Rituximab-Mediated Complement-Dependent Cytotoxicity Enhanced by Gemcitabine in Older Patients with Previously Rituximab-Treated Diffuse Large B-Cell Lymphoma: Study Protocol

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Summary: High-dose chemotherapy and autologous stem cell transplantation is too toxic for elderly patients with relapsed or refractory (DLBCL). Therefore, tolerable and efficient salvage regimens for elderly patients are greatly needed.

In this study, therapy with rituximab, gemcitabine, dexamethasone, and cisplatin (R-GDP) will be performed every 4 weeks, and an interim evaluation will be performed after the completion of the 3rd course. If a complete response (CR) is achieved at the time of interim evaluation, 1 course of R-GDP therapy and 2 courses of monotherapy with rituximab will be additionally performed. If a partial response (PR) is achieved, 3 courses of R-GDP therapy will be additionally conducted. In patients without a PR or CR by the time of the interim evaluation, treatment will be discontinued. Treatment will also be discontinued at any point if disease progression is observed during protocol treatment. After the completion of the final course of R-GDP therapy, final effects of the regimen will be evaluated. A primary endpoint is the efficacy of R-GDP therapy (CR and response rates).

This is the first multicenter phase II clinical study of R-GDP therapy to examine post-treatment activities of daily living in addition to the safety and efficacy of treatment in elderly patients with relapsed or refractory transplant-ineligible DLBCL.

Key words diffuse large B-cell lymphoma, rituximab, gemcitabine, dexamethasone, cisplatin, elderly patients
INTRODUCTION

With the rapid aging of society, the number and mean age of patients with hematological malignancies is increasing every year. Advanced age is reportedly a prognostic factor for hematological malignancies. This may be because aging influences disease and patient factors, reducing the responsiveness to chemotherapy and increasing the risk of treatment-associated death. When relapse is detected after therapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in young patients with diffuse large B-cell lymphoma (DLBCL), high-dose chemotherapy and autologous stem cell transplantation is performed as the standard treatment. However, no therapy has been standardized as salvage chemotherapy for patients aged \( \geq 65 \) years. In the latest National Comprehensive Cancer Network guidelines, many combination therapies with rituximab are recommended for transplantation-ineligible DLBCL. Hayashi et al reported that gemcitabine treatment synergistically increased rituximab-mediated complement-induced cell activity and suggested that a combination of gemcitabine and rituximab might enhance the antitumor efficacy of rituximab against DLBCL due to CD20 upregulation on the lymphoma cells [1]. No clinical trials have been conducted to clarify the superiority or inferiority of various rituximab therapies.

A phase II clinical study involving relapsed or refractory DLBCL patients aged 60 to 70 years in Algeria showed that the incidences of Grade 3-4 leukopenia and thrombocytopenia in patients receiving GDP therapy (gemcitabine, dexamethasone, cisplatin; \( n=48 \)) were significantly lower than in those receiving ESHAP therapy (etoposide, cisplatin, cytarabine, methylprednisolone; \( n=48 \)). The 3-year overall/disease-free survival rates were 63/20.5 and 55/10.9\%, respectively [2]. Prior to that study, another phase II study of GDP therapy (\( n=51 \)) involving patients with relapsed or refractory non-Hodgkin’s lymphoma who received R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin) were 70.0 and 48.0\%, respectively [5], but no study has examined the efficacy of R-GDP therapy in patients aged \( \geq 65 \) years. This is the first multicenter, phase II clinical study of R-GDP therapy to examine posttreatment ADL in addition to the safety and efficacy of treatment in elderly patients with relapsed or refractory transplantation-ineligible DLBCL.

METHODS

Study settings

This is a multicenter, open-label, single-arm phase II study. Twenty medical institutions in Japan will participate. The efficacy and safety of R-GDP therapy will be investigated in 65-year-old or older patients with relapsed or refractory previously rituximab-treated DLBCL.

Eligibility criteria

Patients meeting all inclusion criteria and not meeting any exclusion criterion will be registered. These criteria are presented in Table 1.

Interventions

The outline of test treatment is shown in Fig. 1. Hospital or outpatient care is selected based on the attending physicians’ evaluation. Prior to the start of administration of each course of chemotherapy, the necessary examinations should be conducted from the day before administration until the day of administration, and patients must meet all of the following criteria: 1) neutrophil count: \( \geq 500/\mu L \), 2) platelet count: \( \geq 20,000/\mu L \), 3) the absence of adverse events corresponding to grade 3 or higher non-hematological toxicities, 4) serum creatinine level: \( \leq 2.0 \text{ mg/dL} \), and 5) patients requiring platelet transfusion, and number of episodes requiring admission were lower. The quality of life (QOL) score during the treatment period was higher in the GDP therapy group, suggesting that the QOL was maintained. GDP therapy does not require continuous intravenous drip, and no central venous catheter is required. Therefore, this treatment method facilitates a transition to short-term admission or outpatient care. As a result, the patient’s QOL during treatment and posttreatment activities of daily living (ADL) may be maintained, contributing to a reduction in health/nursing expenditure. Hou et al reported that the 2-year overall and progression-free survival of patients with relapsed or refractory aggressive B-cell non-Hodgkin’s lymphoma who received R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin) were 70.0 and 48.0\%, respectively [5], but no study has examined the efficacy of R-GDP therapy in patients aged \( \geq 65 \) years. This is the first multicenter, phase II clinical study of R-GDP therapy to examine posttreatment ADL in addition to the safety and efficacy of treatment in elderly patients with relapsed or refractory transplantation-ineligible DLBCL.
R-GDP therapy will be performed every 4 weeks. Rituximab at 375 mg/m²/day will be intravenously dripped once per day on Days 1 through 7, and gemcitabine at 1,000 mg/m²/day on Days 1 and 8. Dexamethasone at 40 mg/day will be orally administered or intravenously dripped on Days 1 to 4. Cisplatin at 75 mg/m²/day will be intravenously dripped on Day 1. After the 3rd course of R-GDP therapy, interim evaluation will be performed using computed tomography (CT). If a complete response (CR) is achieved, 1 course of R-GDP therapy and 2 courses of monotherapy with rituximab will be additionally performed, and treatment will be completed. If a partial response (PR) is achieved, 3 courses of R-GDP therapy will be additionally conducted. In patients without a PR or CR (stable disease or poorer) at the intermediate response evaluation, and those who show disease progression at any point during protocol treatment, treatment will be discontinued. After completion of the final course of R-GDP therapy scheduled, final effects of the regimen will be evaluated using CT and positron emission tomography (PET)-CT. Furthermore, posttreatment efficacy assessment will be performed using CT 6 months after the completion of treatment.

Standard for dose adjustment

Gemcitabine
1) In cases where Grade 3 non-hematological toxicity (excluding nausea, vomiting, and hair loss) appears, the dose will be decreased by 25% from the next course.
2) In cases where non-hematologic toxicity or renal dysfunction of Grade 4 (serum Cr > 2.26 mg/dL) appears, administration will be discontinued from the next course and the patient will be removed from the study.
3) In cases where the patient is 80 years of age or older, initial doses will be decreased by 25%.

Dexamethasone
If any of the following adverse events are observed, administration will be discontinued thereafter.
1) Gastric/duodenal ulcer is confirmed by endoscopy despite prophylactic administration of proton pump inhibitor or histamine H2 receptor antagonist (Grade 2 or higher)
2) In cases where hyperglycaemia requiring insulin treatment appears (hyperglycemia Grade 3: fasting blood glucose > 250 mg/dL or more), or when blood glucose control is poor even when insulin is used.
3) If major tranquilizer or antidepressant/antimanic drug administration is required after the initiation of R-GDP therapy.

Cisplatin
1) The dose is 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: discontinuing administration from the next course and the patient will be removed from the study.
2) Non-hematological toxicity
   In cases where Grade 3 non-hematologic toxicity (except nausea, vomiting, and depilation) appears, the dose will be decreased by 25% from the next course.
   In cases where Grade 4 non-hematological toxicity appears, administration will be discontinued from the next course and the patient will be removed from the study.
   In cases where the patient is 80 years of age or older, initial doses will be decreased by 25%.

Endpoints
A primary endpoint is the efficacy of R-GDP therapy (CR and response rates). The response rate is defined as the proportion of CR + PR patients among all eligible patients. Tumor-reducing effects will be evaluated using the Revised Response Criteria for Malignant Lymphoma [6]. Secondary endpoints include the safety (type and incidence of adverse events), 2-year progression-free survival rate (PFS), 2-year overall survival rate (OS), and 2-year freedom from progressive disease (FFPD) rate.
survival rate (OS), time to response (defined as the period from the registration day until the day on which a response of PR or CR is first confirmed), quality of life (QOL), inpatient-to-outpatient period, and expenditure required. The PFS is measured by time from the start of treatment until either the day on which the patient’s condition is deemed to have progression or relapse, or the date of death due to any cause, whichever comes first. Patients without progression are censored at the final day on which the patient’s condition is confirmed not to have progression. Safety will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events ver. 4.0. For QOL, the QOL Questionnaire for Cancer Patients Treated with Anticancer Drugs (QOL-ACD) and SF-36® will be used. The admission and outpatient care

| TABLE 1. | Eligibility criteria |
|-----------|---------------------|
| Inclusion criteria |
| 1) Patients aged 65 years or older. |
| 2) Tissue diagnosis for DLBCL (according to the World Health Organization), documented at initial diagnosis or at relapse. Biopsy proof at relapse is desirable but not mandatory. More than 3 cycles of rituximab in combination with chemotherapy for prior DLBCL. |
| 3) CD20 positive either at diagnosis or relapse. |
| 4) Measurable disease is defined. |
| 5) Eastern Cooperative Oncology Group performance status 0, 1, or 2. |
| 6) Laboratory Requirements: |
| Absolute granulocytes > 1.0 × 10^9/L, Platelets > 50 × 10^9/L, LV ejection fraction of > 50% |
| Pulmonary sufficiency (PaO_2 > 60 mmHg or SpO_2 > 93% on room air), aspartate aminotransferase or alanine aminotransferase < 5 × upper limit of normal, Creatinine clearance > 30 ml/min |
| 7) Patient is able and willing to complete the quality of life questionnaires in validated translations. Inability (illiteracy, loss of sight, or other equivalent reason) to complete the questionnaires will not make the patient ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the patient ineligible. |

Exclusion criteria

1) B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma (intermediate DLBCL/BL) or Burkitt lymphoma

2) Testicular lymphoma or central nervous system involvement by lymphoma. Patients diagnosed with CNS disease at the time of relapse (on-study) are not eligible. Patients diagnosed with CNS disease at initial presentation who achieved and maintained CNS CR at the time of relapse are eligible. Lumbar puncture must be done in this case prior to study entry to demonstrate CNS CR status.

Tests to investigate CNS involvement are required otherwise only if clinically indicated.

3) Uncontrolled liver, kidney, cardiac or pulmonary dysfunction, or diabetes mellitus or hypertension.

4) Interstitial lung disease or pulmonary fibrosis.

5) Uncontrolled bacterial, fungal, or viral infection.

6) Patients with a history of cardiac dysfunction or cardiovascular disease (< 6 months at diagnosis).

7) Patients with a history of other malignancies, except: curatively treated in-situ cancer of the cervix, stomach, or colon, or other solid tumors curatively treated with no evidence of disease for > 5 years.

8) Positive for HBs-Ag, HCV-Ab, and/or HIV-Ab.

9) Drug hypersensitivity syndrome.

10) Patient is not able and willing to complete the consensus.

11) Other serious intercurrent illness or medical condition judged by the local investigator to preclude safe administration of the planned protocol treatment.

DLBCL, diffuse large B-cell lymphoma; BL, Burkitt lymphoma; CNS, central nervous system; CR, complete response.
periods required after the completion of treatment will be investigated using a survey sheet. Concerning the expenditure required (hospitalization fee related to DLBCL), expenditure from the start of treatment until final response evaluation will be surveyed.

Sample size

In a phase II study involving recurrent or refractory DLBCL patients aged 60 to 70 years in Algeria, the response rate for GDP therapy (n=48) was 63% [2]. In another phase II study of GDP therapy (n=51) involving recurrent or refractory DLBCL patients aged 18 to 84 years (median age: 57 years) in Canada, the response rate was 49% [3]. The same research group conducted a phase III study of GDP therapy (n=310) involving recurrent or refractory DLBCL patients aged 19 to 71 years (median age: 55 years), and reported that the response rate was 45% [4]. A retrospective survey at the National Hospital Organization Kyushu Medical Center regarding salvage chemotherapy (carboplatin, dexamethasone, etoposide, and irinotecan) in recurrent or refractory DLBCL patients (median age: 73 years) for whom massive anticancer drug treatment with autologous peripheral blood stem cell transplantation was not indicated, showed an overall response rate of 56%, and a rate of 45% even in patients with a poor prognosis [7]. In this study, patients aged \( \geq 65 \) years will be enrolled, and the response rate is expected to be 55%, considering the difference in age. Among studies regarding GDP therapy, the response rate was the lowest (45%) in the above study conducted by Crump et al. The above survey in the Kyushu Medical Center indicated that the response rate was 45% even in the poor prognosis group. The subjects of this study will consist of high-risk and refractory patients, and the threshold response rate was set at 35%, regarding a response rate 10% lower than the above value as showing the treatment to be ineffective and unacceptable as a clinical treatment.

Null hypothesis was established as a true response rate \( \leq \) threshold response rate, and alternative hypothesis as a true response rate > threshold response rate. The required number of patients was calculated as 38 based on a binomial cumulative distribution function under the following conditions, with expected and threshold response rates set at 55% and 35%, respectively: \( \alpha = 0.05 \) (one-tailed), \( \beta = 0.20 \). Estimating that ineligible patients after registration may account for approximately 10%, the target number of patients was established as 42.

Interim analyses and monitoring

In this study, interim analysis will not be conducted.

Regular monitoring will be performed twice a year. Central monitoring will be conducted based on the data described in case reports collected on electronic data capture.

Pathology review process

The pathology review will be conducted in 2 steps. First, an expert hematopathologist will review and classify all cases according to the WHO classification [8]. The phenotype will be determined using available tissue blocks to perform a standard phenotype panel and, if indicated, cytogenetic and molecular studies including MYC rearrangement in addition to BCL2 and/or BCL6 rearrangements (as detected by FISH or standard cytogenetics) will be done to detect double hit lymphoma [9]. The local and regional phenotype data, along with any cytogenetic or molecular results, will be tabulated for review. Then, the regional expert pathologist will render the diagnosis and will quantify various pathologic parameters.

Statistical methods

The eligible patients receiving protocol treatment after registration is defined as the efficacy analysis set. All patients receiving protocol treatment after registration is defined as the safety analysis set. The point estimation and 90% confidence interval of the response rate will be calculated. The incidence of adverse events and serious adverse events will be calculated. The PFS, OS, and time to response will be calculated using the Kaplan-Meier method. Greenwood’s formula will be used to calculate the 90% confidence interval. Serial changes in the QOL-ACD and SF-36 will be described.

DISCUSSION

GDP therapy is available for patients with relapse after standard-dose R-CHOP therapy, as it is not necessary to pay attention to the total dose of anthracyclines. Gemcitabine has been selected as a standard therapy for solid tumors, such as small cell lung cancer, pancreatic cancer, bile duct carcinoma, urothelial cancer, breast cancer, and ovarian cancer. Many elderly patients have patient factors, especially a history of other diseases or the presence of organ disorders; therefore, it is often difficult to reduce tumors’ resistance to treatment by elevating the intensity of treat-
ment, as compared with young patients. The use of drugs whose safety and efficacy have been established for tumors other than hematological malignancies may meet various medical needs without the large expenditure required for the development of new drugs. This study may contribute to future applications. It is important to comprehensively evaluate medical practice from the viewpoints of clinical effects, QOL, and costs. The influence of treatment selection on the patient’s QOL and medical economic aspects, which has been difficult to investigate, may also be clarified.

COMPETING INTERESTS: The authors declare that they have no competing interests.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE: The protocol of this study was approved by the Clinical Research Central Ethics Review Board of the National Hospital Organization in October 2014. This study has been registered in the Clinical Trial Registry (UMIN-CTR) (UMIN000015492). Prior to this study, the principal investigator or investigators should obtain written informed consent based on patient’s free will.

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