



Clinical characteristics and treatment outcomes of children and adolescents with aggressive mature B-cell lymphoma: a single-center analysis

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Background

Aggressive mature B-cell non-Hodgkin lymphoma (B-NHL) is the most common non-Hodgkin lymphoma in children. The outcome of chemotherapy for B-NHL has improved over decades.

Methods

We reviewed 82 children and adolescents with B-NHL diagnosed at Asan Medical Center between 1993 and 2020. The D-COMP/COMP (daunomycin – cyclophosphamide, doxorubicin, vincristine, and prednisolone), Pediatric Oncology Group (POG)-9219/9315/9317, R-CHOP/CHOP (rituximab – cyclophosphamide, doxorubicin, vincristine, and prednisolone), and Lymphomes Malins B 89 (LMB89)/LMB96 regimens were administered. In 2018, rituximab was added to the LMB protocol (R-LMB) for advanced-staged Burkitt lymphoma (BL). The patients' clinical features and treatment outcomes were retrospectively analyzed.

Results

The most common subtype was BL (61%), followed by diffuse large B-cell lymphoma (DLBCL) (35%). The median age was 7.8 (range, 1.3–16.4) years, and the most frequently used regimen was French–American–British (FAB)/LMB96 (58 patients, 70.7%). The 5-year overall survival (OS) and event-free survival (EFS) rates were 92.5% and 85.7%, respectively. The EFS rates of patients with BL and DLBCL were 90.0% and 79.3%, respectively. Among the FAB/LMB risk groups, group C (85.7%) had a significantly lower 5-year OS ($P=0.037$). Eleven events occurred (6 relapses, 3 deaths, and 2 secondary malignancies) during the median follow-up of 7.1 (range, 3.7–118.5) months. Two patients treated with R-LMB had good outcomes without complications.

Conclusion

Various treatment regimens have favorable outcomes in pediatric patients with B-NHL. However, further studies are needed to improve survival in high-risk patients. In addition, careful monitoring for acute toxicity or secondary malignancy due to intensive multidrug chemotherapy is required.

Key Words Mature B-cell lymphoma, Children, Survival, LMB protocol, Rituximab

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is a diverse group of lymphoid neoplasms categorized according to the characteristics of lymphoma cells (B, T, and natural killer cells), cell morphology, immunophenotype, genetic features, and prognosis.

Children generally present with high-grade lymphomas that tend to be aggressive and fast growing, such as Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), lymphoblastic lymphoma, and anaplastic large cell lymphoma. Among them, aggressive mature B-cell lymphomas account for approximately 60% of NHLs in children [1]. They include many subtypes and variants, such as DLBCL, BL, and high-grade

B-cell lymphoma, not otherwise specified (HGBL-NOS) [2].

Over the recent decades, the outcome of treatment with short-duration, dose-intensive, and stage-based multiagent chemotherapy in pediatric patients with mature B-cell lymphomas has considerably improved, with survival rates of >80% [3, 4]. Since the 1980s, 3 major US and European childhood cancer groups have contributed to the most effective and proven treatment approaches to date: Lymphomes Malins B (LMB) group, Berlin–Frankfurt–Münster (BFM) group, and Children’s Cancer Group/Children’s Oncology Group (CCG/COG). The French–American–British (FAB)/LMB studies divided patients into 3 groups based on disease stage and resection status. The FAB/LMB protocols are based on the COPAD regimen (cyclophosphamide, vincristine, prednisolone, and doxorubicin). Central nervous system (CNS) prophylaxis based on high-dose (HD) methotrexate (MTX) and intrathecal injections of MTX has been proven effective [3, 5, 6].

The BFM protocols are similar to the FAB/LMB protocols, with differences in the details of risk group stratification and treatment intensity. In BFM studies, patients were stratified into 4 risk groups according to stage, resection of localized tumors, lactate dehydrogenase (LDH) level, and CNS involvement [7]. BFM studies revealed that patients with advanced disease benefit from more prolonged HD MTX exposure and HD cytarabine. As the LMB and BFM protocols have provided dramatic improvements in treatment outcomes in pediatric NHL, they have been the most often used treatment strategies. Recently, rituximab was added to the standard LMB chemotherapy (R-LMB), and this combination has shown efficacy in children and adolescents with high-grade, high-risk, mature B-cell NHL (B-NHL) [8].

Since the introduction of effective intensive multiagent chemotherapy, very few children and adolescents (5–15%) with mature B-cell lymphoma have experienced refractory or relapsing disease. However, the prognosis of these patients remains poor, with survival rates of <30% [9]. Several studies have aimed to identify risk factors to determine the prognosis of these patients. Increased serum LDH levels and CNS involvement are considered factors associated with a poor prognosis [10]. For these groups of patients, multiple strategies have been proposed and new therapies are being investigated [1].

The aim of our study was to investigate the clinical characteristics and treatment outcomes of children and adolescents with mature B-cell lymphoma at a single center.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the clinical records of 82 pediatric patients with aggressive mature B-cell lymphomas (BL, DLBCL, or HGBL-NOS) who were diagnosed and treated at Asan Medical Center Children’s Hospital between March 1993 and March 2020.

The diagnosis was made on the basis of tissue biopsy and

cerebrospinal fluid (CSF) or effusion analysis and classified according to the World Health Organization (WHO) classification of lymphoid neoplasms [2]. Disease staging was performed according to the St. Jude staging system [11], which includes physical examination, peripheral blood smear examination, bone marrow (BM) biopsy, CSF analysis, serum LDH level measurement, computed tomography (CT) or magnetic resonance imaging, and positron emission tomography (PET). BM involvement was defined as the presence of tumor cells on a BM smear. CNS involvement was confirmed in the presence of at least one of the following: any lymphoma cells identified with CSF cytology, intracranial or parameningeal lesions on imaging evaluations, cranial nerve palsy, or clinical spinal cord compression. We also assessed the FAB/LMB risk groups according to protocol-defined classifications [12]. This study was approved by the Institutional Review Board of Asan Medical Center (approval no. S2021-2179).

Table 1. Characteristics of the patients.

Characteristics	N=82 (%)
Age at diagnosis, median (range, yr)	7.8 (1.3–16.4)
Sex	
Male	65 (79)
Female	17 (21)
Primary site	
Abdomen	43 (52.4)
Head and neck, except skin and nodes	17 (20.7)
Peripheral lymph nodes	11 (13.4)
Thorax	5 (6.1)
Others	4 (5)
Central nervous system	2 (2.4)
Pathologic subtype	
Burkitt lymphoma	50 (61.0)
Diffuse large B-cell lymphoma	29 (35.4)
High-grade B-cell lymphoma, not otherwise specified	3 (3.6)
BM involvement	
Yes	14 (17)
No	68 (83)
CNS involvement	
Yes	8 (9.8)
No	74 (90.2)
Stage	
I	4 (4.9)
II	26 (31.7)
III	30 (36.6)
IV	22 (26.8)
Chemotherapy protocol and group	
LMB89/LMB96	68 (82.9)
Group A	6 (8.8)
Group B	35 (51.5)
Group C	27 (39.7)
POG-9219/9315/9317	9 (11.0)
D-COMP/COMP	3 (3.7)
R-CHOP/CHOP	2 (2.4)

Abbreviations: BM, bone marrow; CNS, central nervous system.

Statistical analysis

The rates of overall survival (OS) and event-free survival (EFS) were estimated using the Kaplan–Meier method and compared using the log-rank test. OS was defined as the time from the date of diagnosis to the date of death of any cause or the date of the last follow-up visit. EFS was defined as the time from the date of diagnosis to the date of the first relapse, progression, secondary malignancy, death, or the last follow-up visit. All analyses were performed using SPSS (version 27.0, IBM Corp., Armonk, NY, USA), and the threshold for statistical significance was set at $P < 0.05$.

Treatment

The 82 patients were treated using a variety of chemotherapy protocols (Table 1, Fig. 1). From the 1990s to the early 2000s, the initial treatment was as follows: 3 patients received the D-COMP/COMP (daunomycin-cyclophosphamide, doxorubicin, vincristine, and prednisolone) regimens [13]; 3 patients received the Pediatric Oncology Group (POG)-9219 regimen [14]; 3 patients received the POG-9315 regimen [15]; and 3 patients received the POG-9317 regimen [16]. Two patients with DLBCL received the R-CHOP/CHOP

RESULTS

Patient characteristics

The demographic and clinical characteristics of the 82 patients are summarized in Table 1. The median age was 7.8 years (range, 1.3–16.4 yr), with a male predominance (males vs. females, 79% vs. 21%). BL (61.0%) was the most common pathologic subtype, followed by DLBCL (35.4%) and HGBL-NOS (3.6%). According to the St. Jude classification, 4 (4.9%), 26 (31.7%), 30 (36.6%), and 22 (26.8%) patients had stage I, II, III, and IV disease, respectively. At diagnosis, BM involvement was present in 15 patients and CNS involvement was observed in 8 patients. Forty-three patients (52.4%) had primary tumors in the abdomen, whereas 17 patients (20.7%) had primary tumors in the head and neck. Only 4 patients had primary masses in the conjunctiva or bone.

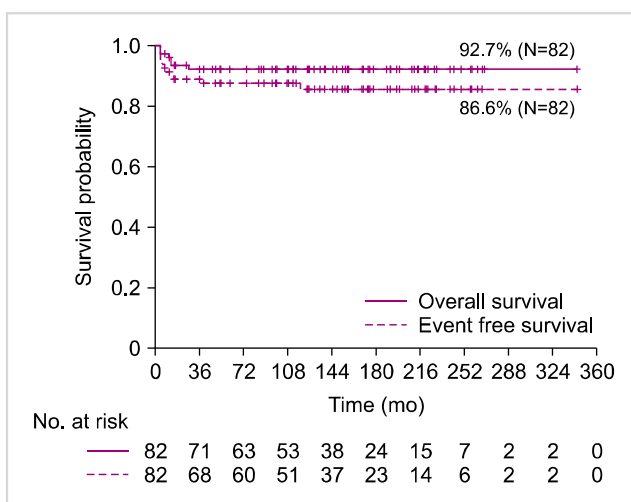


Fig. 2. Survival outcomes of the 82 patients.

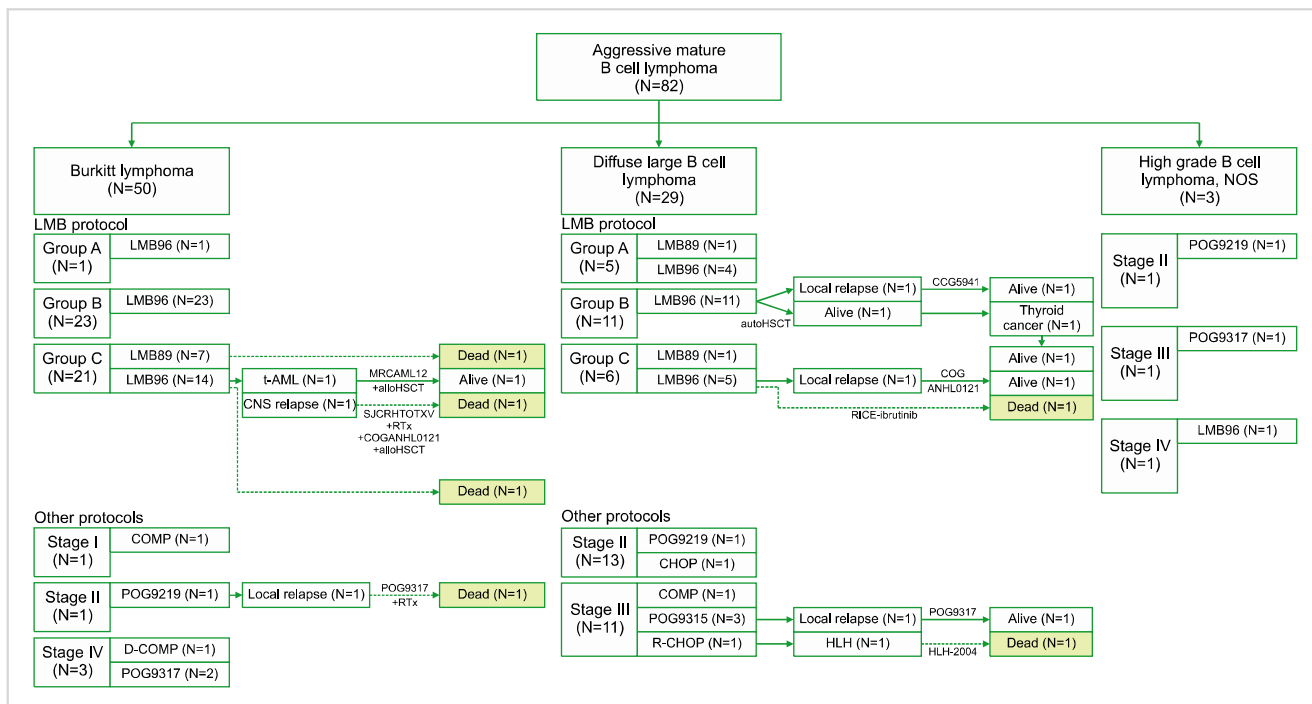


Fig. 1. Events and outcomes according to treatment protocol.

Abbreviations: HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplantation; NOS, not otherwise specified; RTx, radiotherapy; t-AML, therapy-related acute myeloid leukemia.

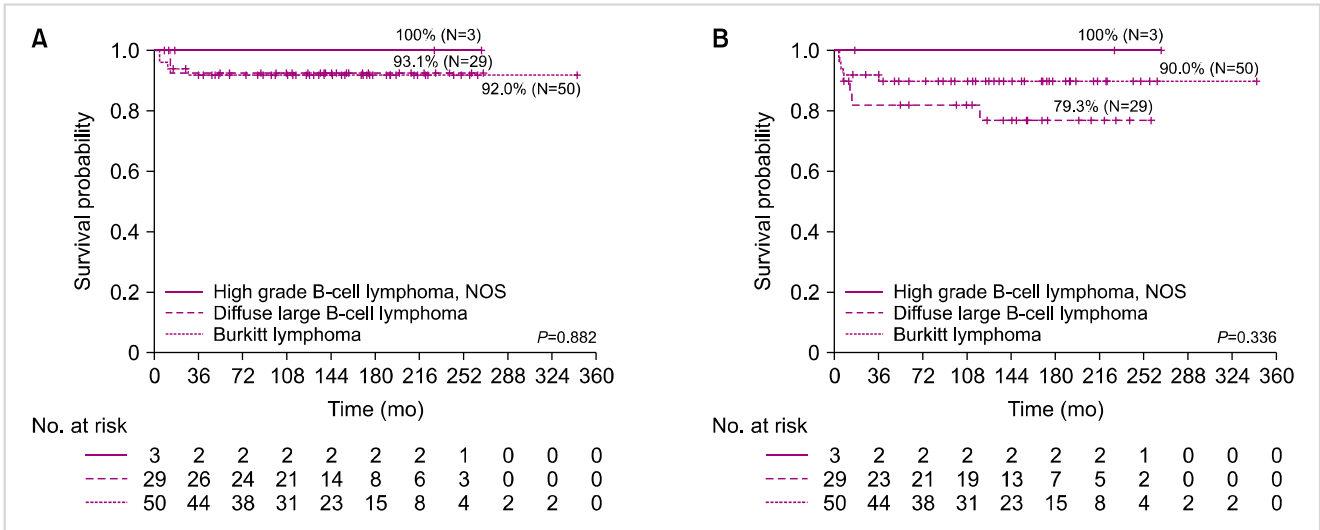


Fig. 3. Treatment outcomes according to histopathologic subtype: overall survival (A) and event-free survival (B) rates. Abbreviation: NOS, not otherwise specified.

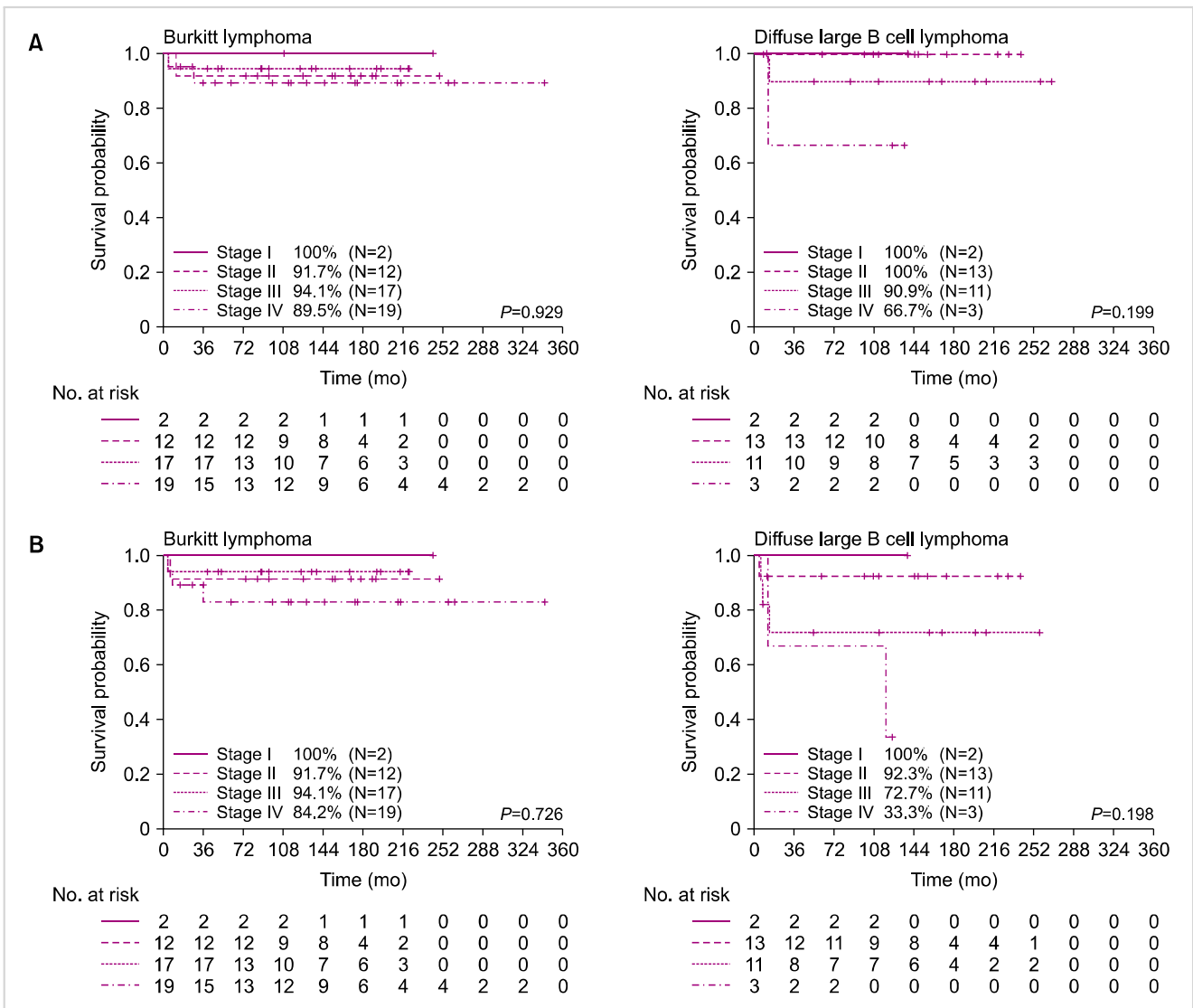


Fig. 4. Overall survival (A) and event-free survival (B) rates of patients with Burkitt lymphoma and diffuse large B-cell lymphoma according to initial stage.

(rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisolone) regimens. After 1998, the LMB backbone protocols (LMB89, FAB/LMB96) [5, 6] have mainly been used. Nine patients received the LMB89 regimen, and 58 patients received the FAB/LMB96 regimen. In 2018, we started using the R-LMB protocol in patients with BL classified as group C [8], and 2 such patients were included in this study.

Survival

As of February 2021, the 5-year OS and EFS rates were 92.5±2.9% and 85.7±4.1%, respectively, with a median follow-up duration of 136.4 months (range, 3.7–344.2 mo; Fig. 2). According to the histopathologic subtypes, the 5-year OS rate was 100% for patients with HGBL, 91.9±3.9% for patients with BL, and 92.6±5.0% for patients with DLBCL. The difference in the 5-year OS among the 3 subtypes was not statistically significant ($P=0.882$) (Fig. 3). The 5-year EFS rate was 100% for patients with HGBL, 89.9±4.3% for patients with BL, and 82.2±7.2% for patients with DLBCL ($P=0.336$). When comparing survival rates according to the initial stage, a tendency for lower OS and EFS was observed in those with advanced disease stages, especially in patients with DLBCL. The OS and EFS rates of patients with stage IV DLBCL were only 66.7% and 33.3%, respectively (Fig. 4). However, no statistically significant difference was found in the overall trends [5-year OS of patients with BL ($P=0.929$) and DLBCL ($P=0.199$); 5-year EFS of patients with BL ($P=0.726$) and DLBCL ($P=0.198$)]. We also investigated the survival rates according to risk groups in patients with BL and DLBCL treated with the LMB protocols (Fig. 5). The 5-year OS of patients in the group C risk group (84.5±7.1%) was significantly poorer than that of patients in groups A and B ($P=0.037$). The 5-year EFS was also low in patients in group C (76.5±8.4%); however, the differences were not statistically significant ($P=0.081$).

According to the initial protocol, no statistically significant

difference was observed in both OS ($P=0.179$) and EFS ($P=0.332$). The 5-year OS rate was 100%, 94.7±3.0%, 88.9±10.5%, 88.9±10.5%, and 50.0±35.4% and the EFS rate was 100%, 89.5±4.1%, 88.9±10.5%, 77.8±13.9%, and 50.0±35.4% in patients treated with the D-COMP/COMP, LMB96, LMB89, POG, and R-CHOP/CHOP regimens, respectively (Fig. 6).

Events

A total of 11 events occurred during the follow-up period (Table 2).

Relapse: Six patients (7.3%) experienced disease relapse at a median of 6.8 months (range, 4.3–13.9 mo) from the initial diagnosis. Of these 6 patients, 2 had stage II disease, 3 had stage III disease, and 1 had stage IV disease at diagnosis. All patients with recurrence were treated with salvage chemotherapy. Three patients with local relapse survived after salvage chemotherapy with CCG-5941, COG-ANHL0121, or POG-9317 (Fig. 1).

Three of the patients who experienced relapse eventually died. A 4-year-old female patient with BL had peritoneal and bone masses with BM involvement. She had CNS relapse after the completion of the initial LMB96 group C regimen. St. Jude Children’s Research Hospital Total Therapy Protocol XV and additional radiotherapy (20 Gy delivered in 10 fractions to the whole body) were administered as rescue treatment; however, the BM lymphoma relapsed [17]. Eventually, the patient died of aggressive disease 16 days after haploidentical hematopoietic stem-cell transplantation (HSCT) with her father as the donor. One male patient with stage II BL had a local relapse on the nasopharynx after the completion of the initial chemotherapy with the POG-9219 protocol. He restarted treatment with the POG-9317 protocol and additional radiation therapy (30 Gy delivered in 15 fractions to the local site); however, he died of respiratory failure due to progressive lymphoma. A 4-year-old female patient

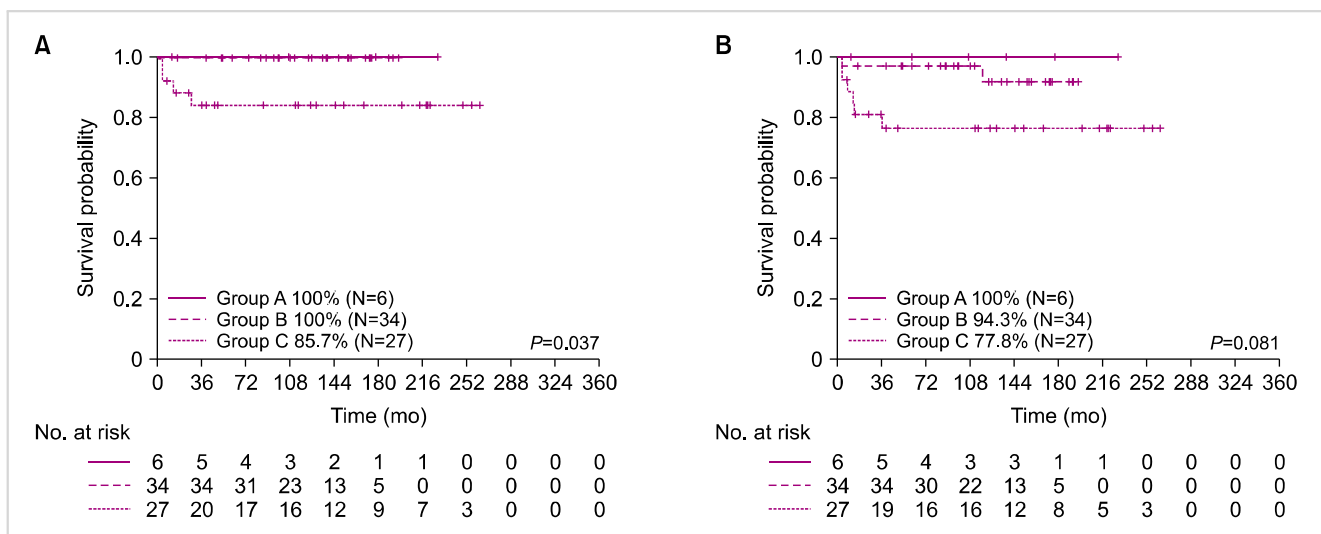


Fig. 5. Survival outcomes of patients with Burkitt lymphoma and diffuse large B-cell lymphoma treated with the LMB protocols according to risk group classification: overall survival (A) and event-free survival (B) rates.

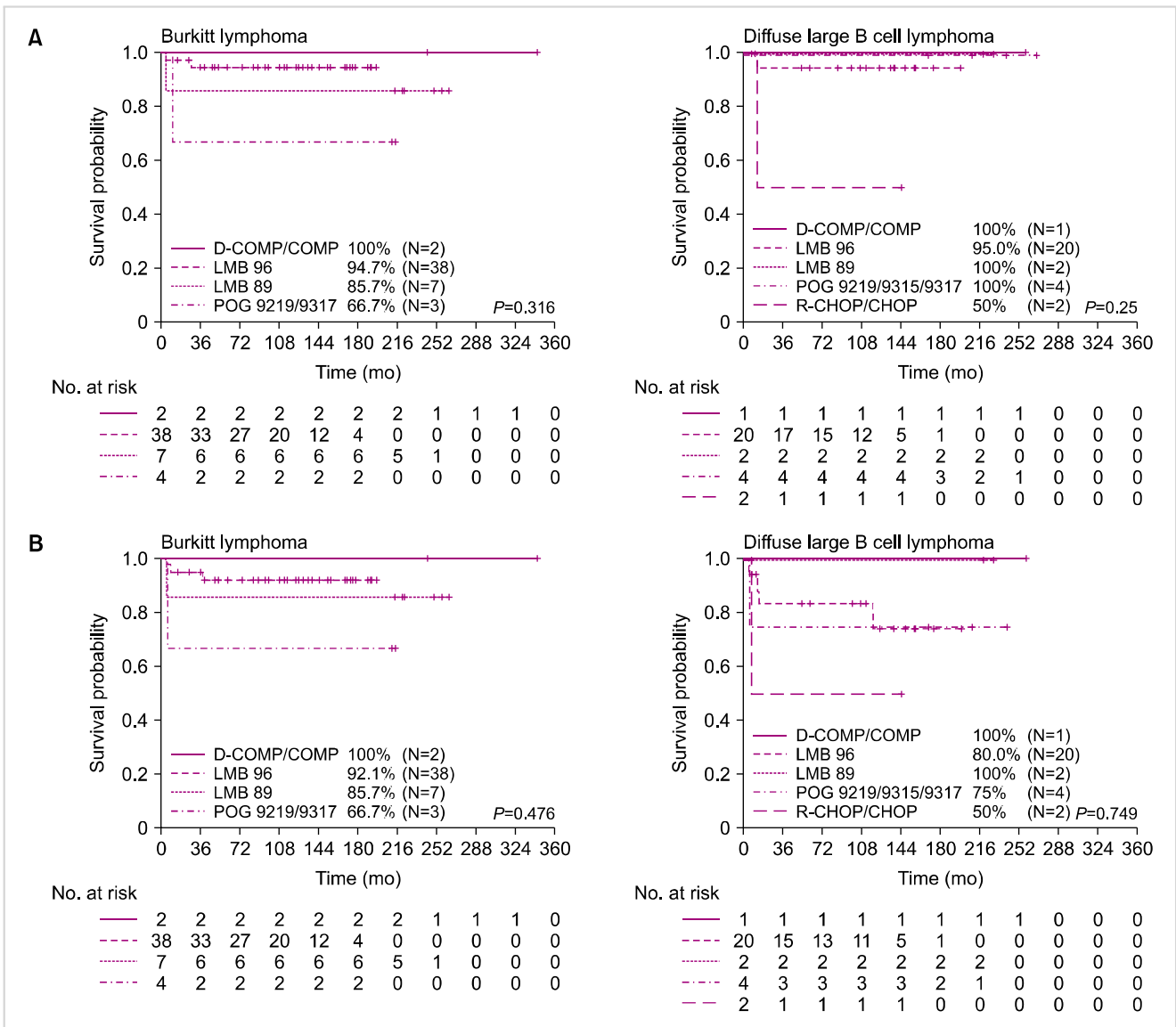


Fig. 6. Survival outcomes of patients with Burkitt lymphoma and diffuse large B-cell lymphoma according to the initial chemotherapy: overall survival (A) and event-free survival (B) rates.

with stage III DLBCL started treatment with the R-CHOP protocol. After 9 cycles of the R-CHOP protocol, she developed fever, abdominal pain, and pancytopenia and was evaluated for relapse. BM biopsy showed evidence of BM involvement of the DLBCL and findings of hemophagocytosis. The patient was newly diagnosed with hemophagocytic lymphohistiocytosis (HLH) because she satisfied >5 of the 8 HLH criteria. She completed therapy with 10 cycles of the R-CHOP protocol followed by the HLH-2004 protocol; however, she eventually died of acute respiratory distress syndrome associated with cytomegalovirus infection during the HLH therapy.

Death: Three patients died without experiencing disease relapse. One patient with stage IV BL died of gastrointestinal tract bleeding due to chemotherapy-induced thrombocytopenia (treatment-related death), and one patient with stage IV DLBCL died of intracranial hemorrhage due to refractory

thrombocytopenia associated with uncontrolled disease. Another patient with stage III BL died of intestinal obstruction during induction.

Secondary malignancy: During the follow-up period, 2 patients were diagnosed with secondary malignancies after the initial treatment. A 12-year-old male patient had an ileocecal mass and underwent surgical resection. He was diagnosed with stage IV BL without CNS involvement. He received the LMB96 group C regimen as chemotherapy and achieved complete remission (CR) without acute complications. At 36 months from the initial diagnosis, BM examination was performed because of fever, recurrent oral ulcers, and thrombocytopenia. The patient was diagnosed with therapy-related acute myeloid leukemia and treated with the Medical Research Council Acute Myeloid Leukemia 12 protocol [18], followed by matched-sibling HSCT. He was still alive 1 year after HSCT, with complications of acute

Table 2. Characteristics of the events.

Event characteristics	
Total events (N of patients)	11
Relapse (N)	6
Local relapse	4
BM relapse	1
CNS relapse	1
Median time to relapse (range, mo)	6.8 (4.3-13.9)
Pathologic subtype	
Burkitt lymphoma	2 (33.3%)
Diffuse large B-cell lymphoma	4 (66.7%)
Stage	
II	2 (33.3%)
III	3 (50.0%)
IV	1 (16.7%)
Salvage regimen	
CTx only	4 (66.7%)
CTx+RTx	1 (16.7%)
CTx+RTx+allo-HSCT	1 (16.7%)
Death after relapse (N)	4
Death of any cause other than relapse (N)	3
Progressive disease	2
Treatment related	1
Median time to death (range, mo)	10.5 (3.7-27.1)
Secondary malignancy (N)	2
Therapy-related acute myeloid leukemia	1
Follicular thyroid carcinoma	1

Abbreviations: BM, bone marrow; CNS, central nervous system; CTx, chemotherapy; HSCT, hematopoietic stem cell transplantation; RTx, radiotherapy.

graft-versus-host disease. He was treated with prednisolone for 1 month, followed by cyclosporine as secondary treatment for 1 year.

Another 12-year-old female patient with DLBCL had multiple masses on the lymph nodes, bones, kidneys, and pancreas at diagnosis. She underwent initial chemotherapy with the LMB96 group B regimen; however, multiple lesions suspicious for residual bone involvement were detected on bone scan and PET-CT after the second cycle of maintenance chemotherapy. For salvage treatment, total body irradiation with cyclophosphamide and etoposide conditioning and autologous HSCT were performed. An endocrinologic evaluation was conducted 9 years after HSCT because of low body mass index and amenorrhea. On thyroid ultrasonography, a mass measuring approximately 3 cm was detected in the left thyroid gland and follicular thyroid carcinoma was finally diagnosed after left hemithyroidectomy. She was still alive 12 years after the initial diagnosis.

Rituximab with LMB chemotherapy

Two patients were treated with the LMB96 protocol added with rituximab as the initial treatment. A 4-year-old male patient with stage IV BL classified as group C had right ophthalmoplegia and facial palsy at diagnosis. He received chemotherapy according to the protocol of Goldman *et al.* [19]. Rituximab (375 mg/m²/dose) was administered on days

-2 and 0 of each of the two induction cycles and on day 0 of each the two consolidation cycles (6 total doses). He achieved CR without chemotherapy-related adverse events and was still alive 19 months after the initial diagnosis.

A 6-year-old female patient with stage IV group C BL had multiple masses in the bone and lymph nodes with BM involvement at diagnosis. She underwent chemotherapy with the LMB96 protocol and received 2 doses of rituximab during the consolidation phase. She also achieved CR and was still alive without complications after 29 months.

DISCUSSION

Mature B-cell lymphoma is a common type of NHL. It presents as a high-grade and aggressive tumor in the pediatric population. Several research groups have conducted various studies on chemotherapy for NHL, and the treatment strategies are complex. The prognosis of pediatric mature B-cell lymphoma has substantially improved over the decades, with good long-term survival. In 2020, the National Comprehensive Cancer Network (NCCN) guidelines for pediatric aggressive mature B-cell lymphomas provided guidance on the pathology and diagnosis, staging, initial treatment, and therapy for relapsed or refractory disease [1]. Our retrospective study reviewed the clinical characteristics of patients, outcomes of various protocols, and treatments of relapsed patients with mature B-cell lymphoma over 28 years at a single institute.

The clinical trials by the LMB, BFM, and CCG/COG groups reported EFS rates of >90% in early-stage disease and 67-79% in advanced-stage disease [3, 6, 12, 20]. In our study, the overall OS and EFS rates in our patients were 92.7% and 86.6%, respectively. Even when compared according to stage, the OS and EFS rates were 96.2% and 93.3% for stage I-II and 90.4% and 82.7% for stage III-IV, respectively. These results were comparable to those of previous studies. However, the treatment outcomes are still poor for advanced BL or DLBCL, and no standard treatment has been suggested for salvage therapy, especially in cases of relapse [21]. In our study, stage IV DLBCL particularly had a very poor outcome even with the LMB group C protocol. The 5-year OS of patients in group C was 85.7%, with a statistically significant difference between patients in group C and those in groups A and B.

For these high-risk patients, rituximab combination therapy has been reported to provide a good outcome. Rituximab is a chimeric murine/human monoclonal antibody with a high affinity against CD20 in B cells. In adults with B-NHL, rituximab has shown efficacy and has become a standard component of care [22]. Goldman *et al.* [19] suggested the safety and improved efficacy of therapy with the addition of rituximab compared with the standard LMB96 protocol in pediatric patients with BL who had BM ($\geq 25\%$ blasts) or CNS involvement. The efficacy of rituximab in high-risk patients classified as group B was also supported by Goldman *et al.* [23]. In this trial, patients with stage III/IV and group B mature B-NHL who received rituximab with the

FAB/LMB96 protocol showed an improvement in the 3-year EFS rate (95% in the R-LMB group), without serious adverse events.

Recently, Minard-Colin *et al.* [8] conducted a randomized trial in 328 patients aged <18 years with high-risk (stage III with an elevated LDH level or stage IV) mature B-NHL to compare the R-LMB protocol with the standard LMB protocol alone. They reported markedly improved 3-year EFS and OS rates of >93% in the R-LMB group. On the basis of these reports, the NCCN guideline recommended rituximab-combined chemotherapy in high-risk patients classified as groups B and C [1]. In our study, 2 patients underwent therapy with the combination of rituximab and the LMB96 protocol, both of whom showed good treatment outcomes without treatment-related complications.

In HGBL, a new separate entity with *MYC*, *BCL2*, or *BCL6* rearrangements, also known as double-hit or triple-hit lymphoma, has been defined in the 2016 revised WHO classification of lymphoid neoplasms [2]. Currently, HGBL with *MYC* and *BCL2* translocations accounts for approximately 10% of all lymphomas and occurs in older patients (median age, 60 yr; range, 6–82 yr) [24]. Although several studies reported such cases as a poor prognostic group in both pediatric and adult patients [25, 26], the recommended treatment for double-hit and triple-hit lymphomas in the pediatric population is similar to that for other high-grade mature B-cell lymphomas. Among 51 patients with available immunohistochemistry or fluorescence *in situ* hybridization data in our study, 6 patients were suspicious for double-hit lymphoma with *MYC* and *BCL6* rearrangements. The survival outcomes in this group could not be analyzed owing to the small number of patients; however, only 1 death occurred, in a 4-year-old patient with stage IV BL treated with the LMB96 regimen who had relapse in the CNS and BM and eventually died of progressive lymphoma. Future extensive studies on the prognosis of double-hit and triple-hit lymphomas in pediatric patients with high-grade mature B-cell lymphoma are needed.

The long-term treatment outcomes in pediatric patients with mature B-cell lymphoma have considerably improved over the recent decades. Particularly, a gradual increase in the EFS rate was achieved by eliminating local and CNS radiotherapy, reducing the total doses of cyclophosphamide and doxorubicin, and, recently, adding rituximab [27]. Nevertheless, treatment-related toxicity and mortality remain important concerns and less toxic treatment modalities are continuously being studied. Cairo *et al.* [12] reported a toxicity-related death rate of 3%, with a high incidence of grade III/IV mucositis, infection, myelosuppression, and prolonged hospitalization during the induction courses. Tumor lysis syndrome (TLS) is also a well-known treatment-related toxicity, especially in BL, due to the high turnover rate of tumor cells. To prevent TLS, vigorous alkaline diuresis needs to be obtained, with furosemide, if necessary, and urate oxidase needs to be administered before the initiation of treatment. BL/B-cell acute lymphoblastic leukemia and LDH levels ≥ 500 U/L were associated with the highest

incidence of TLS among patients with NHL (14.9%) [28]. In patients treated with the LMB89 protocol, the use of urate oxidase reduced mortality due to TLS. In our study, of the total of 50 patients with BL, 15 had TLS (30.0%) and all of them had stage III/IV disease. Among the 11 patients with TLS who underwent continuous renal replacement therapy, no cases of TLS-related death occurred. Conversely, treatment-related mortality occurred in 1 male patient during consolidation chemotherapy. He died of gastrointestinal bleeding caused by myelosuppression-related thrombocytopenia.

Secondary malignancy after the treatment of pediatric NHL is also a concern for long-term treatment outcomes. In the North American Childhood Cancer Survivor Study cohort, 229 secondary malignant neoplasms (SMNs) occurred among 206 survivors treated with chemotherapy alone after a childhood cancer diagnosis [29]. The survivors had a 1.9-fold, 4.6-fold, and 3.8-fold increased standardized incidence ratio of subsequent leukemia/lymphoma, breast cancer, and thyroid cancer, respectively. Recently, Ehrhardt *et al.* [30] reported the occurrence of SMNs in children and adolescents with NHL by investigating a total of 570 survivors over 5 years after the initial diagnosis. None of the 126 survivors treated with the contemporary LMB protocol between 1987 and 1999 developed SMNs. However, patients treated with non-LMB protocols had an SMN incidence rate of 2.2 per 1,000 person-years (5,871 total person-years). Two cases of SMN were observed in our study: therapy-related acute myeloid leukemia and thyroid cancer. These were successfully treated with allogeneic HSCT and surgery.

Our study had several limitations. First, it was a retrospective study with a small sample of patients recruited from a single center. Second, as the criteria for selecting the treatment strategy have changed over the last 25 years, various treatment regimens were applied with different indications. Therefore, the number of patients significantly differed among the different treatment protocols, making it difficult to compare the treatment outcomes. In addition, detailed data on treatment-related toxicities for each chemotherapy regimen were not available.

In summary, this study revealed favorable treatment outcomes in children and adolescents with aggressive mature B-cell lymphoma despite the long study period (>25 yr). However, further studies are needed to improve the survival rate of patients with advanced-stage disease or disease relapse. Targeted therapies such as rituximab are expected to become more widely used to improve the outcomes of high-risk patients. In addition to efforts to improve the survival rates, careful monitoring for acute toxicity or secondary malignancy due to intensive multidrug chemotherapy is required. The development of guidelines for the follow-up observation of these patients may help in monitoring chemotherapy-related complications.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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