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Clinical Study Protocol

Phase II Trial Using Romidepsin after Gemcitabine, Dexamethasone, and Cisplatin Therapy in Elderly Transplant-Ineligible Patients with Relapsed/Refractory Peripheral T-Cell Lymphoma: Study Protocol

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Romidepsin is an important therapeutic option for patients with peripheral T-cell lymphoma (PTCL). However, the timing of romidepsin administration remains controversial. Romidepsin was launched in Japan as a consolidation therapy agent after conventional salvage chemotherapy with gemcitabine, dexamethasone, and cisplatin (GDP). GDP therapy will be administered every 3 weeks. If complete response, partial response, or stable disease is confirmed after 2-4 GDP cycles, romidepsin will be administered every 4 weeks. The primary endpoint is a 2-year progression-free survival rate. Patients participating in this study and undergoing treatment can expect results similar to or better than those of conventional therapies.

Key words: peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma, gemcitabine, cisplatin, romidepsin

With the increasing number of older adults worldwide, the average age of patients with hematopoietic malignancies is expected to increase every year. One of the diseases for which old age is a particularly poor prognostic factor is lymphoma [1]. In addition, there is an increase in the risk of treatment-related mortality in elderly patients. Finally, old age increases the likelihood of various disease factors and patient factors, including a history of other diseases and organ disorders, resulting in a poor response to chemotherapy.

To date, no treatment has been found to be superior to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) therapy as an initial therapy in both peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) and angioimmunoblastic T-cell lymphoma (AITL). The International T-cell Lymphoma Project [2], a retrospective analysis of a prospective clinical trial [3], and a small-scale prospective clinical trial [4] reported an overall survival (OS) rate of 30-45% and a progression-free survival (PFS) rate of 20-30% among patients who received CHOP therapy. According to a Swedish data registry [5], in CHOP or cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone (CHOEP) therapy, the OS and PFS rates were respectively 28.1% and 21.3% in PTCL-NOS and 31.6% and 20.4% in AITL. Although the international prognostic index is low in these cases,

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indicating good prognosis, the survival rate remain poor. A retrospective analysis of a prospective clinical trial in Germany found that PTCL patients with normal levels of lactate dehydrogenase showed improved PFS rates using CHOEP therapy [3] as did PTCL patients under the age of 60 years in the Swedish data registry [4]. However, neither study showed a difference in OS rates between CHOP and CHOEP therapies. A previous clinical trial in which PTCL patients were administered 4-6 courses of CHOEP therapy as an initial therapy for CHOP [6] and a review of various studies and trials using this same protocol [7]. However, the efficacy of CHOEP therapy has not yet been investigated in transplant-ineligible patients aged 65 years and older. In young people, upfront autologous or allogeneic transplantation was generally recommended, but multiple trials have found no difference in long-term survival following the use of CHOEP or CHOP therapy alone [4]. A multicenter study in Japan found that dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-EPOCH) therapy was effective [8], although this has not yet been confirmed.

There are no standard treatments in elderly transplant-ineligible relapsed/refractory PTCL patients. There have been reports on the effectiveness of gemcitabine, dexamethasone, and cisplatin (GDP) therapy in relapsed/refractory PTCL patients, although it has been used in only a small number of cases [9, 10]. The 60-70% response rate to GDP therapy is promising, but the median disease-free survival rate is still unsatisfactory at 9-10 months. To date, no treatment methods with the potential to prolong OS have been developed, and studies focusing on the prolongation of OS as the primary endpoint are difficult to conduct.

Phase I/II trials on romidepsin have been conducted in Japan [11]. These trials found that romidepsin caused few critical side effects other than temporary reduced blood cell count, and despite its being a single-agent therapy, the overall response rate was 25% (15% complete remission) [11]. Clinical trials on the prevention of relapse following autologous transplants are in progress in the United States, and no large-scale adverse events have been reported thus far. However, there are no clinical trials on consolidation therapies following salvage chemotherapy in elderly transplant-ineligible patients with relapsed/refractory PTCL. In Japan, only single-agent administration is covered by insurance and is deemed safe. Although a standard treatment has not been established in PTCL, future developments in treatment can be facilitated by introducing romidepsin, which was launched in Japan as a consolidation therapy agent following conventional salvage chemotherapy and from which only short-term effects can be expected.

Endpoints

The primary endpoint is a 2-year PFS rate. The PFS rate is measured from the start date, which is the day of registration, until either the day on which the patient's condition is deemed to have progressed/relapsed or the date of death from any cause, whichever comes first. Patients without progression are censored on the final day on which the patient's condition is confirmed not to have progressed.

The secondary endpoints are as follows: complete response (CR) in GDP + romidepsin therapy rate; response [CR + partial response (PR)] rate; adverse events; OS; time to response (defined as the period from the registration day until the day on which a response (PR and higher) is first confirmed); the best response to GDP therapy; the best response to romidepsin therapy; the best response to treatment according to disease risks *(e.g.*, international prognostic index, prognostic index for T-cell lymphoma); quality of life (QOL); inpatient-outpatient period; necessary expenses; and pathology-centered diagnosis.

Safety will be evaluated on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events ver. 4.0. The SF-36®, a comprehensive survey to measure patient health, and the Quality of Life Questionnaire for Cancer Patients Treated with Anticancer Drugs (QOL-ACD), a QOL measurement tool specifically for cancer patients, will be used to survey QOL. The inpatient-outpatient period will be surveyed during the inpatient and outpatient treatment periods after the completion of treatment. To determine the necessary expenses, the total estimated charges on all the patients' bills delivering the treatment from the start of therapy until the final response evaluation will be added.

Eligibility Criteria

Patients who meet all the inclusion criteria and do

not fall under any of the exclusion criteria can register in this study. The inclusion and exclusion criteria are provided in Table 1.

Methods

Study design. This study is a phase II multicenter open-label, single-arm trial. We will examine the efficacy and safety of GDP therapy and romidepsin therapy as salvage chemotherapies for elderly transplant-ineligible patients with relapsed/refractory PTCL. Currently, there is no standard treatment for relapsed/refractory PTCL in elderly transplant-ineligible patients; therefore, we will perform this study as a nonrandomized confirmatory trial to determine whether the aforementioned therapies should be standardized. This study has been registered in the Japan Registry of Clinical Trials (jRCT, registration number: jRCTs031180445).

Table 1 Eligibility criteria

Inclusion criteria
1) The patient is aged 65 years or older at the time of registration.
2) The patient received a diagnosis of peripheral T-cell lymphoma (PTCL-NOS or AITL according to the 2016 WHO classification), previously underwent more than one treatment regimen, is not eligible for autologous or allogeneic stem-cell transplantation, and presents with relapsed/refractory disease.
3) The patient has a lesion that is measurable.
4) The patient's Eastern Cooperative Oncology Group Performance Status at the time of registration is 0–2. This status can be achieved after a previous prednisone dose (approximately 1 week of prednisone administration is permissible).
5) The patient's major organ functions have been maintained and the patient satisfies the following criteria:
5-a) The patient has a neutrophil count of at least 1,000/μl.
5-b) The patient has a platelet count of at least 50,000/μl.
5-c) The patient's cardiac function has an ejection fraction of over 50% (echocardiogram or myocardial scintigraphy).
5-d) The patient's arterial blood gas analysis shows a PaO_2 of over 60 mmHg or the percutaneous oxygen saturation measurement shows an SpO_2 of over 93% (room air).
5-e) The patient's serum aspartate aminotransferase or alanine aminotransferase is less than five times the maximum value of the facility standard.
5-f) The patient's creatinine clearance is over 30 ml/min (Cockcroft–Gault).
6) The patient has received a notification and the trial has been adequately explained to the patient by the facility investigator (assigned) using the designated consent form and explanatory materials. The patient has provided written informed consent for voluntary participation in the trial.
Exclusion criteria
1) The patient has been clinically diagnosed with testis or central nervous system (brain, spinal cord, medullary cavity) invasion. (Examination of the cerebrospinal fluid or an MRI of the brain is not mandatory.)
2) The patient has severe hepatic, renal, cardiac, or pulmonary dysfunction, diabetes, or hypertension.
3) The patient has interstitial pneumonia or pulmonary fibrosis. (If either is determined by a plain X-ray image of the chest, the patient shall not be able to register. Mild cases indicated for the first time on a chest CT scan shall not be excluded. Patients whose lungs have been previously exposed to radiation shall be excluded, as they are at a high risk of developing interstitial pneumonia.)
4) The patient presents with a QTc interval that measures over 500 ms on an electrocardiogram.
5) The patient has tubercular disease, herpetic simplex keratitis, systemic mycoses, or any other active infection.
6) The patient has had acute myocardial infarction, deep vein thrombosis, or pulmonary embolism within the past 6 months.
7) The patient has an active and advanced-stage double cancer (synchronous double cancer and metachronous double cancer with a disease-free interval of less than 5 years. However, lesions that correspond to carcinoma *in situ* of the uterine cervix, stomach, or colon deemed to have been cured by local treatment are not considered active double cancers).
8) The patient is HBs antigen-positive, HCV antigen-positive, HTLV-1 antigen-positive, or HIV antibody-positive. (HBs antibody- and HBc antibody-positive patients shall not be excluded. If HBV-DNA is detected, the patient shall be excluded. An HIV antibody test is not mandatory).
9) The patient has a history of severe drug hypersensitivity.
10) The patient lacks the ability to provide consent or is suffering from symptoms such as those of dementia.
11) The patient has undergone local radiotherapy less than 2 weeks prior to the trial.
12) The representative doctor of the facility or investigator deems the patient unfit to participate in the trial.

Intervention. The protocol will commence within 4 weeks after patient registration. The attending physician will decide whether the patient should undergo inpatient or outpatient treatment. Figure 1 outlines this trial treatment. GDP therapy will be administered every 3 weeks. A 1,000 mg/m^2/day dosage of gemcitabine will be administered intravenously on days 1 and 8, a 40 mg/day dosage of dexamethasone will be administered orally or intravenously on days 1-4, and a 75 mg/m^2/day dosage of cisplatin will be administered intravenously on day 1. After two courses of GDP therapy, an interim response evaluation will be carried out via positron emission tomography-computed tomography (PET-CT) or CT scan. The evaluation criteria in the Revised Response Criteria for Malignant Lymphoma [11] will be used to evaluate the tumor shrinkage response. In cases of CR, PR, or stable disease (SD), two additional courses of GDP therapy will be added. However, if the doctor in charge determines that the patient does not have the required tolerability for reasons unrelated to his or her disease status, no additional GDP therapy will be added, or they may choose to add just one additional course. Patients who are unable to achieve a result better than SD before the interim response evaluation after the two courses of GDP therapy [progressive disease (PD)] and those who are confirmed as having a PD during the treatment protocol shall stop the treatment protocol at that point. Patients who complete the planned GDP therapy will undergo a GDP therapy final response evaluation via CT and PET-CT scan after the conclusion of the final course.

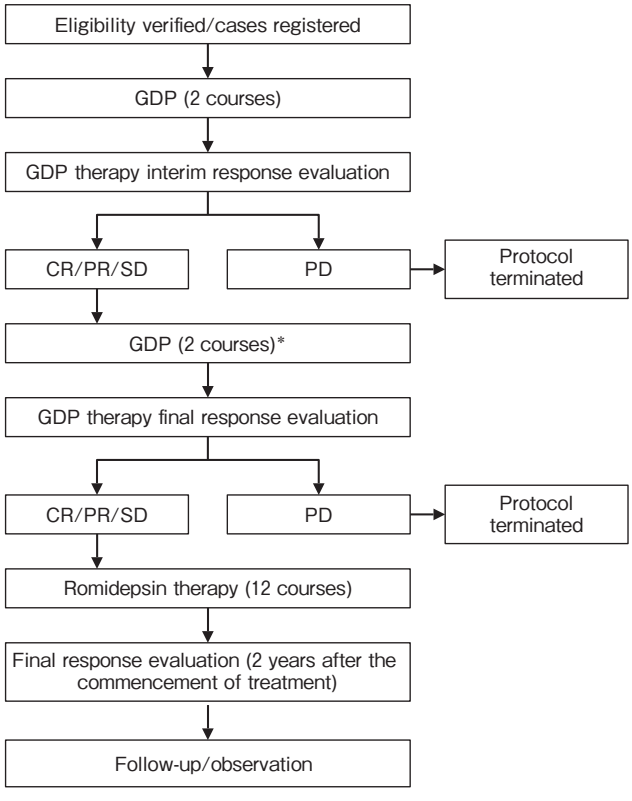

Fig. 1 Treatment outline
*The addition of 0–2 courses of GDP therapy will be determined by the doctor in charge according to the patient's tolerability.

Those who are deemed to have achieved CR, PR, or SD based on the response evaluation after the final GDP therapy will undergo romidepsin therapy every 4 weeks. One course comprises romidepsin 14 mg/m^2/day administered intravenously once per day on days 1, 8, and 15. A final response evaluation will be carried out 6 months after the end of the treatment, which is to continue for 12 courses over the course of one year.

Standard for dose adjustment.

Gemcitabine

1) In cases where Grade 3 nonhematological toxicity (excluding nausea, vomiting, and hair loss) appears, the dose will be decreased by 25% in the next course.
2) In cases where nonhematological toxicity or renal dysfunction of Grade 4 (serum Cr > 2.26 mg/dl) appears, administration will be discontinued immediately and the patient will be withdrawn from the study.
3) In cases where the patient is 80 years old or above, the initial dose will be decreased by 75% in the next course.

Dexamethasone

If any of the following adverse events are observed, administration will be discontinued.

1) If gastric/duodenal ulcer is confirmed by endoscopy despite the prophylactic administration of a proton pump inhibitor or histamine H2 receptor antagonist (Grade 2 or higher).
2) If hyperglycemia requiring insulin treatment occurs (hyperglycemia Grade 3: fasting blood glucose ≥ 250 mg/dl) or if blood glucose control is poor even after insulin is used.
3) If administration of a major tranquilizer or antidepressant/antimanic drug is required after the initiation of R-GDP therapy.

Cisplatin

1) The dose will be reduced depending on renal function at the beginning of each course (including the initial starting dose).
   Serum Cr 1.58-2.25 mg/dl: 25% decrease from the next course.
   Serum Cr >2.26 mg/dl: administration will be discontinued from the next course, and the patient will be taken off the study.
2) Nonhematological toxicity
   In cases where Grade 3 nonhematological toxicity (except nausea, vomiting, and depilation) appears, the dose will be decreased by 25% from the next course.
   In cases where Grade 4 nonhematological toxicity appears, administration will be discontinued from the next course, and the patient will be withdrawn from the study.
3) In cases where the patient is 80 years old or above, the initial dose will be decreased by 75%.

Romidepsin

In patients with platelet count < 50,000 /μl, neutrophil count <1,000 /μl, Grade 3 nonhematological toxicity, QTc interval >500 ms, or arrhythmia, administration will be discontinued.

Safety evaluation following the conclusion of treatment

Post-therapy follow-up and observation will include a medical examination and blood test once every 3 months, and diagnostic imaging (CT scan) and evaluation of the intercurrent lesions at the time of registration once every 6 months. During follow-up, the presence or absence as well as the levels of adverse events will be evaluated and recorded on the patient's medical chart.

Efficacy evaluation following the conclusion of treatment

Efficacy evaluation following the end of the treatment will consist of a medical examination and blood test once every 3 months, and diagnostic imaging (CT) and evaluation of the intercurrent lesions at the time of registration once every 6 months. The absence or presence of a relapse, deterioration, or secondary cancer will be clinically assessed during all other times.

Statistical Considerations

Sample size. In a South Korean report on patients treated with GDP therapy, the median PFS was 9.3 months and the 2-year PFS rate was 20% [8], while in a Chinese report utilizing GDP the median PFS was 5.4 months [10]. Using these data as a reference, the 2-year PFS rate threshold will be set at 20%. In a Japanese study on romidepsin [11], the PFS rate was 20% at 17 months, and the median PFS was 5.6 months. In an overseas study on romidepsin [12], the 2-year PFS rate was 20% and the median PFS survival was 4 months. Based on these data, 20% will be added to GDP and the expected value will be set at 40%. When the number of patients necessary was calculated via a simulation based on survival analysis under the conditions of $\alpha = 0.10$ (one sided), $\beta = 0.20$, registration period of 3 years, and observation period of 2 years, the number of patients was calculated as 27. Considering patients who may be ineligible after registration, the sample size was set at 30.

Interim analyses and monitoring. No interim analyses will be carried out. Routine monitoring will be conducted once a year. Centralized monitoring will be conducted based on the data on case reports collected via Electronic Data Capture.

Statistical methods. The full analysis set (FAS) will include all registered patients. Regarding the protocol rules for treatment and combination therapy, the per-protocol set will exclude patients from the FAS who do not meet the eligibility criteria or who meet the exclusion criteria, as well as those who have taken prohibited concomitant medication or prohibited combination therapy. In addition, patients for whom serious violations of the protocol are noted (approval not obtained, serious violations concerning trial procedures) will be excluded. From the registered patients, the group excluding those who do not undergo any treatment will be identified as the safety analysis set.

Regarding efficacy evaluation, FAS is the main analysis set. To measure the response rate, the point estimate and an 80% confidence interval will be calculated. The PFS, OS, and time to response will be estimated using the Kaplan-Meier method. The 80% confidence interval for survival function will be calculated using Greenwood's formula. All the safety analyses will be performed relative to the safety evaluation set. For adverse events and serious adverse events, the point estimate of the proportion of occurrence and a 95% confidence interval will be calculated. Regarding the SF-36® and QOL-ACD, any temporal changes will be summarized.

Discussion

Results similar to or better than those of conventional therapies are anticipated in patients participating and receiving treatment in this study. The median PFS after GDP therapy in patients with PTCL has been reported to range from 9 to 10 months. Currently, no therapy is available to prolong the OS in patients with PTCL [9, 10]. Many patient factors affect OS in elderly patients, and their conditions are often complicated by previous illnesses and organ damage. Therefore, when the treatment intensity in elderly patients is increased to a level similar to that in a young person, it often becomes difficult to counter a tumor's resistance to therapy. Romidepsin has the potential to be effective against tumors other than hematopoietic malignancies. Hence, we can expect romidepsin to influence treatment development and to provide useful data for other cancerous tumors such as acute lymphocytic leukemia [13]. Two studies have described that the median time for response to romidepsin was 11.1 months [11, 12]; thus, we hypothesize that 12 months of treatment may be acceptable in elderly patients. It is important to comprehensively conduct medical evaluations by considering the clinical, QOL, and financial aspects. To date, we have been able to obtain information only on the impacts of therapy choices on patients' QOL and financial circumstances, the latter of which is difficult to verify. However, from the results of this clinical study, we can also expect to obtain information on the establishment of better therapies in patients with PTCL in the future.

Ethics approval and consent to participate. This study was approved in January 2019 by the clinical research central ethics review committee of a national hospital organization.

Prior to the commencement of this study, the principal investigator or investigators will obtain written informed consent based on each patient's free will.

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