

Clinical Study Protocol

R-mini CHP in ≥ 80 -year-old Patients with Diffuse Large B-cell Lymphoma: A Multicenter, Open-label, Single-arm Phase II Trial Protocol

Yasuhiko Miyata^{a*}, Akiko M. Saito^b, Takahiro Yano^c, Isao Yoshida^d,
Youko Suehiro^e, Naoki Harada^f, and Hirokazu Nagai^a

^aDepartment of Hematology, ^bClinical Research Center, Nagoya Medical Center, Nagoya 460-0001, Japan,
^cDepartment of Hematology, Tokyo Medical Center, Tokyo 152-8902, Japan,
^dDepartment of Hemato-oncology, Shikoku Cancer Center, Ehime 791-0280, Japan,
^eDepartment of Hematology, Kyushu Cancer Center, Fukuoka 811-1395, Japan,
^fDepartment of Hematology, Kyushu Medical Center, Fukuoka 810-8563, Japan

In very-elderly diffuse large B-cell lymphoma (DLBCL) patients, treatment intensities must be lowered due to the risks of comorbidities and organ function deterioration, and treatment outcomes are worse compared to younger patients. Very-elderly patients are often excluded from DLBCL clinical trials, and optimal treatments and dosages are not established. In this clinical trial, we examined the efficacy and safety of 6 courses of R-mini CHP therapy (cf., CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone]) in which vincristine is omitted to avoid the peripheral neuropathy that reduces elderly patients' quality of life, as remission induction therapy in DLBCL patients aged ≥ 80 years.

Key words: rituximab, diffuse large B-cell lymphoma, open-label, single arm trial

Treatment for advanced aggressive non-Hodgkin's lymphoma (NHL)—the most common type of which is diffuse large B-cell lymphoma (DLBCL)—has progressed rapidly since the 1970s. CHOP therapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) was developed in 1976 as a first-generation cancer regimen requiring the once-monthly administration of a combination of the several different types of chemotherapeutic agents. Based on the hypothesis the intensification of treatment would lead to improved outcomes, second-generation cancer regimens were developed by combining 6 or more drugs with different mechanisms of action over a short period. Since the late 1980s, third-generation regimens have been developed by adding drugs with relatively less bone-marrow suppression activity to be administered between intensive

chemotherapy courses, with the aim of reducing the treatment intervals.

The results of a large-scale randomized controlled trial of untreated, advanced-stage aggressive NHL (predominantly DLBCL) were reported in 1993. The 3-year survival rate did not differ significantly between the patients who were treated with first-generation CHOP therapy and those treated with second-/third-generation combination chemotherapy, but the CHOP therapy was the least toxic. CHOP therapy has thus been established as a standard therapy for aggressive NHL, including DLBCL [1].

A controlled trial for untreated, limited-stage aggressive NHL compared 8 courses of CHOP therapy and three courses of CHOP therapy followed by involved field radiation therapy (IFRT), and the patients who received three courses of CHOP therapy

Received July 7, 2017; accepted December 4, 2017.

*Corresponding author. Phone: +81-52-951-1111; Fax: +81-52-972-7740
E-mail: miyatay@nnh.hosp.go.jp (Y. Miyata)

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

followed by IFRT achieved significantly better 5-year progression-free survival (PFS) and overall survival (OS) rates [2]. However, in the follow-up surveillance, recurrence after 5 years was more frequent in the three CHOP courses/IFRT group, and the PFS after 7 years and OS after 9 years were found to be better in 8 courses of CHOP group.

The CD20 antigen is a differentiation antigen expressed in nearly all mature B lymphocytes (plasma cells are an exception), and it plays an important role in B-cell activation. CD20 expression is also observed in around 95% of mature B-cell lymphomas and essentially all cases of DLBCL. Rituximab is a chimeric monoclonal antibody targeted against the CD20 antigen and a chimeric anti-CD20 antibody with a recognition site (variable region) originating from mouse and a remainder (constant region) originating from human. The CD20 antigen has excellent properties as a target for antibody therapy because it does not exhibit the shedding and internalization associated with antibody binding. Rituximab monotherapy was first used in the treatment of B-cell follicular lymphoma (FL), and it has shown significant clinical activity. It thus became evident that rituximab would improve outcomes by being administered concomitantly with chemotherapy, and this combination is now considered a standard therapy for FL.

DLBCL is also a mature B-cell lymphoma and is CD20-positive; therefore, the combined use of rituximab with chemotherapy has been hypothesized to be an effective treatment for DLBCL. In fact, CHOP therapy combined with rituximab (R-CHOP therapy) significantly improved the complete response rate, PFS rate, and OS compared to CHOP therapy alone in untreated patients with DLBCL aged 60-80 years [3]. In addition, R-CHOP therapy was demonstrated to be beneficial in young low-risk DLBCL patients [4], and it has been established as a standard therapy for low-risk DLBCL in patients up to the age of 80 years.

Many clinical trials have been conducted with the aim of improving outcomes in elderly patients with DLBCL, and it was shown that adding rituximab to chemotherapy and maintaining the treatment intensity improves the outcomes [3,5]; however, the patients enrolled in those trials were aged 61-80 years.

Very elderly patients (aged ≥ 80 years) often have comorbidities and/or a loss of major organ reserve such as that of the heart, liver, kidneys, and bone marrow,

and these patients experience poorer outcomes [6,7]. In the cases of very elderly patients, it is difficult to adapt high-intensity treatments similar to those used for patients below the age of 80, and the dosages of anti-cancer drugs are frequently reduced by physicians' choices. Consequently, therapy with an unnecessarily-lowered intensity may be administered [8,9], or chemotherapy may be even considered contraindicated based on age alone [10,11]. These are thought to be one of the causes of poorer outcomes in the elderly patients.

In addition, very elderly patients are much more likely to experience more intense treatment-related toxicities, and thus they are also more likely to experience a decline in quality of life (QOL). Thus, very elderly patients are often excluded from clinical trials, and optimal treatments and dosages for these patients are not established. Only a limited amount of information is available about these cases; this is a single report by Peyrade in which the 2-year PFS rate was 47%, the 2-year OS rate was 59%, and the overall response rate was 73% [5].

As the populations of most industrialized countries have continued to age, there has been a significant increase in the number of elderly patients, including very elderly patients, with DLBCL. Thus, the purpose of the present clinical trial is to establish candidate treatments that are effective and minimize any decline in QOL for very elderly patients with DLBCL (aged ≥ 80 years). This is also regarded as important for the establishment of treatment strategies for elderly patients with other types of malignant lymphoma in Japan.

Endpoints

Primary endpoint. The primary endpoint of this trial is the 2-year progression-free survival (PFS) rate.

Secondary endpoints. The secondary endpoints are (1) the 2-year overall survival (OS) rate, (2) the complete remission rate, (3) the safety profile of the mini-CHP regimen, *i.e.*, the incidences of adverse events, and (4) the incidence of febrile neutropenia.

Eligibility Criteria

Inclusion criteria. The inclusion criteria for the trial are as follows. (1) Pathological diagnosis: diffuse large B-cell lymphoma, NOS (not otherwise specified); (2) CD20 antigen-positive; (3) CS (clinical stage)

I bulky, CSII/III/IV; (4) presence of measurable lesions; (5) no prior therapy for lymphoma except pre-treatment with prednisolone; (6) age ≥ 80 years old; (7) Performance Status (PS) (ECOG [Eastern Cooperative Oncology Group]) 0-2; (8) adequate organ functions; (9) informed consent is provided by the patient.

Exclusion criteria. The exclusion criteria for the trial are as follows. (1) The presence of active infection, (2) the presence of central nervous invasion, (3) a past history of glaucoma, (4) a past history of severe drug allergy, (5) HIV Ab-positive or HTLV-1 Ab-positive, (6) HBsAg-positive or HCV Ab-positive, (7) severe cardiac disease, (8) hepatic cirrhosis, (9) uncontrollable diabetes mellitus, (10) being on dialysis, (11) lung fibrosis or interstitial pneumonitis, (12) other active malignancies, (13) pregnant or breastfeeding female, (14) severe mental disorder, (15) continuous systemic administration of a steroid, and (16) judged inappropriate for other reasons.

Methods

Study design. This is a multicenter, open-label, single-arm phase II clinical trial involving 24 institutions. The trial was approved by Japan's National Hospital Organization Central Research Ethics Committee (H24-NHO (hematology)-01). Registration of the trial participants began in May 2013 and was completed in October 2016. The observation period is ongoing. The study was registered in the UMIN-CTR (University Hospital Medical Information Network Clinical Trials Registry) on July 19, 2013 (UMIN 000011234).

The trial's design is shown in Fig. 1.

Treatment methods. For elderly patients, the intensification of treatment will cause severe adverse effects, reducing their QOL. We will thus examine whether six courses of R-mini CHP therapy as remission induction therapy is effective and minimizes any decline in QOL in very elderly DLBCL patients (*i.e.*, those aged 80 years or older). R-mini CHP therapy is a modification of the R-mini CHOP therapy which has successfully reduced febrile neutropenia as a backbone regimen, and but R-mini CHP therapy omits vincristine in comparison with R-mini CHOP therapy. R-mini CHP therapy can reduce the incidence of severe infections such as febrile neutropenia to the same extent as R-mini CHOP therapy. Moreover, R-mini CHP therapy

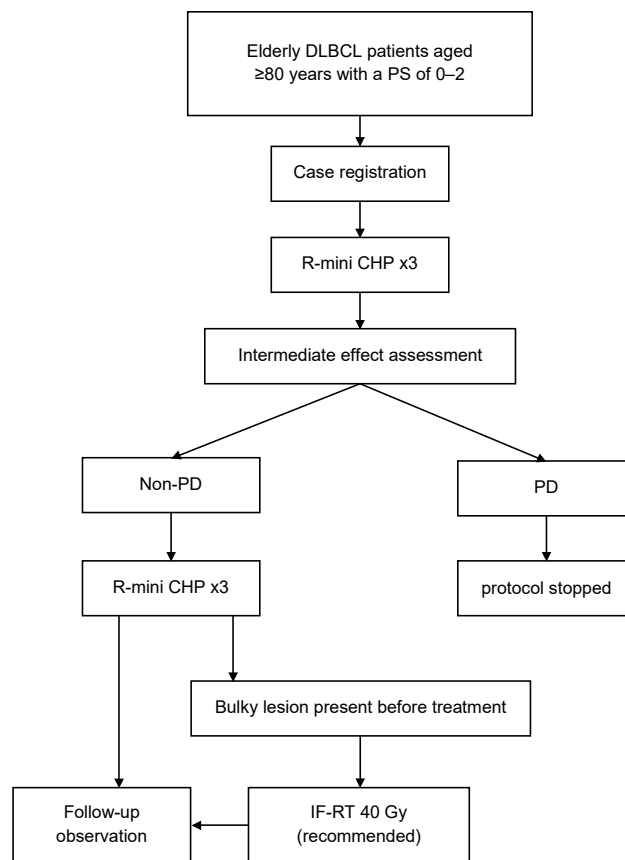


Fig. 1 Trial design.

can avoid peripheral neuropathy by omitting vincristine. Consequently, R-mini CHP therapy is expected to contribute to the maintenance of QOL in this patient population.

One course of R-mini CHP therapy consists of rituximab (375 mg/m² of body surface area/day) administered on day 1, doxorubicin hydrochloride (25 mg/m² of body surface area/day) and cyclophosphamide (500 mg/m² of body surface area/day) administered on any one day of day 1 to day 3, and prednisolone (40 mg/m² of body surface area/day) administered from one of day 1-day 3 for 5 days. For cases in which progression disease (PD) is confirmed as an intermediate therapeutic effect after three courses of R-mini CHP therapy, the protocol treatment will be discontinued.

Although no particular stipulations will be made in terms of subsequent treatment if bulky lesions are present before treatment, involved field radiation (IFRT) will be recommended, with consideration given to the patient's condition. Up to two courses of an additional

administration of rituximab within 6 months of the completion of six courses of R-mini CHP therapy will also be allowed.

Statistical Considerations

Sample size. Patients are followed up for 2 years after the last patient has been included. The primary endpoint is the 2-year PFS rate. We assume the expected and threshold values for the primary endpoint of 54% and 40%, respectively. Forty patients are required with an α error of 0.10 (two-sided) and a β error of 0.80.

Statistical analysis. The primary analysis will verify whether R-mini CHP therapy for patients with DLBCL aged ≥ 80 years is sufficiently effective and whether it has an acceptable range of adverse events (treatment-related toxicity and treatment-related mortality). The 2-year PFS rate, which is the primary endpoint, is to be estimated using the Kaplan-Meier method, with the 95% confidence interval calculated using Greenwood's formula. All patients will be analyzed, with the exceptions of patients who subsequently become ineligible cases of duplicate registration or mis-registration, and patients excluded from the analysis as a result of investigations by the Protocol Review Committee/Monitoring Review Committee.

Interim analysis and monitoring. An interim analysis will not be conducted. Monitoring will be performed twice annually, in principle, in order to assess whether the study is proceeding safely and in accordance with protocol, and whether data are being collected correctly.

Discussion

The purposes of this clinical trial are to establish candidate treatments that are effective and to minimize any decline in QOL for DLBCL patients aged ≥ 80 years. This is also regarded as important for the establishment of treatment strategies for elderly patients with other types of malignant lymphoma in Japan.

Acknowledgments. H.N. has received research funding and honoraria from Chugai Pharmaceutical Co., Ltd. The other authors declare that they have no competing interests.

References

1. Fisher RI, Gaynor ER, Dahlborg S, Oken MM, Grogan TM, Mize EM, Glick JH, Coltman CA Jr and Miller TP: Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med* (1993) 328: 1002–1006.
2. Miller TP, Dahlborg S, Cassady JR, Adelstein DJ, Spier CM, Grogan TM, LeBlanc M, Carlin S, Chase E and Fisher RI: Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. *N Engl J Med* (1998) 339: 21–26.
3. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, Morel P, Nester EVD, Salles G, Gaulard P, Reyes F, Lederlin P and Gisselbrecht C: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* (2002) 346: 235–242.
4. Pfreundschuh M, Trumper L, Osterborg A, Pettengell R, Trnony M, Imrie K, Ma D, Gill D, Walewski J, Zinzani PL, Stahel R, Kvaloy S, Shpilberg O, Jaeger U, Hansen M, Lehtinen T, López-Guillermo A, Corrado C, Scheliga A, Milpied N, Mendila M, Rashford M, Kuhnt E, Loeffler M and MabThera International Trial Group: CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol* (2006) 7: 379–391.
5. Peyrade F, Jardin F, Thieblemont C, Thyss A, Emile JF, Castaigne S, Coiffier B, Haioun C, Bologna S, Fitoussi O, Lepeu G, Fruchart C, Bordessoule D, Blanc M, Delarue R, Janvier M, Salles B, André M, Fournier M, Gaulard P, Tilly H and Groupe d'Etude des Lymphomes de l'Adulte (GELA) investigators: Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. *Lancet Oncol* (2011) 12: 460–468.
6. Corazzelli G, Frigeri F, Arcamone M, Lucania A, Rosariavilla M, Morelli E, Amore A, Capobianco G, Caronna A, Becchimanzi C, Volzone F, Marcacci G, Russo F, De Filippi R, Mastrullo L and Pinto A: Biweekly rituximab, cyclophosphamide, vincristine, non-pegylated liposome-encapsulated doxorubicin and prednisone (R-COMP-14) in elderly patients with poor-risk diffuse large B-cell lymphoma and moderate to high 'life threat' impact cardiopathy. *Br J Haematol* (2011) 154: 579–589.
7. Thieblemont C and Coiffier B: Lymphoma in older patients. *J Clin Oncol* (2007) 25: 1916–1923.
8. van Spronsen DJ, Janssen-Heijnen ML, Lemmens VE, Peters WG and Coebergh JW: Independent prognostic effect of co-morbidity in lymphoma patients: results of the population-based Eindhoven Cancer Registry. *Eur J Cancer* (2005) 41: 1051–1057.
9. Kobayashi Y, Miura K, Hojo A, Hatta Y, Tanaka T, Kurita D, Iriyama N, Kobayashi S and Takeuchi J: Charlson Comorbidity Index is an independent prognostic factor among elderly patients with diffuse large B-cell lymphoma. *J Cancer Res Clin Oncol* (2011) 137: 1079–1084.
10. Bairey O, Benjamini O, Blickstein D, Elis A and Ruchlemer R: Non-Hodgkin's lymphoma in patients 80 years of age or older. *Ann Oncol* (2006) 17: 928–934.
11. Thieblemont C, Grosseuvre A, Houot R, Broussais-Guillaumont F, Salles G, Traulle C, Espinouse D and Coiffier B: Non-Hodgkin's lymphoma in very elderly patients over 80 years. A descriptive analysis of clinical presentation and outcome. *Ann Oncol* (2008) 19: 774–779.