Nelarabine-containing salvage therapy and conditioning regimen in transplants for pediatric T-cell acute lymphoblastic leukemia and lymphoma

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Abstract

Background. Therapy for relapsed or refractory (r/r) T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) in children is challenging, and new treatment methods are needed. Previous studies have shown a promising response to the addition of nelarabine to chemotherapy for r/r T-ALL and T-LBL. *Methods.* We retrospectively analyzed the therapy of nelarabine in combination with etoposide, cyclophosphamide, and intrathecal therapy in eight pediatric patients with r/r T-ALL and T-LBL. The treatment regimen consisted of five consecutive days each of nelarabine (650mg/m ^{2}/dose) and etoposide (100mg/m ^{2}/dose)/cyclophosphamide (440mg/m ^{2}/dose) separated by at least three days. *Results.* Five patients had T-ALL, and three patients had T-LBL. Of all patients, five achieved complete response, and the other three achieved partial response. All the patients underwent hematopoietic stem cell transplantation (HSCT) after two cycles of the treatment, except for one case with one course. Three patients who had previously received HSCT were treated with reduced-intensity conditioning regimens, including fludarabine, melphalan, and nelarabine; one of whom is still alive over five years after the second HSCT. Grade 2 neuropathy occurred in one patient, and other severe toxicities commonly associated with nelarabine were not observed during nelarabine-containing salvage therapy. With a median follow-up of 900 days for survivors, the 2-year overall survival and event-free survival rates were 60.0% and 36.5%, respectively. *Conclusion.* The addition of nelarabine to reinduction chemotherapy was useful for HSCT in remission and did not lead to excessive toxicity. In addition, a conditioning regimen including nelarabine appeared to be effective in previous HSCT patients.

Introduction

In recent years, advances in molecular genetic diagnosis, stratification of treatment, and the development of novel therapeutic agents have dramatically improved the outcome of newly diagnosed pediatric acute lymphoblastic leukemia (ALL)[1-6]. However, outcomes for relapsed/refractory (r/r) T-cell ALL (T-ALL) remain very poor (5-year overall survival (OS) $< 35\%$), mainly due to difficulty in achieving remission[7-9]. Recently, patients with r/r B-lineage ALL have had more options for reinduction with the introduction of immunotherapy such as chimeric antigen receptor T-cell immunotherapy, inotuzumab ozogamicin, or blinatumomab, but new therapeutic agents for T-ALL have not yet been developed. Moreover, although hematopoietic stem cell transplantation (HSCT) is the only treatment that can provide long-term survival, the outcome in patients who do not achieve remission at the time of HSCT is not very successful[10]. In short, the lack of options for achieving remission in r/r T-ALL is a major challenge.

Nelarabine (NEL), a prodrug of 9-arabinofuranosylguanine (Ara-G), is markedly more toxic to T lymphoblasts than to blasts derived from other leukemic cell types, probably due to the accumulation of Ara-G triphosphate (ara-GTP) in T cells compared with B cells[11-13]. Initially, there were reports of its use as a single agent in r/r T-ALL[14-16], and there have been gradually increasing reports of its use in combination

with chemotherapy[17-20]. Recently, NEL has been used for high-risk T-ALL / T-cell lymphoblastic lymphoma (T-LBL) as one of the agents during frontline chemotherapy[6,21]. Addition of NEL to chemotherapy improved disease-free survival in children and young adults with newly diagnosed T-ALL without increased toxicity[6].

From 2013 to 2021, eight pediatric and adolescent patients with first or multiple relapses of T-ALL or T-LBL had been treated using a reinduction regimen with NEL at our hospital. In this report, we have described the results of these 8 patients treated with combination chemotherapy consisting of NEL, etoposide (VP), and cyclophosphamide (CPM), based on the treatment protocol of Commander et al.[17], for r/r T-ALL and T-LBL at Saitama Children's Medical Center (Saitama, Japan). Here, we reported the safety and efficacy of NEL combination chemotherapy, especially bridging it with transplantation, and also reported the efficacy of a NEL-containing conditioning regimen for patients with post-HSCT relapse.

Methods

From 2013, NEL became available through insurance approval in Japan, to 2021, we retrospectively reviewed the following regimens for relapsed T-ALL/LBL at Saitama Children's Medical Center based on medical records. Patients were eligible with or without having previously received NEL. Eight patients received treatment with NEL combined with VP, CPM, and intrathecal prophylaxis. The Scheme of the treatment regimen is similar to that of Commander et al.[17] (Figure 1). Five days each of NEL (650 mg/m^2/dose) and VP (100 mg/m^2/dose) / CPM (440 mg/m^2/dose) were administered, separated by at least three days. In cases of post-HSCT relapse, the VP and CPM doses were reduced to 75%. Triple intrathecal therapy (TIT, methotrexate, cytarabine, and prednisolone) was administered to seven patients, typically preceding a nelarabine dose by seven days or following NEL for three days for the central nervous system (CNS)-negative patients. Only one patient (Patient 1) received TIT consisting of methotrexate, cytarabine, and hydrocortisone 4 weeks before NEL combined chemotherapy. Patients with CNS positivity were treated with TIT, at the discretion of the attending physician (for example, weekly TIT was administered till confirmation of cytospin negativity for blasts, regardless of WBC count).

Toxicities were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The response was assessed after approximately four weeks at the end of each treatment cycle. Disease response was determined by the attending physician and categorized as complete remission (CR), complete remission with incomplete recovery (CRi), partial response (PR), no response (NR), or progressive disease (PD). CR was defined as $< 5\%$ blasts in the bone marrow, no evidence of extramedullary disease, recovery of peripheral counts with an absolute neutrophil count [?] 1,000 /μL, and platelet count [?] 100×10^9 /L. CRi was defined as, CR with no other evidence of disease but with incomplete hematological recovery. PR was defined as bone marrow blast count $>5\%$ but [?]25% and/or persistent evidence of extramedullary disease and $>50\%$ reduction in total lymphoma volume. NR was defined as a bone marrow blast count $>25\%$, blasts in peripheral blood, failure of hematological recovery, or persistent evidence of extramedullary disease not meeting the PR criteria. PD was defined by the presence of one or more new clinical symptoms, the new appearance of blasts in peripheral blood, elevated blasts in bone marrow, the appearance of extramedullary disease manifestations, and an increase in the volume of any lesion or total lymphoma volume of $>25\%$. Minimal residual disease was not assessed in this study. The classification of intensity of the conditioning regimen was based on criteria given by the Center for International Blood and Marrow Transplant Research[22]. Data were described using median and ranges. The Kaplan-Meier method was used to examine the effect of NEL combination chemotherapy by analyzing OS and event-free survival (EFS). OS was defined as the time from the start of NEL combined chemotherapy to death from any cause or last contact, and EFS as the time to relapse, progression, second malignant neoplasm, death, or last contact. All statistical analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University), a graphical user interface for R commander version 2.5-1 (The R Foundation for Statistical Computing, Vienna, Austria)[23]. This study was approved by the institutional review board of Saitama Children's Medical Center.

Results

Patient characteristics are detailed in Table 1. Five patients had T-ALL, and three patients had T-LBL. All

patients were male in the age range of 1–22 years at the time of NEL combined chemotherapy. Of the five patients with T-ALL, four patients had bone marrow relapse, one patient had CNS relapse. All the patients had achieved one or two remissions previously and were refractory to the most recent treatment. Three patients with T-ALL (Patients 1, 2, and 3) underwent HSCT. Two patients (Patients 7 and 8) had a history of nelarabine administration. Four patients were treated without NEL before NEL combined chemotherapy after relapse, and the remaining four received NEL combined chemotherapy in the first salvage regimen after relapse.

The responses to NEL combined chemotherapy are presented in Table 2. All patients underwent post-therapy bone marrow evaluation or CT approximately 3–5 weeks after the start of therapy when hematopoiesis had recovered. Five patients achieved CR and the remaining three achieved PR at the time of HSCT. Seven patients received two courses of treatment, and only one patient received one course due to the limited efficacy of the treatment (patient 7). All patients received HSCT after treatment, including the three who had previously received it. The median interval of HSCT was 84 days (range, 45–94 days) after initiation of NEL combined chemotherapy.

Hematological and non-hematological side effects observed after NEL combined chemotherapy are listed in Table 2. Infections were most frequent with three patients having grade 3 febrile neutropenia but no infectious agent was identified. Regarding neurotoxicity, which is the greatest concern during the administration of NEL, only one patient (patient 2) with a history of HSCT experienced grade 2 sensory neuropathies. Nausea, vomiting, and diarrhea were adequately controlled or prevented with appropriate therapy and never reached grade 3.

The conditioning regimens for HSCT were determined for each case, and the details are presented in Table 3. Five patients with the first HSCT (patients 4, 5, 6, 7, and 8) used a total body irradiation (TBI)-based myeloablative regimen. Three patients with the second HSCT (patients 1, 2, and 3), who used a TBI-based myeloablative regimen for their first HSCT, were administered reduced-intensity conditioning (RIC) regimens including fludarabine (Flu), melphalan (L-PAM), and NEL, expecting an antitumor effect. All patients received standard graft-versus-host disease (GVHD) prophylaxis with short-term methotrexate and cyclosporine or tacrolimus in peri-SCT. Seven patients achieved neutrophil engraftment, except for one patient, who was transplanted with RIC (patient 2). Four patients relapsed at a median of 281.5 days (range: 73–586 days) from NEL combined chemotherapy and a median of 197 days (range: 28–524 days) from HSCT. With a median follow-up of 900 days (range: 96–2,183 days) for survivors, the 2-year OS and EFS were 60.0% (95% confidence interval [CI], 19.5–85.2) and 36.5% (95% CI 5.3–70.6), respectively (Figure 2). Notably, one patient (Patient 3) who received the second HSCT, survived disease-free for more than 5 years.

Discussion

We reported the outcomes of eight patients with r/r T-ALL and T-LBL treated with NEL combined with reinduction therapy using CPM, VP, and TIT. This combination resulted in an overall high response rate (CR + CRi + PR) of 100% with acceptable toxicity. Patients were heavily pretreated and had experienced one or two prior relapses, with three patients having received HSCT previously.

The utility of NEL began with reports of monotherapy for r/r T-ALL[14-16], followed by reports of high response to combination therapy[17-19]. Commander et al. administered NEL in sequential combination with CPM and VP to pediatric patients with r/r T-ALL and T-LBL[17]. All seven patients in their study responded to this therapy, with five achieving CR and four contributing to the bridge to SCT. Six of the seven patients experienced some form of neurotoxicity, but no grade 4 neurotoxicity was reported. Luskin et al. reported the same combination therapy as Commander et al., for adults with first relapse T-ALL / T-LBL[18]. Three of their five patients achieved CR, and the remaining two died from toxicity before disease reassessment. The two patients with T-LBL who achieved CR were bridged with SCT. Two of the five patients developed neurotoxicity, and one died of complications from respiratory failure associated with progressive neuromuscular weakness. Recently, the Therapeutic Advances in Childhood Leukemia

and Lymphoma Consortium reported a phase I dose-escalation study with the combination of concurrently administered NEL, VP, and CPM with a cohort expansion at the recommended phase II dose for children with relapsed T-ALL and T-LBL[20]. In this report, the recommended doses were NEL 650 mg/m^2/day, VP 100 mg/m^2/day, and CPM 400 mg/m^2/day when given every 3 weeks for five days. The overall best response rate was 38% (8/21), with details of 33% (4/12) for T-ALL and 44% (4/9) for T-LBL. Kumamoto et al. reported the combination therapy of nelarabine with Flu and VP for pediatric first-relapse T-ALL[19]. Three of the five patients achieved CR or PR, and the remaining two had a poor response to the treatment.

We used the original dosage of NEL combined with chemotherapy by Commander et al., for patients without HSCT and reduced the dosage of CPM and VP to 75% of the original dosage for patients with a history of HSCT. Although this was a study with a small number of patients with various disease backgrounds and stages, all patients achieved a certain level of response (CR + CRi + PR). Hence, this therapy could be a very useful tool for providing bridge therapy to transplantation during remission.

Our study did not have any adverse results or incur any serious complications, including neurotoxicity, which is the most important factor to consider during this treatment. Although this is a study of a small number of cases, it may be important to adjust treatment according to individual cases, such as reducing the dose of VP and CPM, especially in cases of post-HSCT relapse, as was done in our study.

Another important aspect of our study was the introduction of a conditioning regimen containing NEL. We used a TBI-based myeloablative regimen, which is the standard conditioning regimen for pediatric ALL patients with first HSCT[24,25]. In contrast, in cases of post-HSCT relapse, we used a conditioning regimen that included NEL (all patients received a TBI-based myeloablative regimen during their first transplant). Below, we outline the rationale for planning this NEL-containing conditioning regimen. NEL is rapidly metabolized to Ara-G by adenosine deaminase and phosphorylated to Ara-GTP in plasma[26]. Gandhi et al. have demonstrated a positive relationship between the accumulation of Ara-GTP and response to NEL therapy[27]. The combination of Flu and NEL had a significantly higher treatment response than NEL monotherapy[28,29]. To the best of our knowledge, there are no reports of a conditioning regimen containing NEL, but we planned to introduce the same for three patients with post-HSCT relapse who had responded to NEL combined chemotherapy, with the expectation of further anti-tumor effects. Two of the three patients died after the second HSCT due to disease progression (patient 1) and treatment-related complications (patient 2), respectively. Only one patient (patient 3) who relapsed after 1st HSCT was a long-term survivor for over five years after the second HSCT without obvious GVHD, and this patient may have benefited greatly from a salvage/conditioning regimen including NEL. Regarding the safety of this conditioning regimen, one patient (patient 2) developed paralysis in both limbs on day 9 after HSCT was diagnosed as transverse myelitis on imaging, and died due to infection or DIC on day 12 after HSCT, while the other two patients (patients 1 and 3) had no complications beyond CTCAE grade 4, although patient 1 died of disease progression. The usefulness and feasibility of this preparative regimen require further observations resulting from an accumulation of cases in the future.

In conclusion, we performed salvage therapy including NEL for r/r T-ALL and T-LBL, which proved to be a safe and useful treatment. We also demonstrated the utility of a new conditioning regimen that included NEL in some patients. Although we used NEL as a conditioning regimen for the second HSCT, the introduction of a NEL-containing conditioning regimen for the first HSCT is an issue that needs to be considered. In addition, NEL is being used worldwide as a front-line treatment for T-ALL, and the development of other therapeutic strategies for patients with r/r T-ALL who have previously received NEL will become more important in the future.

Conflicts of interest

The authors have no conflicts of interest or sources of funding to disclose.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figure legends:

Figure 1; Chemotherapy schema

Regimens A and B were selected randomly by the attending physician. Five days each of nelarabine and etoposide/cyclophosphamide were separated by at least three days. In cases of post-HSCT relapse, the etoposide and cyclophosphamide doses were reduced to 3/4. Triple intrathecal therapy (TIT) was administered to all patients on the first day of etoposide/cyclophosphamide administration. Below, details of the dosage of anticancer drugs and intrathecal injections are given. Cyclophosphamide; 440 mg/m^2/dose, Etoposide; 100 mg/m^2/dose, Nelarabine; 650 mg/m^2/dose, TIT; methotrexate, cytarabine and hydrocortisone

Figure 2A; Overall survival (OS) of all patients

The two-year OS rate was 60.0% (95% confidence interval, 19.5-85.2)

Figure 2B; Event-free survival (EFS) of all patients

The two-year EFS rate was 36.5% (95% confidence interval, 5.3-70.6)

Regimen A	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Cyclophosphamide	○	○	○	○	○									
Etoposide	○	○	○	○	○									
Nelarabine								○	○	○	○	○		
Triple IT	○													

Regimen B	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Cyclophosphamide								○	○	○	○	○		
Etoposide								○	○	○	○	○		
Nelarabine	○	○	○	○	○									
Triple IT								○						

Fig.2A

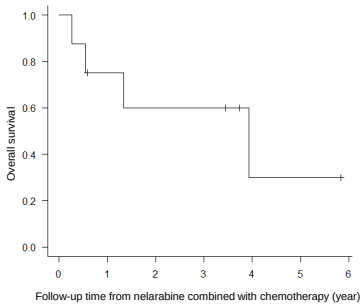

Fig.2B

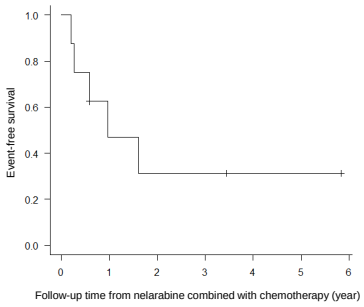

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Table 1 Characteristics of patients.doc available at https://authorea.com/users/349380/articles/614939-nelarabine-containing-salvage-therapy-and-conditioning-regimen-in-transplants-for-pediatric-t-cell-acute-lymphoblastic-leukemia-and-lymphoma

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Table2 Summary of response and side effects observed with nelarabine combined chemotherapy.doc available at https://authorea.com/users/349380/articles/614939-nelarabine-containing-salvage-therapy-and-conditioning-regimen-in-transplants-for-pediatric-t-cell-acute-lymphoblastic-leukemia-and-lymphoma

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Table 3\begin{CJK}{UTF8}{gbsn}\end{CJK}\selectlanguage{english}Conditioning regimens for HSCT determine available at https://authorea.com/users/349380/articles/614939-nelarabine-containing-salvage-therapy-and-conditioning-regimen-in-transplants-for-pediatric-t-cell-acute-lymphoblastic-leukemia-and-lymphoma