

Clinical Study Protocol

The Effect of Interim FDG-PET-guided Response-Adapted Therapy in Pediatric Patients with Hodgkin's Lymphoma (HL-14): Protocol for a Phase II Study

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This trial enrolls patients with untreated Hodgkin's lymphoma aged < 20 years at diagnosis and examines the effects of omitting radiation therapy if the FDG-positron emission tomography (PET) findings after two completed cycles of combination chemotherapy are negative. It thereby aims to determine whether patients who truly require radiation therapy can be identified by FDG-PET. If so, this modality could be used to omit radiation therapy for all other patients, decreasing the risk of serious long-term complications without affecting survival rates. The outcomes of patients for whom FDG-PET is used to assess early treatment response will also be determined.

Key words: Hodgkin's lymphoma, pediatric, fludeoxyglucose positron emission tomography

Pediatric Hodgkin's lymphoma (HL) accounts for approximately 4% of cases of pediatric cancer

overall and 40% of cases of malignant lymphoma in Western countries; the incidence is lower in Japan. In the 1970s, combination chemotherapy was demon-

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strated to be an effective treatment, and the concomitant use of irradiation yielded high cure rates. However, this led to serious long-term complications (gonadal disorders, second cancers, cardiac disorders, pulmonary disorders, etc.) and non-tumor-related deaths [1]. Therefore, since the 1990s, clinical trials have been conducted (primarily in the West) with the goal of reducing long-term complications (*i.e.*, alleviating the burden of treatment) while maintaining high survival rates.

An increasing number of attempts are being made to omit irradiation in the treatment of pediatric HL [2-5]; some trials have demonstrated that among patients who have achieved a complete response (CR) through chemotherapy, the overall survival (OS) of those for whom irradiation was omitted is at least equal to that of patients who undergo irradiation. However, to date, no prospective clinical trial for pediatric HL has been designed or conducted in Japan.

Positron emission tomography (PET) is an essential tool for assessing the initial staging of cancers, including lymphoma, and therapeutic responses. Recent prospective clinical trials of HL have already used PET after completing 2-3 cycles of combination chemotherapy (interim PET), and incorporated it to change the content of treatment during the treatment course. However, there is currently little evidence that PET-guided changes in therapeutic strategies lead to improved therapeutic outcomes; hence, such changes must be assessed with a clinical trial.

Among pediatric clinical trials that attempted omission of radiotherapy, the actual omission rate was 29.9% in the COG 5942 study (in which all risk cases were enrolled and irradiation was performed only for non-CR cases) [2], 10.8% in the GPOH HD 2002 study (all risk cases were enrolled and irradiation was performed only for non-CR cases with low-risk) [4], 38.8% in the COG 59704 study (high-risk cases were enrolled and irradiation was performed only for non-CR cases) [5], and 53.4% in the Stanford, St. Jude and Dana Farber consortium (low-risk cases were enrolled and irradiation was performed only for non-CR cases) [3], respectively. Some of these trials reported that the OS was equivalent between cases using chemotherapy with radiation and those using chemotherapy without radiation therapy.

Endpoints

The primary endpoint of the present study is the event free survival (EFS) rate at 5 years. EFS is defined as the duration from the day of registration in the study until the first day of remission-induction failure, relapse, secondary-cancer, or death. If there are no events, the patients will be censored at the final day of observation. The day of event for remission-induction failure is the day of registration in the study. The day of event for secondary-cancer or relapse is the assessment day for evaluation.

The secondary endpoints are: (1) overall survival (OS) rate at 5 years; (2) proportion of complete response (CR) at either PET2 or PET3; (3) OS and EFS in the irradiation group; (4) OS and EFS in the no-irradiation group; (5) the proportion of patients with negative interim PET results (the proportion not undergoing irradiation); (6) assessment of diagnosis (agreement between conventional testing using CT/magnetic resonance imaging [MRI] and FDG-PET); (7) assessment of response at end of treatment (agreement between conventional testing using CT/MRI and FDG-PET); (8) incidence of complications (pulmonary disorders, cardiac disorders, failure to thrive, hypothyroidism, gonadal disorders, and second cancers) during the follow-up period; (9) incidence of adverse events; and (10) associations between serum cytokine levels and outcomes.

Eligibility Criteria

Inclusion criteria. Patients who fulfilled all of the following criteria were deemed eligible: (1) histological diagnosis of HL, (2) age <20 years at diagnosis, (3) completed prior-case registration to the JPLSG CHM-14 study, and (4) consent from the patient or their guardian based on sufficient verbal and written explanation.

Exclusion criteria. Patients to whom any of the following applied were excluded from registration. (1) Hepatic, renal, or cardiac dysfunction that would interfere with trial treatment. This assessment was based on the following laboratory values obtained within 14 days prior to or on the day of registration: Total bilirubin level ≥ 3 times the reference value for the patient's age; creatinine level ≥ 3 times the reference value for the patient's age; serious cardiac abnormali-

ties requiring treatment, as detected by electrocardiography; and a Lansky score [6] < 30 (however, if deterioration in the Lansky score is believed to be due to HL, a score as low as 10 is acceptable). (2) Past use of anticancer agents and/or irradiation. (3) Degenerative central nervous system lesions. (4) Intracranial bleeding that would interfere with treatment (Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0; grade ≥ 3). (5) Difficult-to-control infections (including active pneumonia and human immunodeficiency virus infection, the latter determined by antibody testing). (6) Current pregnancy or potential pregnancy. (7) Lactating women. (8) Past history of malignant neoplasm or multiple cancers. (9) Past history of congenital or acquired immunodeficiency syndrome. (10) Deemed ineligible for any other reason, as determined by the investigator.

Methods

Study design. This is a multicenter, single-treatment trial of the risk-adapted omission of irradiation for patients with negative PET results, following an initial treatment response to combination chemotherapy. The trial is registered with the University Hospital Medical Information Network (UMIN) clinical trial registration system (UMIN000019093). The protocol for the present trial was reviewed and approved by the Institutional Review Board of the Japanese Society of Pediatric Hematology/Oncology.

Intervention. All patients will undergo FDG-PET as many as 3 times: prior to starting treatment (PET1); during treatment, after completing 2 cycles of

chemotherapy (PET2); and after the conclusion of treatment (PET3) (see Fig. 1). Low-risk patients (IA, IB, IIA) will undergo 2 cycles of OEPA (vincristine, etoposide, prednisolone, and doxorubicin) (boys) or OPPA (vincristine, procarbazine, prednisolone, and doxorubicin) (girls); if PET2 results are negative, treatment is concluded and no irradiation will be given. Intermediate-risk patients (IEA, IEB, IIEA, IIB, IIIA) will undergo 2 cycles of OEPA (boys) or OPPA (girls) and 2 cycles of COPDAC (cyclophosphamide, vincristine, prednisolone, and dacarbazine) (boys) or COPP (cyclophosphamide, vincristine, procarbazine, and prednisolone) (girls); if the PET2 results are negative, treatment is concluded and no irradiation will be given. High-risk patients (IIEB, IIIEA, IIIEB, IIIB, IVA, IVB) will undergo 2 cycles of OEPA (boys) or OPPA (girls) and 4 cycles of COPDAC (boys) or COPP (girls); if the PET2 results are negative, treatment is concluded and no irradiation will be given. All patients with positive PET2 results will undergo involved-field irradiation, or involved-site or node irradiation (20-36 Gy) following completion of chemotherapy. To balance the risk of irradiation with the long-term complications that can result from the intensification of chemotherapy to compensate for the omission of radiation, the framework of the chemotherapy regimen in the present study is based on that used in the GPOH-02 study [4], in which cardiotoxicity and infertility were successfully reduced by omitting radiation therapy for CR cases of low-risk patients and by substituting a less gonadotoxic alkylating agent, dacarbazine, for procarbazine for boys, without compromising outcomes.

The results of PET scans will be interpreted in cen-

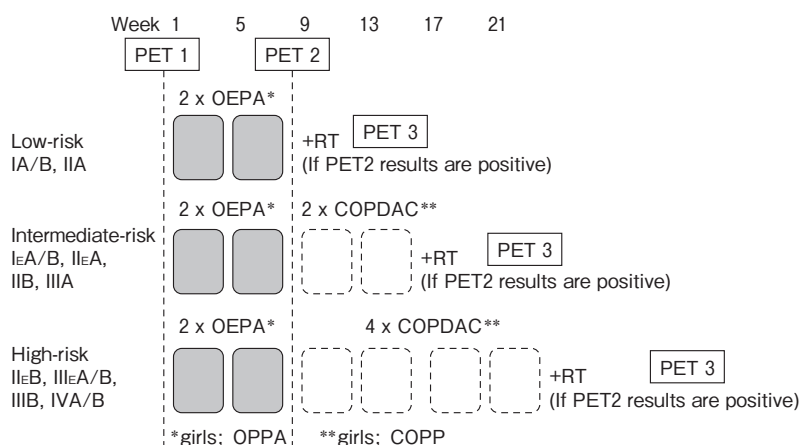


Fig. 1 COPDAC, cyclophosphamide, vincristine, prednisolone, dacarbazine; COPP, cyclophosphamide, vincristine, procarbazine, prednisolone; OEPA, vincristine, etoposide, prednisolone, doxorubicin; OPPA, vincristine, procarbazine, prednisolone, doxorubicin.

tral review using the Deauville criteria (a 5-point scale) [7]. For patients who discontinue protocol treatment or do not undergo PET, no treatment will be prescribed; however, these patients will be followed up.

Statistical Considerations

Sample size. In a retrospective study conducted in Japan, the EFS rate at 5 years of patients with HL was 81.5% for the overall population and 73% for the intermediate-to-high-risk population. In the present study, we presume that the EFS should be at least as high as that of intermediate-to-high-risk patients; therefore, the threshold EFS rate was set at 73% [8]. Also, non-Japanese studies that have attempted to reduce the use of irradiation have reported EFS rates at 5 years of 78-96%; in the GPOH-HD 2002 study, which is similar to the PET-based early diagnosis used in the present trial, the EFS rate at 5 years was 89% [4]. Therefore, the expected EFS rate was set at 89%. Assuming a 5-year registration period and 5-year follow-up period, and using a level of statistical significance of 0.05 (one-tailed) and power of 90%, nonparametric calculation revealed that a sample size of 47 patients was necessary. Taking dropouts into account, the number of patients was set at 50.

Analysis set. The efficacy analysis set is the full analysis set. It comprises registered eligible patients who began the protocol treatment, excluding the following: registered patients later deemed ineligible, and incorrectly registered patients. The safety analysis set comprises patients for whom protocol treatment was begun following registration.

Statistical analysis. EFS and OS rates will be estimated using the Kaplan-Meier method, overall and stratified according to whether irradiation was given or omitted. The 90% CI for yearly survival rates will be calculated using Greenwood's formula. The confidence interval of the proportion of CR will be calculated based on the binomial distribution. For PET positive/negative results and CR achievement/non-achievement at diagnosis and assessment of response at the end of treatment, the agreement, sensitivity, specificity, and positive and negative predictive values will be calculated. The effect of serum cytokine levels at diagnosis on EFS will be examined using a Cox proportional hazard model. The incidence of severe adverse events (grade ≥ 3) and of complications occurring during follow-up

will also be calculated.

Discussion

The present study aims to determine, within the confines of safety, whether assessing treatment response using PET (which is highly sensitive and specific) enables the identification of patients who truly require radiation therapy, thereby enabling omission of radiation therapy for all other patients without affecting survival rates. The present study also aims to determine pediatric HL treatment outcomes in patients for whom FDG-PET is used to assess early treatment response. This is anticipated to lead to the development of alternative therapeutic methods with fewer long-term complications.

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