara-C) and etoposide (VP-16) [5, 6].

In our institution, the D-COMP or CCG-106B protocols were used earlier, but since the late 1990s, the LMB protocol has been uniformly applied for the treatment of BL. The authors previously reported preliminary data on the treatment outcomes and toxicity in 10 patients treated using LMB 96 [7]. In this report, we aimed to analyze differences in the survival outcomes of patients treated using LMB 96 [8] and using D-COMP [9] or CCG-106B [10].

MATERIALS AND METHODS

1. Patients

Forty patients treated with the LMB 96 protocol from July 1996 to December 2007 (LMB group), and 26 patients treated with D-COMP (stage I-III) [9] or CCG-106B (stage IV) [10] from January 1990 to June 1998 (early-period group) were enrolled. Two patients who were lost to follow-up in the LMB group and 4 in the early group (3 discharged themselves against medical advice and the medical records of 1 were lost) were excluded from this analysis. This study was approved by the institutional review board.

2. Treatment and response criteria

The primary tumor site(s), lactate dehydrogenase (LDH) levels, and stage were investigated. The primary site(s) were categorized as follows: head and neck, abdomen, chest, peripheral lymph node, etc. The staging study included evaluation of peripheral blood and bone marrow (BM) aspirate smears, cerebrospinal fluid (CSF) analysis, radiography, ultrasonography, computed tomography (CT) or magnetic resonance imaging (MRI), and skeletal scintigraphy. BL was diagnosed on the basis of morphological and immunohistochemical characteristics. A mature B-cell immunophenotype was defined by reactivity of B-cell antigens (CD10, CD19, CD20 in cell suspension or CD20, CD79a, BCL2 in fixed tissue) and monoclonality of surface immunoglobulins. Chromosomal translocations such as t(8;14), t(8;22), and t(2;8) were evaluated by karyotyping analysis. A diagnosis of L3 ALL was made when blasts had infiltrated more than 25% of the BM aspirates. CNS disease was diagnosed in cases with CSF containing more than 5 cells/μL and showing morphologically identifiable blasts on cytospin preparations, and in the presence of cerebral infiltrates on cranial CT or MRI scans. The Murphy staging system was used [11].

Risk groups were stratified into classes A, B, or C according to the definition of the LMB group (Fig. 1) [8]. Patients diagnosed between 1990 and 1998 were treated using D-COMP or CCG-106B, and patients diagnosed between 1996 and 2007 were treated using the LMB 96 protocol. Complete response (CR) was defined as no evidence of residual disease. Partial response (PR) was defined as at least 50% reduction in tumor burden from the onset of treatment. Progressive disease (PD) was defined as at least 25% increase in the size of lesions.

3. Statistical analysis

Differences in the distribution of individual parameters among patient subsets were analyzed using the chi-square test or Student's *t* test. Overall survival (OS) was calculated from the date of diagnosis to the last follow-up. EFS was calculated from the date of diagnosis to the first event (death from any cause, tumor relapse, or progression) or to the date of last follow-up. The cut-off date for data analysis was December 2010. Analysis of OS and EFS was performed using the Kaplan-Meier method, with the differences com-

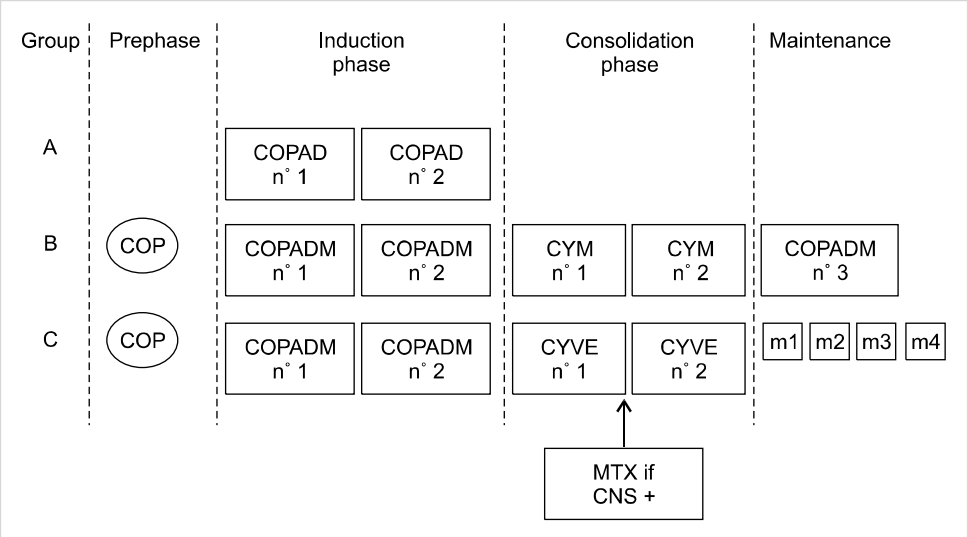

Fig. 1. LMB 96 protocol schedule [8]. Patients were stratified into 3 risk groups: A, B, and C, depending on stage, resection status, percentage of blasts in BM, and CNS involvement. Group A: Resected stage I and abdominal stage II. Group B: Patients not eligible for inclusion in group A or C. Group C: Patient with CNS involvement and more than 70% of blast in bone marrow. In the LMB 96 protocol, cranial irradiation was skipped and replaced with high-dose methotrexate (MTX) between consolidation phases in patients with CNS-positive disease.

pared using the log-rank test [12]. Statistical analysis was carried out using the SPSS statistical program (version 13). *P*-values less than 0.05 were considered statistically significant.

RESULTS

1. Primary site and stage of disease

Median age at diagnosis in the LMB group was 7 years (range, 0.8-15.1 years), and 10 patients (26.3%) were over 10 years old. The most common primary sites, in descending order of frequency, were the head and neck (50%), abdomen (26.3%), chest (10.5%), and peripheral lymph node (5.3%). Twenty-eight of the 38 patients (78.3%) were diagnosed with stage III or IV disease, including 7 L3 ALL (18.4%) and 8 CNS-positive (21.1%) cases. In the LMB group, 2 patients were in risk group A, 21 in B (55%), and 15 in C (39%). Group B had a heterogeneous distribution of stages: stage I, 2 patients; stage II, 6 patients; stage III, 6 patients; and stage IV, 7 patients. Differences in the demographic data, primary site(s), and stage distribution between the LMB and early-period group are summarized in Table 1. There were no differences in the distribution of age, disease stage, or risk group between the 2 groups.

2. Initial LDH levels

LDH levels of 22 of the 38 patients in the LMB group were analyzed. Fifteen patients (62.5%) had 2-fold elevated LDH levels, and the mean LDH level of these patients was 1,071.1±1,435.3 U/L (range, 178-6,336 U/L), whereas in the early-period group, the corresponding value was 834.4±613.8 U/L (range, 130-2,113 U/L). This difference between the 2 groups was statistically significant ($P<0.01$).

3. Treatment duration

The mean treatment duration was 6.7 months (range,

Table 1. Demographic and disease characteristics.

	Early period (1990.1-1998.5)	LMB 96 (1996.6-2007.12)	*P*
N	22	38	
Male, No. (%)	22 (100)	32 (82)	0.03
Mean age, years (range)	8.2 (3.5-14.6)	7 (0.8-15.1)	1.0
No. ≥10-15 years	5	10	
Pathologic diagnosis			
Burkitt	21	31	0.07
Mature B-ALL	1	7	
Primary site			0.41
Head and neck	10	19	
Abdomen	10	10	
Thorax	1	4	
Peripheral LN	1	2	
Not specified	-	3	
BM involvement			0.19
<25%	4	10	
≥25%	1	7	
Stage			0.19
I	6	3	
II	2	7	
III	4	6	
IV	10	22	
LMB grouping			0.10
A	6	2	
B	9	21	
C CNS^{-ve}	0	7	
CNS^{+ve}	7	8	

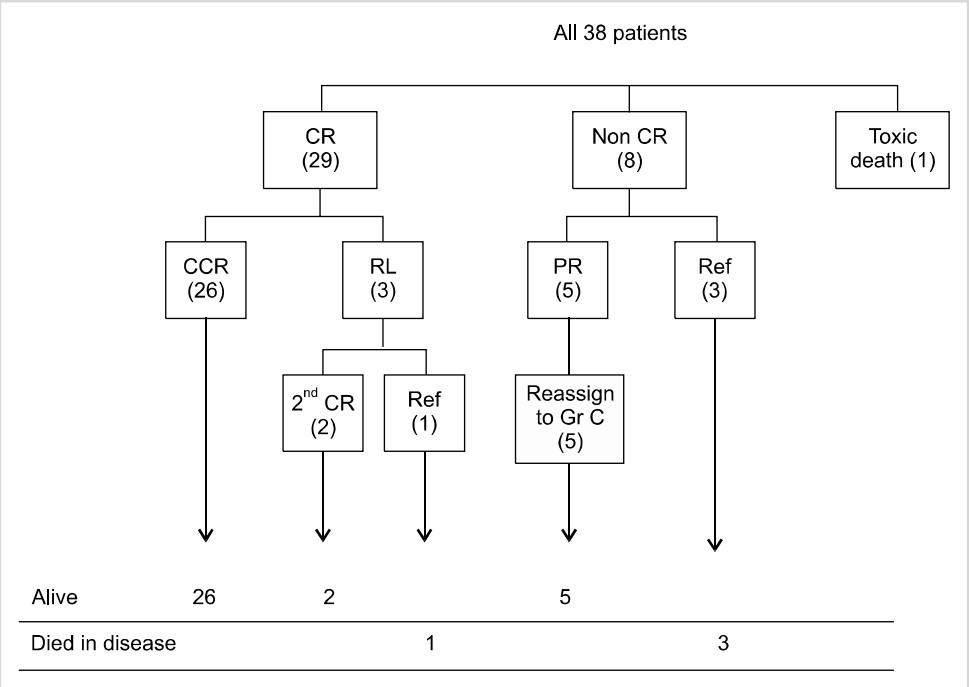

Fig. 2. Outcome in patients treated using the LMB protocol. Three patients showed relapse (RL) after complete response (CR), and 2 of them responded to salvage therapy and are alive with no evidence of disease. Cases that did not show CR after the first consolidation chemotherapy included 5 cases of partial response (PR) and 3 refractory (ref) cases. One case of toxic death occurred during induction chemotherapy.

0.8-10.6 months) for the LMB group and 20.6 months (range, 17.6-38.3 months) for the early-period group ($P<0.01$).

4. Treatment response and outcomes

Treatment outcomes in patients treated with LMB 96 are shown in Fig. 2. Of 38 patients, 8 (21%) had not reached

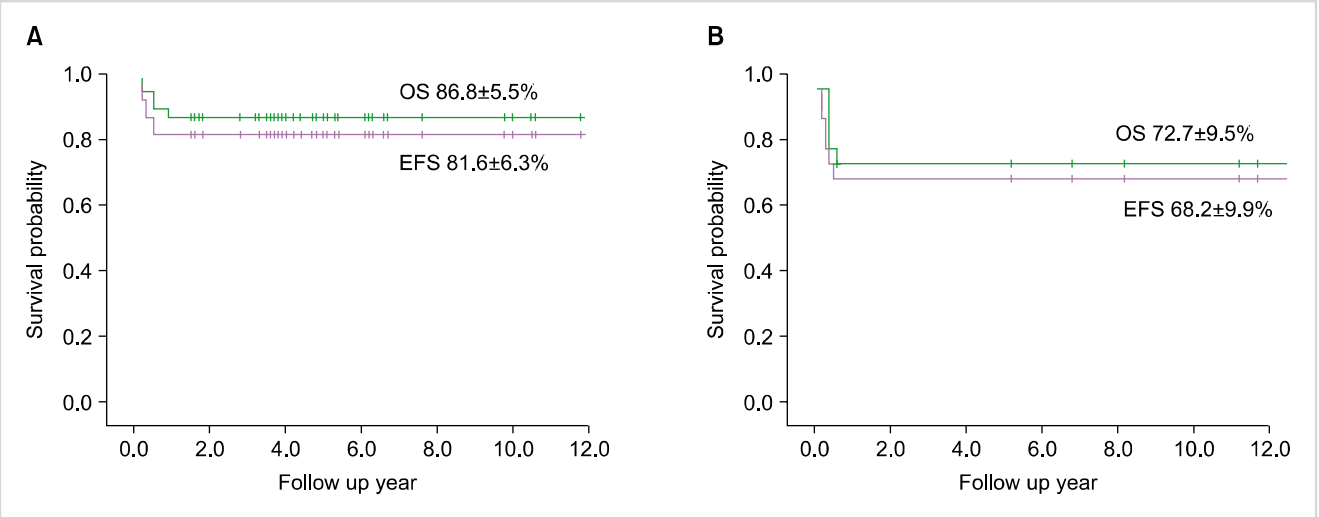

Fig. 3. Survival outcome of patients treated using LMB 89 (1996-2007) **(A)**, and according to protocols used in the early period (1990-1998) **(B)**.

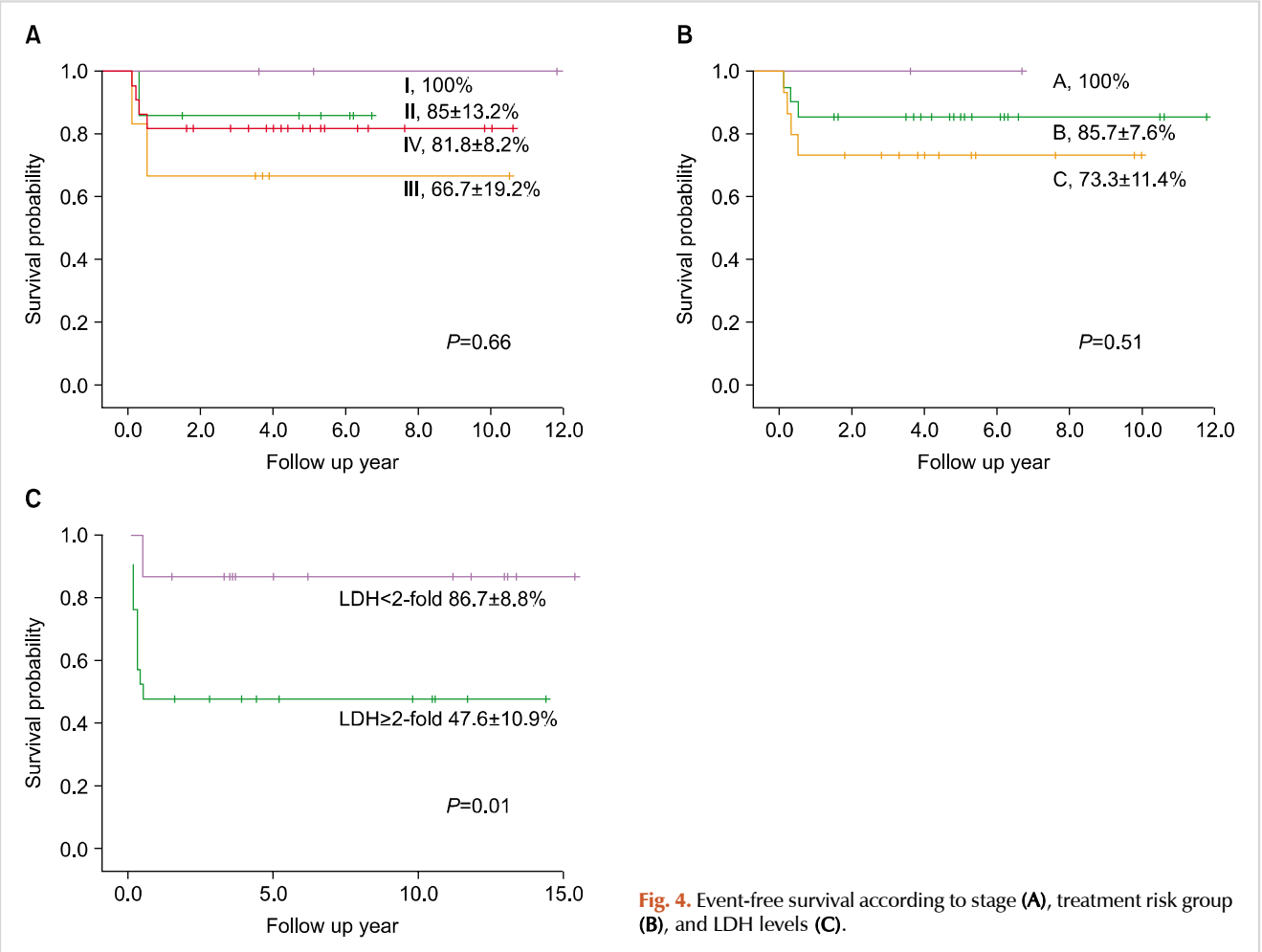

Fig. 4. Event-free survival according to stage **(A)**, treatment risk group **(B)**, and LDH levels **(C)**.

CR when evaluated after their 1st consolidation chemotherapy. Five of them were reassigned to risk group C, and after continuous consolidation with Ara-C and VP-16, they showed disease-free survival. One patient who was reassigned to risk group C had residual lesions at the end of chemotherapy and thus received high-dose chemotherapy (HDC) with ACNU, cyclophosphamide, and etoposide, followed by autologous stem cell transplantation (ASCT), and survived disease-free. However, 3 patients with primary refractory disease eventually died of the disease.

Treatment-related mortality occurred in 1 patient with bowel involvement (risk group B) during her 1st induction chemotherapy. She suffered from bowel perforation in the neutropenic period and died of sepsis.

Three patients showed relapses at 3.7, 6.9, and 6.5 months after diagnosis; one of them had a cerebral mass at diagnosis. All 3 received retrieval chemotherapy following the CCG-106B protocol. Two patients who responded to chemotherapy were administered continuous HDC/ASCT 8 and 10 months after relapse, but 1 patient who showed no response to salvage chemotherapy had PD and eventually died of the disease.

5. Survival analysis

The median follow-up time of the 33 live patients in the LMB group was 72 months (range, 36-170 months); 5-year OS and EFS were 86.8±5.5% and 81.6±6.3%, respectively. The OS and EFS of patients in the early-period group were 72.7±9.6% and 68.2±9.9%, respectively. Although there was

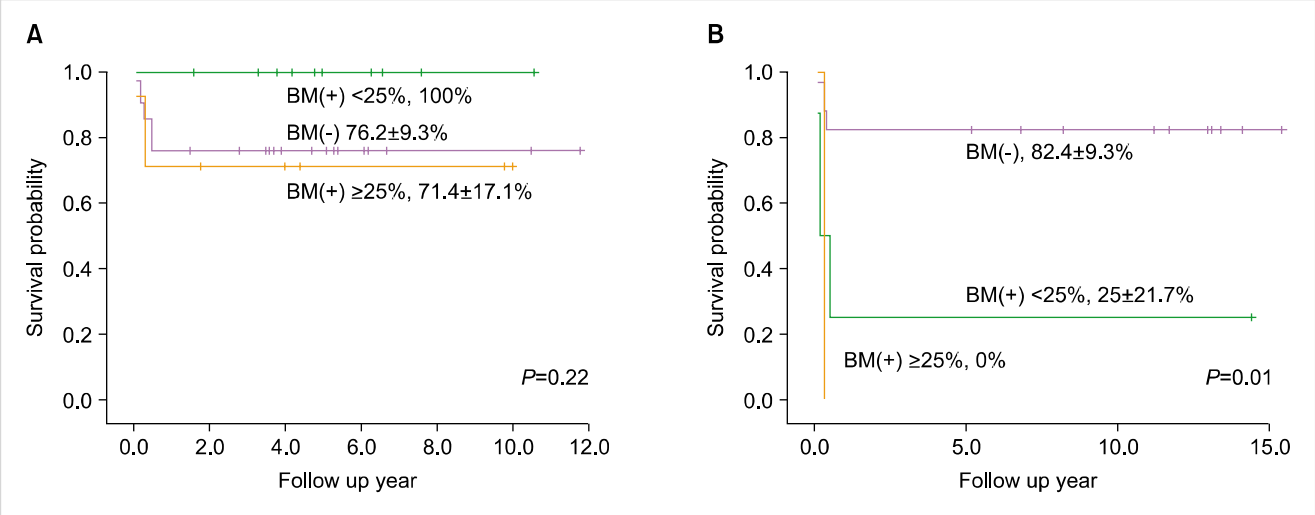

Fig. 5. Comparative analysis of event-free survival (EFS) according to the involvement of bone marrow. EFS of patients treated using the LMB protocol **(A)** and D-COMP or 106B protocols **(B)**. In the early period, differences in EFS between groups with or without bone marrow involvement were significant ($P=0.01$). However, the differences between these groups were not significant in patients treated using the LMB protocol.

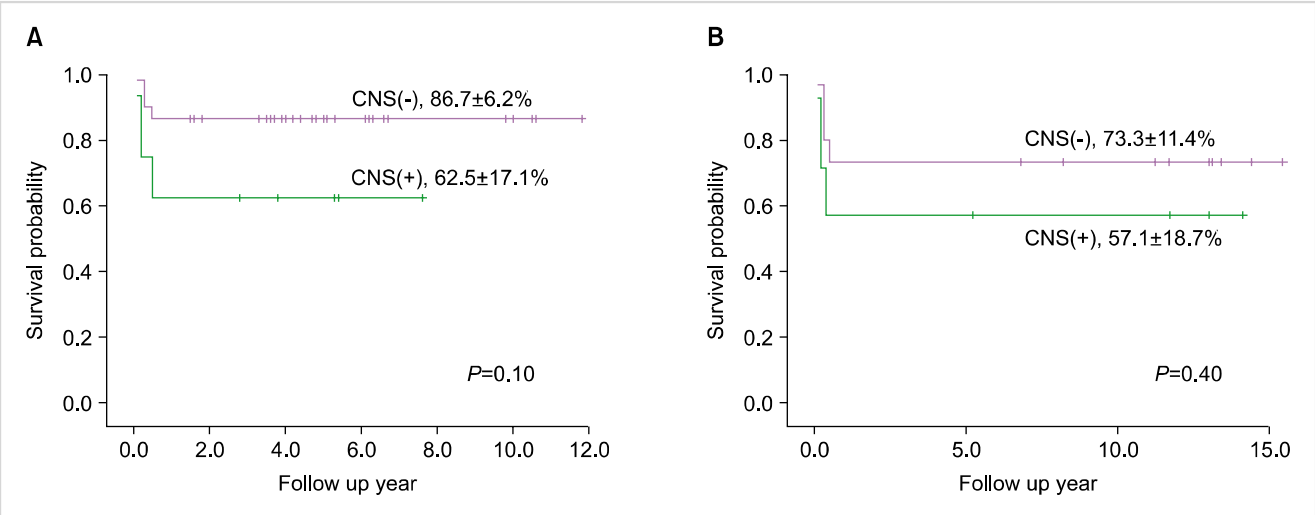

Fig. 6. Comparative analysis of event-free survival (EFS) according to the involvement of the central nervous system (CNS). EFS of patients treated using the LMB protocol **(A)** and D-COMP or 106B protocols **(B)**. In either treatment group, there was no significant difference in EFS between groups with or without CNS involvement.

no significant difference in either OS (P=0.15) or EFS (P=0.22) between the early and LMB groups, patients in these groups showed a tendency of improved survival (Fig. 3). EFS according to the disease stage is shown in Fig. 4A. The EFS of patients with stage IV disease treated using the LMB 96 protocol (81.8±8.2%) was significantly higher than that of patients treated using D-COMP or CCG-106B (40±15.5%). Survival outcomes according to the LMB risk groups are shown in Fig. 4B. The EFS of patients with LDH levels ≥2-fold was 47.6±10.9%, which was significantly lower than that of patients with LDH <2-fold (P=0.01) (Fig. 4C).

There was no difference in survival outcome with respect to the involvement of BM in the LMB group, whereas the EFS of early-period patients with BM involvement was less than 25±21.7%. This indicates that BM involvement is no longer a poor prognostic factor (Fig. 5). However, the EFS of patients with CNS involvement, another known poor prognostic marker, showed no difference between the 2 groups (LMB group, 62.5±17.1%; early-period group, 57.1±18.7%, P=0.81) (Fig. 6).

In the LMB group, EFS rates of non-CR patients (62.5±17.1%) were significantly different from those of CR patients (89.7±5.7%; P=0.03), and OS of relapsed or primary refractory cases (N=6) was 33.3±19.3%.

DISCUSSION

Treatment outcomes of BL have drastically improved over the past 25 years following the work of international cooperative study groups, including SFOP. Therefore, we aimed to analyze the survival outcome of patients treated using the LMB 96 protocol from 1996 to 2007 in a single institution, and compare these findings with the outcome of patients treated using other induction protocols from 1990 to 1998 at the same institution. As described above, OS of the LMB group in our study was 86.8%, which is a great improvement from that of the early-period group (68.2%); this outcome was also similar to that of the LMB 89-treated patients of SFOP [8].

At diagnosis, risk groups were stratified as A, B, or C according to the tumor stage and resectability in the LMB study group, and treatment intensity was adjusted according to the risk group. The next assessment was a step-up strategy based on the treatment response after initial prephase chemotherapy and the first consolidation chemotherapy. Patients who did not achieve an adequate response (tumor response less than 20%) subsequently received group C chemotherapy. Patte et al. [8] reported that 14 of 21 patients who did not show an adequate response after prephase chemotherapy were reallocated to group C, and EFS of group B was therefore improved up to 92%. Unfortunately, we did not evaluate tumor response immediately after prephase chemotherapy, and thus, therapeutic intervention was not made according to chemotherapy response at this point. However, 5 patients with PR after the first consolidation chemotherapy were reassigned to risk group C, and were administered continued consolidation and maintenance chemotherapy; all the 5 patients are alive without disease. Because more than 55% of patients (21/38) at various stages (I-IV) were included in group B, risk group reassignment according to drug response could help improve the survival of this heterogeneous group.

We confirmed that survival of patients with BM involvement drastically improved, and therefore, BM involvement is no longer a poor prognostic factor. However, the EFS of patients with CNS involvement treated with the LMB protocol was not significantly different from that of patients with CNS involvement in historical controls. CNS involvement and high LDH levels at diagnosis were confirmed to be poor prognostic factors in this study.

There were 8 non-CR cases and 3 relapsed cases in our cohort. Patients with PR and those who underwent salvage chemotherapy after relapse were all alive, but all patients with primary refractory BL or those who showed no response to salvage chemotherapy succumbed to the disease. In particular, 1 patient with PR and 2 patients who responded to retrieval chemotherapy underwent HDC/ASCT. Overall, EFS of non-CR patients (21%) was 62.5±17.1%. Previously, relapsed or refractory BL has been reported to have a very poor outcome despite treatment with HDC/ASCT [13-16] or CD-20 monoclonal antibody [17, 18]. Therefore, innovative treatment modalities using new drugs or prognostic factors discovered through cancer cell biology research are warranted for this small proportion of patients.

Treatment-related acute and late complications are no less important than treatment outcome in pediatric oncology. We previously reported preliminary data on acute complications during treatment with the LMB protocol. Neutropenia with fever and uncontrolled severe infection were complications in 87% and 27% of the patients, respectively. Stomatitis caused by toxicity greater than grade II was observed in 39% of the patients [7], and these data are comparable to those of the original LMB 89 study (neutropenia with fever, 85%; RBC transfusion, 71%; and stomatitis, 33% after $COPADM_8$ chemotherapy) [8]. Second malignancy and long-lasting organ toxicities are also unacceptable side effects. A randomized international FAB/LMB 96 trial for dose-reducing treatment of early responding patients (tumor response > 20% at day 7) showed that dose-reducing treatment was possible without jeopardizing survival. A 4-course treatment, including a total dose of 3.3g/m^2 cyclophosphamide and 120-mg/m^2 doxorubicin, has been reported to help patients in achieving 90% cure rate for early responding patients [19]. However, long-term follow-up is required for thorough evaluation of infertility, cardiotoxicity, and second malignancy.

Short-term intensive multi-agent chemotherapy was effective in treating 90% of BL and L3 ALL patients, but about 40% of patients with CNS involvement were not cured by this regimen. Relapsed patients or those with primary refractory disease also had very poor outcomes; thus, we should make efforts to identify new prognostic markers correlating with drug response or survival outcome, and to find new

drugs that can be used effectively in first-line or salvage therapy for relapsed or primary refractory patients.

ACKNOWLEDGEMENTS

The authors Eun Sil Park and Hyery Kim contributed equally to this article.

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