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Clinical Study Protocol

A Multicenter, Open-label, Clinical Trial to Assess the Effectiveness and Safety of Allogeneic Hematopoietic Stem Cell Transplantation Using Reduced-intensity Conditioning in Relapsed/refractory Anaplastic Large-cell Lymphoma in Children

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No standard treatment for relapsed or refractory anaplastic large-cell lymphoma (ALCL) has been established. This study is a multicenter, open-label trial to examine the effectiveness and safety of transplantation with reduced-intensity conditioning (RIC) for patients under 20 years old with relapsed or refractory ALCL. We defined RIC as the administration of fludarabine (30 mg/m^2/day) for five days plus melphalan (70 mg/m^2/day) for two days and total body irradiation at 4 Gy, followed by allogeneic hematopoietic stem cell transplantation.

Key words: anaplastic large-cell lymphoma, relapsed/refractory, fludarabine, melphalan, total body irradiation

The long-term event-free survival (EFS) of anaplastic large-cell lymphoma (ALCL) in children is about 70%. About 30% of all ALCL cases in children are relapsed/refractory cases [1]. No standard treatment for these relapsed/refractory cases has been established.

A previous study reported that vinblastine monotherapy had an objective response rate of 86% and a complete remission rate of 56% in patients with ALCL, but the long-term EFS rate was only about 30% [2]. Hematopoietic stem cell transplantation (HSCT) is a curative treatment option in relapsed/refractory ALCL. However, the effectiveness and safety of this approach have been examined in only a few studies with a limited number of cases. As for allogeneic transplantation, the Center for International Blood and Marrow Transplant

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Research in the USA reported a 5-year EFS rate of 46% and a 5-year cumulative relapse rate of 20% in 12 patients [3]. In France, results were reported for 34 allogeneic transplantation patients aged 18 years or younger and adolescents with relapsed/refractory anaplastic lymphoma kinase (ALK)-positive ALCL, and they similarly showed a 5-year EFS rate of 58% and a 5-year cumulative relapse rate of 18% [4]. In Japan, the results for relapsed/refractory child cases based on the Transplant Registration Unified Management Program (TRUMP) data of the Japan Hematopoietic Cell Transplantation Society were also similar to those of the reports from overseas, with a 5-year EFS rate after autologous transplantation of 38%, a 5-year cumulative relapse rate of 49%, a 5-year EFS rate after allogeneic transplantation of 50%, and a 5-year cumulative relapse rate of 28% [5]. Although the cumulative relapse rate was lower in allogeneic transplantation compared to autologous transplantation, treatment-related death was a problem in allogeneic transplantation, and the 5-year cumulative treatment-related mortality rates from the TRUMP data were 12% for autologous transplantation and 25% for allogeneic transplantation.

In recent years, ALK inhibitors such as crizotinib, alectinib, ceritinib, and an anti-CD30 antibody, brentuximab vedotin (BV), have been developed as molecular target therapeutic agents for ALCL, and a positive impact on relapsed or refractory ALCL in children is expected. However, the current treatment is to introduce a single agent to achieve (re-)remission. In addition, information on the safety of crizotinib and BV is based on a phase I study, and there is no information on their safety and efficacy over the course of long-term administration. With these new drugs, intensive/consolidation therapy that achieves (re-)remission is considered to be a basis for allogeneic HSCT. Allogeneic HSCT following crizotinib monotherapy for relapsed/refractory ALCL in 6 patients was reported with the following results: 5 patients remained in remission, and 1 patient developed isolated central nervous system relapse [6]. In this study, we defined reduced-intensity conditioning (RIC) as total body irradiation (TBI) 4 Gy + fludarabine 150 mg/m^2 plus melphalan 140 mg/m^2 in accordance with 2 previous representative definitions [7, 8]. The aim of the present study was to examine the effectiveness and safety of RIC for patients under 20 years old with relapsed or refractory ALCL.

Endpoints

Primary endpoints. The primary outcome is the proportion of one-year EFS after transplantation. Events are defined as all-cause death, relapse, progression, re-transplantation, secondary neoplasm (including myelodysplastic syndrome: MDS), and stabilization at one year after transplantation. If observation is discontinued within one year, it will be treated as an event.

Secondary endpoints

- Overall survival (up to 2 years after transplantation)

We define overall survival as the duration from the date of transplantation to the date of all-cause death. If an event occurs before transplantation, we will consider it to be an event on the start date. Survivors will be censored on the last observation date.

- EFS (up to 2 years after transplantation)

We define EFS as the duration from the date of transplantation to the date of the first event confirmed, including all-cause death, relapse, progression, reimplantation, secondary neoplasm (including MDS), or stabilization at one year after transplantation. If an event occurs before transplantation or if the ALCL does not remit even after transplantation during a stable state at one year after transplantation, we will treat it as an event on the start date. Survivors will be censored on the last observation date.

- Cumulative relapse rate (up to 2 years after transplantation)

We define the time to cumulative relapse as the duration from the date of transplantation to the date of the examination that confirmed either relapse after transplantation, progression, or stabilization at one year after transplantation. If an event occurs before transplantation, or if the ALCL does not remit after transplantation in a stable state at one year after transplantation, we will treat it as an event on the start date. Survivors will be censored on the last observation date. We will calculate the cumulative relapse rate with the competing risk of death that does not depend on the original disease up to relapse after transplantation and re-transplantation.

- Neutrophil engraftment graft status after transplantation

We define engraftment as the number of neutrophils (calculated from the number of white blood cells × the

neutrophil percentage) reaching 500/μL or more on consecutive examination days with 3 or more time points, with this first day as the engraftment date. Also, if recovery of hematopoietic function occurs after 28 days due to another cause such as infection, and the donor type is confirmed by chimeric examination, we will treat this as delayed engraftment.

- Treatment-related death after transplantation
- Incidence and severity of acute graft versus host disease (GVHD)
- Incidence and severity of chronic GVHD
- Frequency, number of cells, and reasons for conducting donor lymphocyte infusion
- Frequency of re-transplantation
- Chimeric analysis (30 days and 100 days after transplantation)
- Toxicity from the start date of RIC to four weeks after transplantation
- Days in a febrile state of more than 38 degrees up to 100 days after transplantation
- Adverse events occurring at 100 days, one year, and two years after transplantation

Treatment Methods

Study design. This study is a multicenter, open-label, clinical trial. As it was impossible to set a concurrent control group due to the small number of patients, we designed it as a single-arm study. In addition, we will decide on early discontinuation of this study using the Bayesian method proposed by Thall and Simon [9]; this approach has the characteristics which enable to make sequential decisions whether a treatment is promising while taking account for uncertainty of response rates. This study was approved by the National Hospital Organization Review Board for Clinical Trials (Nagoya) in May 2019 and is registered in the Japan Registry of Clinical Trials (registry number: jRCTs041190066).

Participants. We will register patients who satisfy all the inclusion criteria shown in Table 1 and who do not meet any of the exclusion criteria. We will conduct registration using an electronic data capture system that issues registration numbers. This is an open-label study.

Interventions. The administration schedule is shown in Table 2. Fludarabine 30 mg/m^2/day will be administered on day −7 to day −3. The dose will be

Table 1 Eligibility criteria

Inclusion criteria
(1) With anaplastic large cell lymphoma aged 19 years or younger at the time of registration
(2) Remission cannot be achieved by first-time chemotherapy, or relapse after chemotherapy and autologous transplantation
(3) With indication for hematopoietic cell transplantation
(4) With ECOG Performance status of 0–2
(5) With organ functions satisfying all the following criteria within 21 days before registration:
(5-a) no uncontrolled heart failure, and a left ventricular ejection fraction of 50% or more;
(5-b) forced expiratory volume (FEV) 1.0% of 50% or more and predicted vital capacity 50% or more. If a lung test is impossible, SpO_2 ≥95% without the need for oxygen administration;
(5-c) AST/ALT of less than 5 × ULN (CTCAE grade 2 or less) and total bilirubin 3 × ULN (CTCAE grade 2 or less);
(5-d) no uncontrolled renal failure, and less than 2 × ULN serum creatinine.
(6) have been registered in the JPLSG prospective study (JPLSG-CHM-14)
(7) have obtained written informed consent (including assent) from representatives/themselves for participation in this study
Exclusion criteria
(1) With central nervous system infiltration at the time of first symptoms or relapse
(2) With a history of allogeneic hematopoietic stem cell transplantation and organ transplantation
(3) With uncontrollable infection
(4) With congenital diseases or psychiatric disorders that interfere with study treatment
(5) With multiple cancers
(6) With a history of hypersensitivity to drugs used in RIC or drugs used to prevent acute GVHD
(7) With a possibility of pregnancy or being pregnant
(8) Judged inappropriate to receive the study treatment by the attending doctor

Table 2 Administration schedule

Contents	Method	−7	−6	−5	−4	−3	−2	−1	0
Fludarabine	30 mg/m^2/day for 5 days (30-minute infusion) 1 mg/kg/day for children under one year old or less than 10 kg	●	●	●	●	●			
Melphalan	70 mg/m^2/day for 2 days (30-minute infusion) 2.3 mg/kg/day for children under one year old or less than 10 kg Any two dosing days from day−7 to day−3 are acceptable	■	■						
TBI	4 Gy (testicular shield allowed but not an ovarian shield) Dose rate of less than 20 cGy/min Replacing TBI with total marrow irradiation is not acceptable. Performing on day−8, day−2 or day 0 is acceptable.							○	
Transplantation	Mainly using bone marrow and cord blood. Peripheral blood is also acceptable.								*

1 mg/kg/day if a patient is under 1 year old or weighs less than 10 kg. Melphalan 70 mg/m^2/day will be administered on day −7 and day −6. The dose will be 2.3 mg/kg/day if a patient is under 1 year old or weighs less than 10 kg. We will perform TBI 4 Gy on day −1. Replacing TBI with total marrow irradiation is not permissible. However, performing TBI on day −8, day −2, or day 0 is allowed. We define these treatments as RIC. We will perform allogeneic HSCT on day 0 after the treatments. The source of transplanted cells will largely be bone marrow and cord blood, but peripheral blood is also acceptable. The treatment period for each study subject is about one week, and the follow-up period is two years.

Combination Therapy

- Recommended combination therapy/supportive therapy

1) Antiemetics including steroids. 2) Use of granulocyte colony-stimulating factor after transplantation. 3) During the period of bone marrow suppression by this treatment protocol, a sufficient countermeasure against infectious diseases must be taken to help prevent infection (the administration of prophylactic antibiotics, antifungals, or antivirals) at each institution during stem cell transplantation.

- Unacceptable combination therapy

1) Donor lymphocyte infusion accompanied by the administration of anti-cancer drugs. 2) A combination of treatments aimed at enhancing immunological anti-tumor effects other than donor lymphocyte infusion. 3) Use of anticancer drugs including a molecular target after transplantation for primary disease. However, the indication for molecular-targeted drugs before the start of the pre-transplant treatment can be determined at the institution. 4) Multiple cord blood transplantation.

Statistical Considerations

Sample size. Because patient recruitment will likely be extremely difficult in this study, we will use the Bayesian method proposed by Thall and Simon [9]. Hereinafter, we will describe the proportion of one-year EFS after transplantation as the response rate.

Setting the prior distribution of the response rate. We assume the beta distribution Beta (a, b) in the prior distribution of the effective threshold and expected response rate. An analysis of relapsed and refractory ALCL in Japan using TRUMP data revealed that the response rate was 50% in 24 patients in whom allogeneic HSCT was performed [5]. Reports of allogeneic HSCT in relapsed/refractory ALCL from the United States and France also described 5-year EFS rates of 46% and 58%, respectively, similar to the results from Japan [3, 4]. Because most incidences of relapse after ALCL transplantation occur within one year, it is assumed that the response rate and the 5-year EFS rate are equivalent. Previous reports used myeloablative conditioning, whereas in this study RIC will be performed. Even if the EFS rate is equivalent to the rates in these previous reports, a reduction in therapeutic toxicity is expected. Therefore, we set the threshold rate at 45%, and candidates for the prior distribution of the threshold rate as Beta (29.7, 36.3) and Beta (13.0,

15.9). According to the method of Thall and Simon, we determined the parameters a and b so that the width of the 90% probability interval running from the 5th to the 95th percentiles in the prior distribution became 0.2 or 0.3, below the average of 0.45.

In the analysis of relapsed/refractory ALCL in Japan using the TRUMP data, the response rate in the RIC group was 75% (3/4). In Italy, a phase II prospective study of allogeneic HSCT using RIC was performed in 117 adults with peripheral T cell lymphoma, including four ALK-negative ALCL patients, and the 3-year progression-free survival rate was 64% [10]. Based on these results, we set the expected response rate in this study to 70%. From these, for a case in whom the δ_0 of improvement over the threshold using the Thall and Simon method equals 0.25, and the c_E values for the sums of the 2 hyperparameters of the beta distribution are set to 2 and 4, we determined the candidate for the prior distribution of the expected response rates to be Beta (1.15, 0.85), and Beta (2.3, 1.7).

We defined the criterion for judging whether this therapy is effective as "a posterior probability of the response rate exceeding the threshold of 95% or more," and that for determining that it is not effective as "a posterior probability of the response rate exceeding the threshold of 1% or less."

After calculating the number of boundaries in each scenario in which the prior distribution was changed, we calculated each of the following and evaluated the influence of the prior distribution: the probability that the development regimen is erroneously determined to be effective when the expected response rate is 45% the level of the threshold, the probability that the regimen is judged to be not effective in the same situation, the probability that the development regimen is judged to be effective when the value is 70% of the expected value, and the probability that the regimen is mistakenly judged to be not effective in the same situation. As a result, the difference in the number of boundaries between scenarios is at most one, and when the minimum number is set to 10, in a scenario similar to the number of patients in sum of previous studies, the probability of correctly judging the regimen to be effective was 0.77, and the probability of incorrectly judging it to be effective was less than 0.10. From the above, we set the threshold response rate to 45% (prior distribution: Beta (29.7, 36.3)) and the expected response rate to 70% (prior distribution: Beta (2.3, 1.7)). We will judge this treatment method to be effective when the posterior probability of the response rate exceeding the threshold is 95% or more. If the posterior probability that the response rate exceeds the threshold is 1% or less, we will judge this treatment to be ineffective. The minimum number of cases will be 10, and the maximum number will be 18. Table 3 shows the sample size and number of response boundaries.

Interim analysis. Interim analysis will be performed on the primary endpoint every time after the registration of the 10th patient in order to determine whether the treatment is effective and the study should be stopped, the treatment is ineffective, namely futility in the Table 3, and the study should be stopped, or the study continues. If the number of responses in the patients to be evaluated is the same as or more than the response boundary for effective stop, it will be judged as effective and the study should be stopped. If the number is equal to or less than the response boundary of futility, it will be judged as ineffective and study should be stopped. Otherwise, we will continue the study.

Statistical Consideration. We will analyze the response rate, which is the primary endpoint when the data of all registered patients up to one year after transplantation are fixed. Then, we will estimate the posterior distribution of the response rate (posterior mean, 95% credible interval with highest posterior density, probability of exceeding threshold). For reference, we will calculate point estimates and the 95% confidence interval (CI) of the response rate.

Analyses other than those of the primary endpoint will be done after the final follow-up data are fixed. We will calculate Kaplan-Meier curves for overall survival and EFS, and point estimates and CI for the two-year survival rate after transplantation. We will estimate the cumulative incidence function using the competitive risk model and calculate point estimates and the CI of the 2-year cumulative incidence rate after transplantation.

Table 3 Sample size and number of response boundaries

Sample size	10	11	12	13	14	15	16	17	18
Response boundary for effective stop	8	8	9	10	10	11	11	12	12
Response boundary for futility stop	2	3	3	4	4	5	5	6	6

Discussion

Only reports from Japan have indicated the effectiveness of HSCT using RIC in ALCL [5]. In HSCT using RIC, there is a concern that the relapse rate may increase following attenuation of the pretreatment intensity. However, there were 4 cases of allogeneic HSCT using RIC in the TRUMP data, of which three were in non-remission at the time of transplantation, and all 3 of these cases achieved long-term survival in remission. Although the number of cases was small, this result suggests the effectiveness of HSCT using RIC in relapsed/refractory ALCL. ALCL relapse is common, and relapse often occurs after HSCT. In cases for whom therapeutic toxicity is a concern, using RIC has the potential to reduce the incidence of treatment-related death.

Few child/adolescent patients are indicated for hematopoietic cell transplantation in relapsed/refractory ALCL. To make a clear treatment decision in such a situation, we decided on early discontinuation of this study using the Bayesian method. In this study, we expect to further develop therapeutic methods in allogeneic HSCT using RIC in child/adolescent relapsed/refractory ALCL.

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