

Clinical Study Protocol

Phase II Clinical Trial for Newly Diagnosed Children and Adolescents with Localized Lymphoblastic Lymphoma (Japanese Leukemia/Lymphoma Study Group Trial LLB-NHL03): Study Protocol for Nationwide Multicenter Trial

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Pediatric patients with lymphoblastic lymphoma are generally treated using the Berlin-Frankfurt-Munster (BFM) 90 protocol, which is the standard treatment strategy for pediatric acute lymphoblastic leukemia, and have a favorable outcome. However, this intense regimen includes high total doses of anthracycline and alkylating agents, and is known to cause late complications. We therefore planned a clinical trial to examine the efficacy and safety of a modified BFM regimen. We expect that this phase II, nationwide multicenter trial will help to establish an effective and safer standard therapy for stage I/II pediatric lymphoblastic lymphoma.

Key words: pediatrics, limited stage, lymphoblastic lymphoma, efficacy, safety

Pediatric lymphoblastic lymphoma (LBL) consists of precursor B-cell and precursor T-cell LBL. Pediatric patients with LBL are usually treated using the standard treatment strategy for pediatric acute lymphoblastic leukemia (ALL), since the two diseases are biologically similar; children treated with this approach have a favorable outcome [1-3]. The exact same protocol [1-4] is used for both conditions — namely, chemotherapy consisting mainly of prednisolone, vincristine, and L-asparaginase. The protocol involves a 4-week remission-induction phase with an anthracycline drug and an alkylating agent. Drugs not used for remission-induction are then added to an early intensive phase.

After a central nervous system (CNS) prophylaxis phase (high-dose methotrexate 3×3 g/m²), patients are transitioned to a maintenance phase. The therapeutic regimen adopted for the current trial uses this ALL-type basic framework.

Although the standard treatment described above is generally used for pediatric patients with localized LBL, the optimum treatment remains to be determined due to the small number of patients. Nonetheless, it is apparent that adequate therapy for patients with stage I/II pediatric LBL is an ALL-type therapy with a certain level of therapeutic intensity lower than that required for stage III/IV disease. In previous clinical trials [1, 5], patients with limited stage LBL have received treatment

of the same intensity as patients with advanced stage LBL. It is presumed that the intensity of chemotherapy for limited stage LBL can be attenuated, since event-free survival was obtained in all cases of limited stage LBL in the literature.

Although the Berlin-Frankfurt-Munster (BFM) 90 protocol [5] has been considered as a standard therapy, it has a number of problems when treating patients with stage I/II pediatric LBL. Specifically, even though the protocol achieves a good prognosis for children with limited stage disease, the regimen is too intense and the cumulative doses of both anthracycline and alkylating agents — known to cause late complications — are high. To resolve these problems, we planned a clinical trial to examine the efficacy and safety of a modified BFM regimen.

Endpoints

Primary endpoint. The primary outcome is the 3-year event-free survival (EFS) rate.

Secondary endpoints. The secondary endpoints are (1) occurrence rates of adverse events of grade 3 or higher, according to the National Cancer Institute's Common Toxicity Criteria; and (2) the 3-year overall survival rate.

Eligibility Criteria

Inclusion criteria. The inclusion criteria for the trial are as follows. (1) Newly diagnosed with stage I/II non-Hodgkin's lymphoma — either precursor T-cell LBL or precursor B-cell LBL — based on the World Health Organization's categorization [6]; (2) Younger than 18 years old at the time of diagnosis; (3) Untreated at the time of trial registration; (4) Able to be followed up for at least 3 years after initiating therapy; (5) Provision of written informed consent to participate in the trial, obtained from a legal representative.

Exclusion criteria. The exclusion criteria for the trial are as follows. (1) Down syndrome; (2) History of malignant tumor, hematopoietic stem-cell transplantation or organ transplantation; (3) History of congenital or acquired immunodeficiency; (4) Assessed by the attending physician as being unsuitable for the trial.

Methods

Study design. This is a phase IIb, multicenter trial. The subjects are patients categorized as having stage I/II pediatric LBL according to the Murphy staging system [7]. Fig. 1 provides an overview of the treatment protocol. This study has been registered in the Clinical Trial Registry (University Hospital Medical Information Network Clinical Trials Registry [UMIN-CTR]) under no. UMIN000002213).

Treatment methods. A schema of the treatment regimen is shown in Fig. 2. The following modifications were made to the standard therapy (the BFM90 protocol) for stage I/II [5]:

- (1) In the remission-induction phase, daunorubicin will be administered only twice (reduced from 4 times); this drug will be administered again in the re-induction phase. Because this population

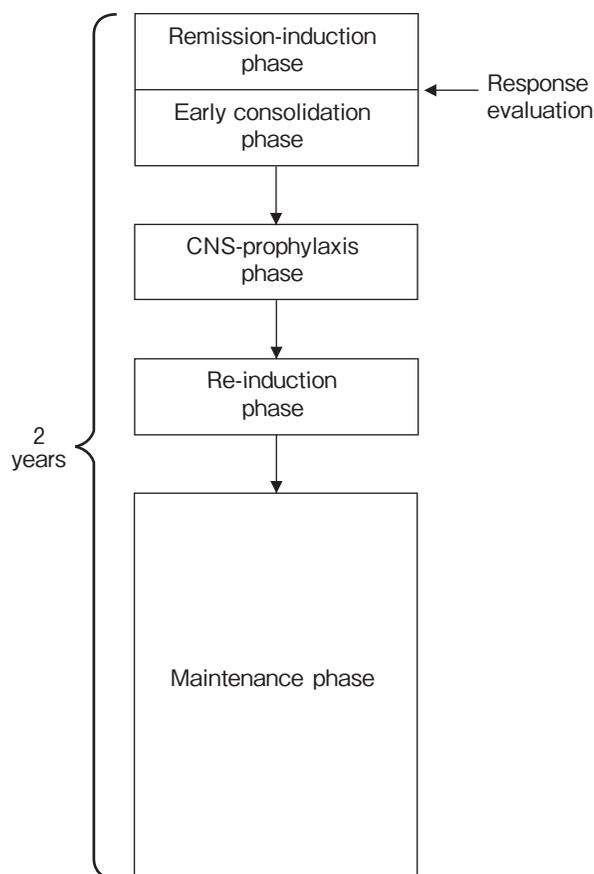
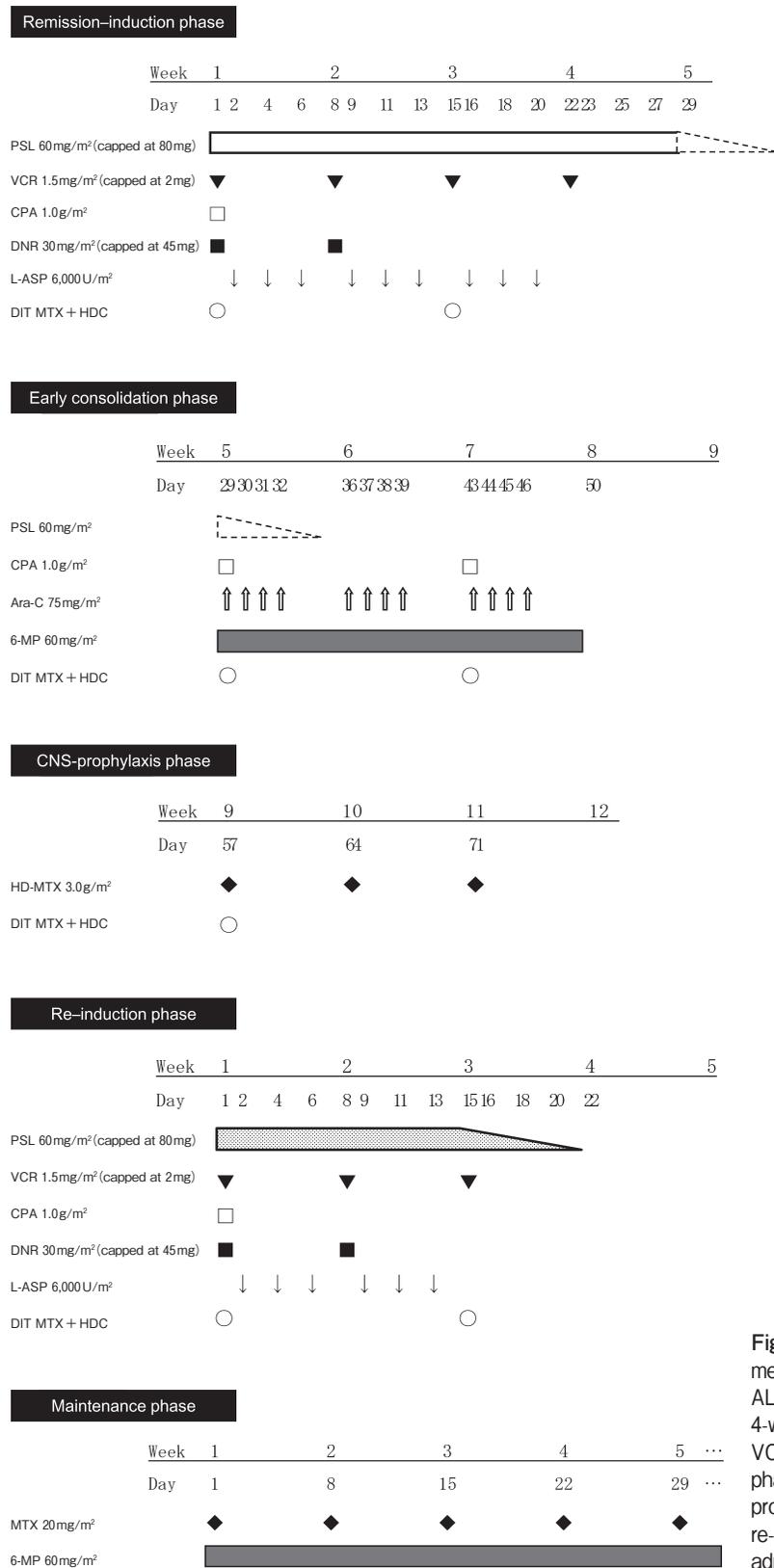


Fig. 1 Overview of the study treatment. After enrolling subjects in this study, we will perform a 2-year modified BFM-type multidrug combination chemotherapy.



- has a favorable prognosis, the daunorubicin administrations were divided to effectively create a re-induction phase without increasing the total anthracycline dose given.
- (2) In the remission-induction phase, cyclophosphamide was moved to day 1. The cyclophosphamide doses usually given on days 36 and 64 were reduced to 500 mg/m² and will be given on days 29 and 43. This will allow maintenance of the total cyclophosphamide dose so as to maintain therapeutic intensity, and so that patients can proceed directly to the early intensive phase, without an interval.
 - (3) In the remission-induction phase, the dosage of L-asparaginase was changed from 10,000 U/m² × 8 times to 6,000 U/m² × 9 times. This will avoid the administration of L-asparaginase and vincristine on the same day.
 - (4) The number of total cytarabine administrations was reduced, from 16 to 12 times. This will reduce the duration of neutropenia.
 - (5) In the CNS-prophylaxis phase the dose per administration of high-dose methotrexate was reduced from 5 g/m² to 3 g/m², and the number of doses was reduced from 4 to 3. This will shorten the CNS-prophylaxis phase, as the standard 2-month period was considered too long [8,9].

Fig. 2 Schema of the treatment regimen. The treatment regimen consists of a basic backbone of BFM-type ALL treatment and contains a re-introduction phase. A 4-week remission induction phase consisting of PSL, VCR, CPA, DNR and L-ASP, an early consolidation phase consisting of 6-MP, CPA and Ara-C, a CNS prophylactic phase with high-dose MTX, a 2-week re-induction phase, and maintenance therapy by oral administration of 6-MP and MTX will be carried out.

- (6) A re-induction phase was newly introduced. The re-induction phase will consist of 5 drugs: prednisolone, vincristine, cyclophosphamide, daunorubicin, and L-asparaginase. This phase will address the treatment of patients with large tumors.
- (7) In regard to the number of intrathecal injections and drugs, instead of 9 solitary intraspinal injections of methotrexate, 7 intraspinal injections comprising 2 drugs (methotrexate and cytarabine) will be given.
- (8) In the maintenance phase, patients will receive daily mercaptopurine (starting at 60 mg/m² and adjusting based on the white blood cell (WBC) count) and weekly methotrexate (starting at 20 mg/m² and adjusting based on the WBC count).

Statistical Considerations

Sample size. Although studies from Japan and overseas have indicated that patients with stage I/II pediatric LBL have favorable prognosis, an EFS rate that could serve as a clear criterion has not been published due to the small number of cases in these studies. Therefore, in this trial we set an expected efficacy rate of 95% and a threshold efficacy rate of 80% for 3-year EFS. Because this is a single arm trial, if the type-1 error is set to 0.05 and the type-2 error is set to 0.2, the number of cases needed is 42. Assuming that 10% of cases will be disqualified, 48 cases are needed. Eight cases are expected to be registered in Japan per year, so a 6-year registration period is required to obtain the necessary number of cases to examine the aforementioned statistical hypothesis.

Statistical analysis. The primary endpoint (3-year EFS rate) will be evaluated using the Kaplan-Meier method. We will calculate 3-year EFS rate point estimates and 95% confidence intervals using Greenwood's formula. If the upper limit of the 95% confidence interval does not reach the expected efficacy rate (95%), therapy with the protocol regimen will be considered ineffective. In principle, the occurrence rate of adverse events will be calculated using a binomial distribution for point estimates and 95% confidence intervals, assessed for the items requiring regular monitoring. The Kaplan-Meier method will be used to evaluate the 3-year overall survival rate.

Discussion

It is expected that this trial will help to establish an effective and safer standard therapy for patients with stage I/II pediatric LBL in Japan. If this trial confirms the protocol's efficacy and safety, its results can be used to establish an optimal therapy with less toxicity.

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