Treatment outcome in children with central nervous system-positive Burkitt lymphoma using only intrathecal and systemic chemotherapy combined with rituximab

Shuang Huang1, Lin Jin1, Jing Yang1, Yan-Long Duan1, Meng Zhang1, Chun-Ju Zhou2, Yong-Hong Zhang1
1Beijing Key Laboratory of Pediatric Haematology Oncology, National Discipline of Pediatrics, Ministry of Education, MOE Key Laboratory of Major Diseases in Children, Haematology Oncology Center, Beijing Children’s Hospital, Beijing 100045, China; 2Pathology Department, Beijing Children’s Hospital, Capital Medical University, National Center for Children’s Health, Beijing 100045, China.

Abstract
Background: With current chemotherapy treatment, >90% of survival has been obtained for Burkitt lymphoma (BL). In this study, the demographic characteristics and treatment outcomes are presented for 78 children in China with central nervous system-positive (CNS+) BL.

Methods: This retrospective study consecutively enrolled 78 CNS+ BL patients in Beijing Children’s Hospital (BCH) from 2007 to 2019 who received the BCH B-cell non-Hodgkin’s lymphoma regimen (modified by French-American-British mature lymphoma B-cell 96 [FAB/LMB96] C1 arm ± rituximab). Clinical characteristics, methods of disease detection in the CNS, and outcomes were evaluated. Univariate and multivariate analyses were used to assess prognostic factors.

Results: The median age of 65 boys and 13 girls at the time of diagnosis was 5.7 years (ranging from 1 to 14 years). Patients were followed up for a median time of 34 months (ranging from 1 to 72 months). Bone marrow invasion was found in 38 (48.7%) patients. There were 48 (61.5%), 44 (56.4%), and 25 (32%) patients with cranial nerve palsy, intracerebral mass (ICM), and parameningeal extension, respectively. Abnormal cerebrospinal fluid (CSF) morphology and CSF immunophenotype appeared in 15 (19.2%) and 15 (19.2%) patients, respectively. There were 69 (88.5%) patients treated with chemotherapy combined with rituximab, and nine patients were treated solely with chemotherapy. Finally, five patients died of treatment-related infection, recurrence occurred for 13, and one developed a second tumor. The 3-year overall survival and event-free survival rates were 78.9% ± 4.7% and 71.4% ± 6.0%, respectively. Treatment with chemotherapy only, ICM positivity, and >4 organs involved at diagnosis were independent risk factors.

Conclusions: Rituximab combined with a modified LMB96 regimen has greatly increased the efficacy of treatment for Chinese children with CNS+ BL, and with the continuous collection of outcome data, treatment-related complications are decreasing. For further verification, a large sample multicentre randomized controlled study should be performed to explore a treatment scheme for Chinese children with even greater efficacy.

Keywords: Burkitt lymphoma; Central nervous system disease; Rituximab; Treatment outcome

Introduction
Burkitt lymphoma (BL) is a cancer of the lymphatic system and is the most common subtype of pediatric non-Hodgkin lymphoma (NHL), accounting for nearly 40% of cases.1–3 Using the standard chemotherapy regimens currently available, combined with rituximab, the 5-year overall survival (OS) rate is nearly 90%.4–6 Approximately one in four children and adolescents with BL in the high-risk group present with central nervous system (CNS) disease and poor prognosis.7,8 The international French-American-British mature lymphoma B-cell 96 (FAB/LMB96) cooperative group trial previously demonstrated that CNS+ B-NHL patients treated with systemic chemotherapy and intrathecal (IT) therapies exhibited similar event-free survival (EFS) (with a 4-year EFS of 84.1% under the FAB/LMB96, C1 arm regimen) and OS when treated with CNS radiotherapy consisting of the LMB89 protocol (with a 4-year EFS of 79% for CNS+ BL).7,8 The LMB96 regimen was improved based on the LMB89 regimen: cranio-cerebral radiotherapy was not administered to CNS+ patients, and the methotrexate (MTX) dosage was increased from 5 to 8 g/m² in the
LMB96 regimen to strengthen the treatment for CNS disease (the total dosage of MTX in the LMB89 regimen was 20 g/m², while that of scheme LMB96 was 32 g/m²).

Our department used the modified LMB96 regimen (non-randomized and with standard intensity arms) combined with rituximab for mature B-cell NHL and obtained successful results for all risk groups. Lymphoma had been treated in our hospital since 2003. Due to lack of clinical experience in the early treatment process at our center, serious treatment complications occurred in some patients, including tumor lysis syndrome and severe infection, which led to chemotherapy delay and ultimately affected the long-term prognosis of patients. In our previous report, we found that tumor lysis syndrome and delayed chemotherapy indicated a poor prognosis for BL patients. Since then, we began to use oxalic acid for patients with bulky disease at the initiation of chemotherapy to reduce the occurrence of tumor lysis syndrome and the risk of transferring to the intensive care unit, to improve the long-term prognosis of patients. In the study using the LMB96 regimen, it was estimated that the craniocerebral radiotherapy treatment reduced the side effects caused by radiotherapy, and the MTX dosage was also increased to achieve effective and feasible treatment of the CNS. In our study, we used an LMB96 regimen combined with rituximab for CNS+ BL patients, which also greatly improved the prognosis of patients. In this study, the cytogenetic analysis, outcome of patients with CNS+ BL treated under the Beijing Children’s Hospital non-Hodgkin lymphoma (Beijing Children’s Hospital B-cell non-Hodgkin lymphoma (BCH B-cell NHL) regimen (Group C-CNS+) are presented.

**Methods**

**Ethical approval**

This study was approved by the Ethical Committee of the BCH (No. IEC-C-006-A03-V.05). Written informed consent was obtained from guardians who enrolled in this study.

**Patient selection**

Through the case system in our hospital, the clinical data for all cases were collected, including age, sex, involvement, stage, and treatment group. The enrolled patients were followed up by telephone, and the date of admission and diagnosis were taken as the start point of follow-up, which was recorded monthly. The reasons for discontinuation were death and follow-up to January 31, 2020. Inclusion criteria: From January 2007 to December 2019, newly diagnosed patients with CNS+ BL who were treated with the BCH-B-NHL regimen (Group C-CNS+) were enrolled in this study. Exclusion criteria: Children who were transferred to our hospital after treatment at other hospitals, or unable to regularly receive and complete chemotherapy during treatment due to various reasons. Patient medical records were retrospectively evaluated. In our study period, there were 92 newly diagnosed patients, of whom 14 patients were excluded from our study (eight children were transferred from other hospitals after treatment, three patients quit treatment due to economic reasons, and three patients died because of progressive disease (PD) and did not start chemotherapy). Thus, 78 patients were enrolled in this study, and chemotherapy combined with rituximab was administered to 69 patients (88.4%).

**Pathology**

All patients underwent biopsies from the tumor site or bone marrow (BM), and a histopathology diagnosis was determined by the Revised European-American Lymphoma classification. A central pathology review of morphological, immunophenotypical, and genetic data from the original diagnostic biopsy were performed. Fluorescence in situ hybridization (FISH) analysis for MYC gene rearrangement was performed on all the specimens submitted for cytogenetic analysis. A dual-color MYC immunoglobulin heavy-chain translocation probe, designed to detect t (8;14) (q24.1;q32), or a dual-color MYC break-apart probe, designed to detect rearrangements of the MYC gene region at 8q24.1 with various partner chromosomes, was used.

**Stage and group**

The staging was performed using the International Pediatric Non-Hodgkin Lymphoma Staging System, and it was determined that all cases were stage IV and Group C (CNS+). The conditions that defined CNS positivity were CNS-positive/mass, CNS-positive/palsy, and CNS-positive/blasts. For cerebrospinal fluid (CSF) status, positivity was based on lymphoma cell evidence. CSFm: CSF positivity by morphology; CSFi: CSF positivity by immunophenotype methods; CSFm: CSF positivity by cytogenetic or FISH analysis; CSFmol: CSF positivity by molecular techniques.

**Treatment**

The systemic and IT chemotherapy backbone for BCH-B-NHL Group C consisted of the (CNS+) regimen, which was modified by the FAB/LMB96 study C1 arm combined with rituximab (375 mg/m² × 6 times), no CNS irradiation, and administration of oxalic acid for a high level of uric acid and/or bulky disease patients. The total dosage of MTX was 29 g/m², combined with a triple intrathecal (ITT) dose of (MTX 15 mg, dexamethasone 4 mg, cytosine arabinoside 30 mg) × 11 times. We empirically reduced the doxorubicin infusion time to 6 h [Table 1]. For patients with suspected residual lesions, biopsy or positron emission tomography (PET-CT) was performed. If positive, autologous stem cell transplant was performed after sequential chemotherapy.

**Evaluation**

Before beginning chemotherapy, all patients were evaluated through blood tests, BM biopsy smear, biopsy pathology (immunohistochemical, immune classification, fusion gene, and chromosome karyotype analysis), CSF examination (routine, biochemical and smear, and immune type), and imaging examination to determine the clinical stage and risk stratification. Three evaluations were conducted during the
treatment process: (i) early evaluation: the tumor lesion size was measured by imaging examination on day 7 of COP (cyclophosphamide + vincristine + prednisone) regimen chemotherapy; (ii) interim assessment: was conducted after four courses of treatment, including BM and CSF minimal residual disease detection, and additionally, biopsy or positron emission tomography/PET-CT was performed for patients with suspected residual lesions; (iii) late evaluation: was performed after six courses of treatment, and the evaluation content was similar to the interim evaluation, with a focus on the inspection of the interim evaluation of problems. Imaging, BM, and CSF examinations were performed.

Evaluation criteria\textsuperscript{[10]}: complete remission (CR): tumor completely disappeared; partial remission: tumor shrank by >50%, but not CR; stable disease: tumor size decreased by <50% or increased by no >25%; PD: tumor enlargement of >25%; recurrence (R): new lesions appeared again after the disease had reached CR.

Follow-up

Seventy-eight children were included in this study: 59 patients with no-event survival had been contacted by telephone with their parents and were confirmed to be alive. One patient experienced complications of a second tumor after treatment withdrawal and remained in the transplantation ward of our hospital. One patient with late progressed disease underwent secondary remission, and after contacting their parents by telephone, the patient was confirmed to be alive. Two patients with early recurrence were still alive for further treatment. Among the 15 death cases, five patients died of infection (two patients died in our center, and three patients died in the pediatric intensive care unit of our hospital), which can be confirmed in the case system. The other ten patients died of primary disease progression, and all declined to participate in further treatment at the end of the period and left the hospital in a state of survival. They died within 1 week to 2 months after discharge, and all deaths were confirmed by telephone.

For the 59 remission patients, after chemotherapy, the children were followed up regularly in the outpatient department. The patients were followed up every 3 months in the first 2 years and every 6 months in the following 2 to 5 years. Blood routine examination, organ function, and imaging of the tumor site were monitored at each reexamination. The patients were followed up until January 31, 2020.

Prognostic factors

In this study, multiple factors were compared before chemotherapy to detect possible prognostic factors in the CNS-positive group of pediatric BL. The factors include the difference in CNS disease manifestation, bulky diseases, >4 organs involved, and lactate dehydrogenase (LDH) level > 1000 U/L.

Statistical analysis

SPSS software version 23.0 (IBM SPSS Statistics; IBM Corp, Armonk, NY, USA) statistical software was used to analyze the data. The quantitative data consistent with normal distribution are expressed as the mean ± standard deviation, and the comparison between groups was performed by t-test. The quantitative data that did not conform to the normal distribution were represented by the median, and the Wilcoxon rank-sum test was used for comparison between groups. Survival analysis was carried out by the Kaplan-Meier method. Cox regression was used to screen for risk factors. $P < 0.05$ was considered statistically significant.

| Parameters | Dosage (mg/m\textsuperscript{2}) | Time (days) |
|------------|----------------------------------|------------|
| COP        |                                  |            |
| CTX        | 300                              | 1          |
| VCR        | 2                                | 1          |
| Pred       | 60                               | 1–7        |
| TIT        | MTX+Dex+Ara-C                    | 1, 3, 5    |
| COPADM1    |                                  |            |
| VCR        | 2                                | 1          |
| HD-MTX     | 5000                             | 1, 4 h     |
| CF         | 15                               | 2–4 (MTX 24 h) |
| DNR        | 30                               | 2–3, 6 h   |
| CTX        | 500                              | 2, 3, 4 (Q 12 h) |
| Pred       | 60                               | 1–5        |
| TIT        | MTX+Dex+Ara-C                    | 2, 4, 6    |
| COPADM2 (same as COPADM1, only except) | | |
| HD-MTX     | 8000                             | 1, 4 h     |
| CTX        | 1000                             | 2, 3, 4 (Q 12 h) |
| CYVE1/CYVE2 |                                  |            |
| Ara-C      | 50                               | 1–5 (8 pm–8 am) |
| HD- Ara-C  | 3000                             | 2–5 (8 am–11 pm) |
| VP16       | 100                              | 2–5 (2 pm–4 pm) |
| HD-MTX     | 8000                             | Day 18–25 after CYVE1 only |
| TIT        | MTX+Dex+Ara-C                    | 24 h after HD-MTX |
| M1 (same as COPADM2, only except) | | |
| HD-MTX     | 8000                             | 1          |
| CTX        | 1000                             | 2, 3 (Q12 h) |
| ADR        | 60                               | 2, 3, 6 h  |
| TIT        | MTX+Dex+Ara-C                    | 2          |
| M3         |                                  |            |
| VCR        | 2                                | 1          |
| ADR        | 30                               | 1, 2       |
| CTX        | 500                              | 1, 2       |
| Pred       | 60                               | 1–5        |
| M2 and M4  |                                  |            |
| VP16       | 150                              | 1–3        |
| Ara-C      | 100                              | 1–5        |
The endpoint for the outcome and survival analysis was chosen from the time of diagnosis to the time of December 31, 2019, or at the time of relapse/progression of the disease, death from any cause, or the last contact time for EFS, and death from any cause or the last contact time for OS. EFS and OS were estimated using the Kaplan-Meier method, and the log-rank test was used for comparison.

**Results**

There were 404 newly diagnosed BL patients enrolled from January 2007 to December 2019 at BCH, and 78 (19.3%) patients were CNS+ and were enrolled in this study. The baseline characteristics of 78 CNS+ patients were 65 boys and 13 girls with an average age of 5.7 years (ranging from 1 to 14 years). Before chemotherapy, 32 cases had the bulky disease (tumor diameter >10 cm), 54 cases of patients had ≥4 organs involvement, 45 cases exhibited an LDH level >1000 U/L, and 38 cases had BM involvement. Chemotherapy combined with rituximab was administered to 69 (88.4%) patients, and nine (11.5%) patients received chemotherapy only.

There were 48 (61.5%), 44 (56.4%), and 25 (32%) patients with cranial nerve palsy (CNP), intracerebral mass (ICM), and para-meningeal extension (PME), respectively. Abnormalities in CSF morphology (CSFm) and CSF immunophenotype (CSFi) were detected in 15 (19.2%) and 15 (19.2%) patients, respectively. There were 27 (34.6%) patients who underwent a CSFi test, and since 2017, 15 patients have tested positive. There were 30 CSF-positive cases and 48 CSF-negative cases. In the 30 CSF-positive cases, five cases were simple CSF+, three cases were CNP+, 11 cases were ICM/PME+, and 11 cases were ICM/PME+ combined with CNP+. In the 48 CSF-negative cases, five cases were CNP+, 20 cases were ICM/PME+, and 23 cases were CNP+ combined with ICM/PME+.

Patients were followed up for a median time of 34 months (ranging from 1 to 72 months). After a COP course, 77 (98.7%) patients were sensitive, six patients exhibited residual disease after CYVE1, five (6.4%) patients died of treatment-related infection, and 12 (15.4%) patients suffered an early relapse after the end of treatment and died from refractory disease; consisting of six (7.7%) patients who were CNS relapsed, six (7.7%) patients who were non-CNS relapsed, and one (1.3%) patient who suffered a late relapse (non-CNS relapsed) and underwent a CR2 (completely remission [CR]) after salvage chemotherapy treatment. A second tumor (acute myeloid leukemia) developed in 1 (6.5%) patient at 6 months after cessation of treatment [Figure 1]. The 3-year OS and EFS rates were 78.9% ± 4.7% and 71.4% ± 6%, respectively.

The prognostic factors for patients with CNS+ BL are summarized in Table 2. In univariate analysis, the independent risk factors for EFS were chemotherapy treatment only, the involvement of ≥4 organs, leukemia stage, and ICM. Other factors did not significantly affect the outcome. In the multivariable analysis, there was no risk factor for EFS.

**Discussion**

Burkitt lymphoma (BL) is the most common NHL in children, representing 40% to 50% of pediatric NHL.[1,2] BL is frequently advanced, involving the BM, CNS, or both, and it requires aggressive therapy. BL is also the most frequently CNS+ pediatric NHL (9%–13%), which is a

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**Figure 1:** Treatment outcome of 78 CNS+ BL patients treated at Beijing Children’s Hospital. AML: Acute myeloid leukemia; BL: Burkitt lymphoma; Chemo: Chemotherapy; CNS+: Central nervous system positive; CR: Completely remission; HSCT: Hematologic stem cell transplant; PD: Progressed disease; PR: Partial remission; R: Rituximab; TIT: Triple intrathecal.
poor prognostic factor in BL patients[2-5]. The previous cases of BL (all stages) from our center showed that the age of onset was approximately 5 years, the male to female ratio was 5.9:1, and 61.8% of the primary tumors were located in the abdominal cavity. The proportion of children with stages III and IV was 93.6%. There were 65 (83.3%) patients (38.4%) patients who were CSF-positive, and 48 (61.5%) patients who were CSF-negative in our study (35.6%) reported from Cario[13]. The present study showed that there were 65 (83.3%) patients (35.6%) reported from Cario[13] who were ICM/PME-positive, which was the most common variant of the CNS-positive subtype in this study. Successful treatment results were obtained in this study, and although our survival rate was lower than that in western countries (analysis reason: it may be related to the high infection mortality caused by insufficient experience in early treatment, or different ethnic heterogeneity, which need to be further confirmed by a large amount of data analysis), the therapeutic effect had been greatly improved compared with the previous treatment. In our study, we used a total of 29 g/m² dosage of MTX (5 g/m² in the first COPADM, to avoid severe infection and mucositis) and a total of 11 TIT doses, and the results obtained were six CNS-relapsed patients (7.69%), seven non-CNS-relapsed patients (8.9%), and five patients who died of infection (6.4%). The 3-year OS and EFS rates were 78.9% ± 4.7% and 71.4% ± 6%, respectively. Treatment with chemotherapy only and ≥4 involved organs at the time of diagnosis were independent risk factors in EFS.

Our modified FAB/LMB96 regimen combined with rituximab for newly diagnosed CNS+ BL resulted in a CNS+ rate that was nearly 19% in our study (vs. 9%-13% from the FAB/LMB96 C1 arm and ANHL01P1 Group C reported)[8,13,14] BM involvement rates were 54.2% in our study (vs. 52.5% and 40.7% from the FAB/LMB96 C1 arm and ANHL01P1 Group C reported)[8,13]. There were 30 (38.4%) patients who were CSF-positive, and 48 (61.5%) patients who were CSF-negative in our study (vs. 54.2% reported from Cario). The present study showed that there were 65 (83.3%) patients (vs. 35.6% reported from Cario[13]) who were ICM/PME-positive, which was the most common variant of the CNS-positive subtype in this study. Successful treatment results were obtained in this study, and although our survival rate was lower than that in western countries (analysis reason: it may be related to the high infection mortality caused by insufficient experience in early treatment, or different ethnic heterogeneity, which need to be further confirmed by a large amount of data analysis), the therapeutic effect had been greatly improved compared with the previous treatment. In our study, we used a total of 29 g/m² dosage of MTX (5 g/m² in the first COPADM, to avoid severe infection and mucositis) and a total of 11 TIT doses, and the results obtained were six CNS-relapsed patients (7.69%), seven non-CNS-relapsed patients (8.9%), and five patients who died of infection (6.4%). The 3-year OS and EFS rates were 78.9% ± 4.7% and 71.4% ± 6%, respectively. Treatment with chemotherapy only and ≥4 involved organs at the time of diagnosis were independent risk factors in EFS.

Table 2: Prognostic factors for 78 CNS+ BL patients in Beijing Children’s Hospital.

| Prognostic factor (n/N) | 3-year EFS value (%) | Univariable P value | HR (95% CI) | P value |
|------------------------|----------------------|---------------------|-------------|---------|
| Treatment              |                      |                     |             |         |
| R+ chemo (14/69)       | 76.1 ± 0.06          | 0.002               | 0.567 (0.110–1.020) | 0.054   |
| Chemo only (6/9)       | 33.3 ± 0.15          |                     |             |         |
| Bulky disease          |                      |                     |             |         |
| Yes (10/33)            | 68.5 ± 0.08          | 0.290               |             |         |
| No (10/45)             | 74.3 ± 0.07          |                     |             |         |
| ≥4 organs involved     |                      |                     |             |         |
| Yes (18/55)            | 63.9 ± 0.07          | 0.035               | 0.781 (0.197–2.739) | 0.197   |
| No (2/23)              | 91.3 ± 0.05          |                     |             |         |
| LDH ≥1000 U/L          |                      |                     |             |         |
| Yes (13/44)            | 69.3 ± 0.07          | 0.290               |             |         |
| No (7/34)              | 75.5 ± 0.08          |                     |             |         |
| CNP                    |                      |                     |             |         |
| Yes (14/48)            | 65.4 ± 0.09          | 0.430               |             |         |
| No (6/30)              | 79.5 ± 0.07          |                     |             |         |
| CNS tumor mass         |                      |                     |             |         |
| Negative (3/13)        | 75.5 ± 0.12          | 0.037               | 0.368 (0.366–1.548) | 0.440   |
| ICM (16/44)            | 59.6 ± 0.08          |                     |             |         |
| PME (1/21)             | 95.2 ± 0.04          |                     |             |         |
| CSF status             |                      |                     |             |         |
| Negative (12/49)       | 72.1 ± 0.07          | 0.700               |             |         |
| CSFi+ (5/14)           | 64.3 ± 0.12          |                     |             |         |
| CSFi+ (3/15)           | 78.6 ± 0.11          |                     |             |         |

The data are presented as mean ± standard deviation, ±: Positive; BL: Burkitt lymphoma; Chemo: Chemotherapy; CI: Confidence interval; CNP: Cranial nerve palsy; CNS: Central nervous system; CNS+: Central nervous system-positive; CSF: Cerebrospinal fluid; EFS: Event-free survival; HR: Hazard ratio; i: Immunophenotype; ICM: Intracerebral mass; LDH: Lactate dehydrogenase; m: Morphology; PME: Para-meningeal extension; R: Rituximab.
certain statistical significance, in our study, we included large sample size, a long follow-up time, and clear statistical significance, and it is a rare report on Chinese CNS+ BL children receiving standardized chemotherapy combined with antibody therapy, which is of great clinical significance.

There are also some limitations to this research. The chemotherapy regimen used in this study is from the LMB collaboration group. However, in this study, rituximab was added based on chemotherapy, and no further randomized controlled studies were conducted. In addition, five patients died of treatment complications in the early stage of this study, which made the OS of this group lower than that reported in the literature. It is anticipated that in the near future, we can find a more suitable chemotherapy scheme for Chinese children that will minimize the side effects of chemotherapy and also minimize the death related to treatment.

We conclude that rituximab combined with a modified LMB96 regimen has greatly improved the efficacy of treatment for Chinese children with CNS+ BL, and as we continuously gain experience regarding treatment administration, there has been a decrease in treatment-related complications. For further verification, a large sample multicentre randomized controlled study should be performed to explore a treatment scheme for Chinese children with even greater efficacy.

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**Conflicts of interest**

None.

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