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Clinical trials of a mouse-human chimeric anti-CD20 monoclonal antibody (rituximab) for B cell non-Hodgkin's lymphoma in Japan

Abstract Rituximab, a mouse-human chimeric anti-CD20 monoclonal antibody, induces apoptosis in B cell non-Hodgkin's lymphoma (B-NHL) cells, in addition to lysis by complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity. A group of 12 patients with relapsed $CD20^+$ B-NHL were enrolled in a phase I study; 4 received rituximab 250 mg/m^2 and 8 375 mg/m^2 once weekly for 4 weeks. Grade 1 or 2 infusion-related toxicity such as 'flu-like symptoms and skin reactions were observed. Of the 11 patients eligible for study enrollment, 2 achieved a complete response (CR) and 5 a partial response (PR). The $T_{1/2}$ of rituximab was 445 ± 361 h, and serum rituximab levels were measurable at 3 months. Thereafter, 90 relapsed patients with indolent B-NHL or mantle cell lymphoma (MCL) were enrolled in a phase II study and received rituximab 375 mg/m^2×4 weekly infusions. A central pathology review and an extramural review disclosed that 13 patients were ineligible for final analysis. Factors affecting response and progression-free survival (PFS) were analyzed in the remaining 77 patients. The overall response rate (ORR) in indolent B-NHL and MCL was 61% (37/61, 95% CI 47–73%) and 46% (6/13, 95% CI 19–75%), respectively. The median PFS time was 245 days in indolent B-NHL and 111 days in MCL patients. Multivariate analysis revealed that the ORR was affected by the number of prior regimens ($P = 0.018$) and that the PFS was affected by the following three factors: disease type ($P = 0.000$), presence of extranodal lesions ($P = 0.001$), and number of prior regimens ($P = 0.007$). The PFS times of patients with higher serum rituximab concentrations at day 14 (≥70 μg/ml) and at 3 months (≥10 μg/ml) were significantly longer than those of patients with lower concentrations ($P = 0.006$ and $P = 0.0001$, respectively). In conclusion, rituximab is more effective in indolent B-NHL than in MCL. Several prognostic factors and serum rituximab concentrations are useful for predicting the therapeutic efficacy.

Keywords Monoclonal antibody therapy · CD20 · B cell lymphoma · Rituximab

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Introduction

The majority of patients with indolent B cell non-Hodgkin lymphoma (B-NHL) are not curable using current treatment modalities. Therefore new agents with different mechanisms of action are required. Monoclonal antibodies (mAbs) have been found to be one of the most promising treatment strategies.

The CD20 antigen is a 35-kDa cell surface nonglycosylated hydrophobic phosphoprotein expressed consistently on nearly all human B cells (Fig. 1). Most B-NHLs express this antigen on the cell surface. The CD20 antigen is not modulated by antibody binding and is not shed from the cell surface, and thus provides an ideal target for mAb therapy. Various types of mAb therapy targeting the CD20 molecule have been investigated, including unconjugated murine anti-CD20 mAbs and radiolabeled murine anti-CD20 mAbs. However, murine mAbs have several limitations when used in humans, such as high immunogenicity, a short half-life, and low efficiency in activating human immune effector cells, which limits further clinical applications.

Rituximab is a chimeric IgG-1κ mAb with mouse variable and human constant regions that recognizes the CD20 antigen [5, 9]. High-level expression of the gene encoding rituximab was obtained by transfection of the relevant gene constructs into Chinese hamster ovary

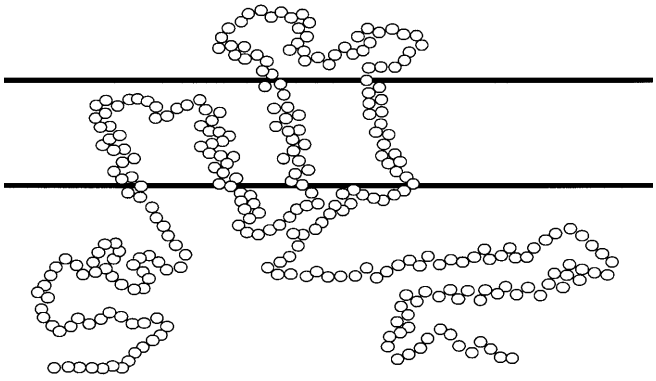

Fig. 1 Schematic representation of the CD20 antigen

cells. In vitro experiments have revealed that rituximab binds human complement C1q, mediating the complement-dependent cytotoxicity to human B cell lymphoma cell lines, and that the antibody lyses human B cells through antibody-dependent cell-mediated cytotoxicity [1, 9].

In the USA, consecutive clinical trials including a single-dose phase I study, a multiple-dose phase I/II study, and a pivotal multicenter study of rituximab have been conducted [5, 6, 7, 8]. The dose selected for the multicenter study was four weekly 375 mg/m^2 infusions [6]. The adverse drug reactions (ADRs) associated with rituximab infusion were mainly nonhematologic grade 1 or 2 episodes, all of which resolved soon after completion of each infusion with supportive treatment [6, 7, 8]. Hematologic toxicities were rare, not severe, and transient [6, 7, 8].

Clinical responses with long-lasting remissions were observed at the dose of four weekly 375 mg/m^2 infusions in the US trials [6, 7]. In the phase II part of the phase I/II study in the USA, in a total of 34 patients with CD20$^+$ B-NHL of low-grade or follicular histology, there were 3 complete and 14 partial responders, with an overall response rate (ORR) of 50% (17/34, 95% CI 33–67%). The median time to progression (TTP) of the responders was 10.2 months (range 4.3–20 months) [7]. The good response rate and relatively long TTP were reproduced in the subsequent pivotal multicenter trial in the USA, in which 166 patients with low-grade or follicular B-NHL were enrolled [8]. Considering the high response rates and acceptable toxicity profiles in the US trials, we investigated the potential use of this chimeric monoclonal antibody in treating Japanese B-NHL patients.

Feasibility and pharmacokinetic study of rituximab

Study design

The starting dosage was 250 mg/m^2 per infusion [6]. The dosage was escalated to 375 mg/m^2 per infusion if none of the three initial patients or not more than two of six patients in the 250 mg/m^2 arm developed critical toxicities. Six patients were scheduled to receive the 375 mg/m^2 per infusion if not more than two of the initial three patients developed critical toxicities, defined as grade 4 hematologic toxicity or grade 3 or higher nonhematologic toxicity.

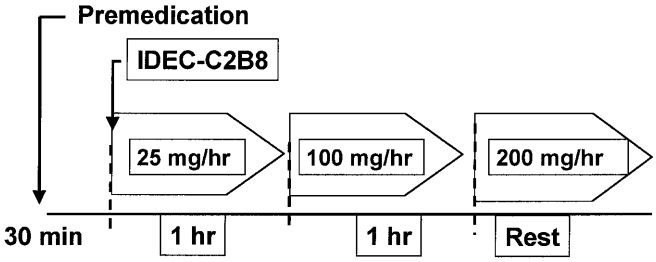

Fig. 2 Rituximab administration schedule

The appearance of human anti-mouse antibody (HAMA) and human anti-chimeric antibody (HACA) were determined before each infusion, and at 1 and 3 months after the final infusion using a sandwich enzyme-linked immunoabsorbent assay [6, 7].

Antitumor responses were evaluated according to the World Health Organization criteria at monthly intervals until tumor progression or for at least 3 months after the final infusion. Complete response (CR) was defined as the disappearance of all evidence of disease for at least 4 weeks. Partial response (PR) was defined as a ≥50% decrease in the product of the perpendicular diameters of the indicator lesion(s) with no new lesion for at least 4 weeks. Progressive disease was defined as a ≥25% increase in the product of the perpendicular diameters of the indicator lesion(s) or the appearance of new lesions. All other categories of tumor response were defined as no change.

Drug formulation and administration

Rituximab was supplied in vials containing 100 mg/10 ml normal saline by IDEC Pharmaceuticals (San Diego, Calif.) through Zenyaku Kogyo Co.,Ltd. (Tokyo, Japan). The agent was diluted to the concentration of 1 mg/ml with normal saline, and was administered as an intravenous infusion starting at an infusion rate of 25 mg/h for 1 h, subsequently at 100 mg/h for 1 h, and finally at a maximum of 200 mg/h. Acetaminophen and diphenhydramine were administered 30 min prior to each rituximab infusion as prophylaxis for 'flu-like and cutaneous symptoms. The dosage and schedule of rituximab administration are shown in Fig. 2.

Patients

The patients enrolled were required to meet all of the following eligibility criteria: (1) histologically proven NHL expressing CD20 antigen as confirmed by immunohistochemistry or flow cytometry; (2) relapsed disease after or refractory to previous chemotherapy; (3) age between 20 and 75 years; (4) Eastern Cooperative Oncology Group performance status (PS) of 0 to 2; and (5) adequate organ function [10]. Each patient enrolled gave written informed consent for participation in the trial, and the study protocol was approved by the Institutional Review Boards of all participating institutions.

Four patients received the rituximab 250 mg/m^2 infusion and eight the 375 mg/m^2 infusion. One patient who was enrolled in the 250 mg/m^2 arm was judged ineligible because he had received granulocyte colony-stimulating factor until 1 day before the first rituximab infusion. All 11 eligible patients had received prior chemotherapy, including at least one combination regimen, and all required therapy due to disease progression. The median interval between the last prior therapy and rituximab administration was 60 days. The majority of patients (8/11) had lymphoma with follicular histology. Histologic subtypes in the remaining patients were diffuse large B cell lymphoma in two and mantle cell lymphoma (MCL) in one.

Pharmacokinetic study

During the 1st and 4th weeks of treatment, serum was collected immediately before starting the infusion and at 10 min, and 24, 48 and 120 h thereafter. During the 2nd and 3rd weeks, the samples were collected immediately before starting the infusion, and at 10 min and 120 h thereafter. Additional samples were taken at weekly intervals for 4 weeks after the final infusion and then monthly for 2 months. The pharmacokinetic parameters were calculated using WinNonlin Pharmacokinetic software (WinNonlin Standard Japanese Edition, version 1.1; Scientific Consulting, Apex, N.C.). The elimination half-life ($T_{1/2}$), and maximum concentration (C_{max}) were determined based upon either a one- or a two-compartment model, and the trapezoidal area under the curve (trapezoidal AUC) based upon a noncompartment model.

Results

Adverse drug reactions

Nonhematologic toxicities

All nonhematologic toxicities were of grade 2 or less, and only two of the eight patients who received the rituximab 375 mg/m^2 infusion developed grade 2 toxicities. The commonly observed toxicities were fever (6/11), chills/rigor (4/11), rash/urticaria (3/11), pruritus (3/11), and perspiration (3/11). These toxicities generally resolved within 24 h with standard supportive medication. They mainly occurred during the first infusion and decreased markedly during subsequent infusions.

Hematologic toxicities

Of 11 patients eligible for the study, 7 developed hematologic toxicities, but none was grade 4. Three patients experienced grade 3 toxicities (one neutropenia, one leukopenia with neutropenia, and one thrombocytopenia). All hematologic toxicities were transient. No infectious episodes were recorded.

Changes in B cell and T cell counts in peripheral blood, and serum levels of immunoglobulins and complement

In samples from 11 of 12 patients, peripheral blood B cells decreased to 0–2% of the total lymphocyte counts within 48 h after the first infusion. The decreased B cell counts did not recover within the 3-month observation period after the final infusion. There were no significant changes in T cell counts, or in serum immunoglobulin (IgG, IgM, and IgA) and complement C3 levels.

HAMA and HACA

HAMA and HACA were not detected in serum samples from any of the 12 patients.

Response

The antitumor effects of rituximab were evaluable in 11 patients. Of the three patients who received rituximab 250 mg/m^2, two achieved objective responses (one CR and one PR). In the eight patients who received rituximab 375 mg/m^2, five achieved objective responses (one CR and four PRs). The median time to response in the seven responders (two CRs and five PRs) was 19 days. The median TTP was 4.5+ months, with a median follow-up of 4.5 months. Seven of eight patients with lymphoma of follicular histology achieved objective responses.

Pharmacokinetics

The pharmacokinetic parameters fluctuated widely even among the patients who received the same rituximab dose. The mean values ($\pm$SD) of trapezoidal AUC and C_{max} in the 375 mg/m^2 dose group were 118,237 $\pm$ 53,412 μg/ml·h and 92.1 $\pm$ 34.3 μg/ml, respectively, which were higher than those in the 250 mg/m^2 dose group (91,343 $\pm$ 70,267 μg/ml·h and 64.3 $\pm$ 21.4 μg/ml). The $T_{1/2}$ was 560.8 $\pm$ 607.5 h in the 250 mg/m^2 group and 378.8 $\pm$ 188.7 h in the 375 mg/m^2 group. Overall, the mean $T_{1/2}$ of rituximab was 445.4 $\pm$ 361.4 h. In most patients, peak and trough levels at each infusion increased in parallel with the course of infusion, indicating a cumulative effect due to the long $T_{1/2}$. The serum levels of rituximab were measurable 3 months after the final infusion in most patients.

Phase II study in relapsed indolent B-NHL and MCL

Study design and endpoints

Patients with indolent B-NHL or MCL who had relapsed or were resistant to conventional chemotherapy were enrolled in our multicenter phase II study and divided into two groups: group I comprised patients with indolent B-NHL other than MCL; and group II patients with MCL [11]. Patients had to have at least one measurable lesion of ≥2 cm in the greatest diameter. The other eligibility and exclusion criteria were the same as those in the phase I study [10]. A total of 90 patients (69 in group I and 21 in group II) were enrolled. All patients gave written informed consent for study participation, and the study protocol was approved by the Institutional Review Boards of all participating institutions.

Of the 90 patients, 12 were judged ineligible by the central pathology review, and 4 were ineligible due to seropositivity for hepatitis B or hepatitis C virus, a concomitant infection, or more than 5000/μl lymphoma cells in the peripheral blood. Overall, 8 of 69 patients in group I and 8 of 21 patients in group II were ineligible. Bone marrow involvement was present in 19 patients (28%) in group I and in 11 (54%) in group II. The median number of previous chemotherapy regimens was 3 (range 1–12) in group I and 2 (range 1–9) in group II. The median time from the last therapy until study entry was 36 weeks in group I and 12 weeks in group II.

The primary endpoint in this study was ORR. Progression-free survival (PFS) and toxicity profiles were secondary endpoints.

Central review of pathology

The pathology of biopsied specimens from all patients enrolled in the study was reclassified according to the Revised

European-American Lymphoma Classification. Immunohistochemical analyses were conducted using anti-CD20, anti-CD3, anti-bcl-2, and anti-cyclin-D1 antibodies. These preparations were examined by a Central Pathology Review Committee composed of three hematopathologists.

Rituximab administration and premedications

The dose and schedule of rituximab in the phase II study was 375 mg/m^2×4 weekly infusions. The infusion schedule of rituximab, premedications, and prophylaxis against infusion-related toxicities were similar to those in our phase I study [10].

ADRs, response rate, and PFS

Evaluation of ADRs and response rates was conducted in a manner similar to that in the phase I study. PFS was defined for all eligible patients including nonresponders as the interval from the first day of rituximab infusion to the day on which disease progression or death from any cause occurred.

Results

Central pathology review

A central pathology review was performed of biopsies from 86 patients (96%). Agreement between the diagnosis at each institution (site diagnosis) and that by the Central Pathology Review Committee (consensus diagnosis) was 93% (62/67) in group I and 84% (16/19) in group II. The pathology of B-NHL was follicular in 83% of group I patients.

Nonhematologic toxicities

The most commonly observed nonhematologic toxicities were infusion-related symptoms such as fever, chills/rigor, nausea/vomiting, rash, pruritus, perspiration, asthenia, headache, pain, and urticaria, which mainly did not exceed grade 2. These symptoms generally occurred during the first infusion and decreased with subsequent infusions. Four patients developed grade 3 toxicities of skin rash, herpes zoster, left hypochondralgia with hypotension, and rigor with systemic perspiration.

Hematologic toxicities

Grade 3 or 4 hematologic toxicities were observed in 23 patients (26%). Five patients (6%) developed grade 4 neutropenia, two developed grade 3 thrombocytopenia, and one grade 4 thrombocytopenia. Five of six patients who developed grade 4 hematologic toxicities had lymphoma involvement of the bone marrow and/or peripheral blood.

Infection

Seven episodes of infection were noted within 6 months after rituximab administration of which five were grade 1. Grade 2 and 3 herpes zoster infections occurred in two patients.

Peripheral blood T cell and B cell counts

All except two patients exhibited a marked decrease in $CD19^+$ and $CD20^+$ cells after the first rituximab infusion. The decrease continued for at least 3 months, but showed a gradual recovery at 6 months or thereafter.

Monitoring of HACA development

Of the 90 patients who received rituximab infusion, 4 developed HACA.

Response rate and PFS

The ORR in 61 eligible patients in group I was 61% (95% CI 47–73%), including 14 patients (23%) who achieved CR and 23 patients (38%) who achieved PR. The ORR in the 13 eligible patients in group II was 46% (95% CI 19–75%), and all six responders achieved PR. The median PFS time in groups I and II was 245 days and 111 days, respectively.

Factors affecting response and PFS

Univariate and multivariate analyses of prognostic factors affecting the ORR and PFS were performed in 77 eligible patients. The ORR was significantly affected by the number of prior chemotherapy regimens ($P = 0.033$ by Fisher's exact test; $P = 0.017$ by logistic regression model). PFS was significantly associated with PS, disease type (indolent B-NHL vs MCL), B symptoms, extranodal disease, number of prior chemotherapy regimens (one regimen vs two or more regimens), and response to previous chemotherapy (all $P < 0.05$ by the log-rank test). Multivariate analysis demonstrated that disease type, extranodal disease, and number of prior chemotherapy regimens were significant factors affecting PFS (all $P < 0.05$ by Cox's proportional hazard regression model).

Serum rituximab levels and correlations with PFS

The precise data will be reported elsewhere, but the PFS of patients with higher serum rituximab concentrations at day 15 (≥70 μg/ml) and at 3 months (≥10 μg/ml) were significantly longer than for those with lower concentrations ($P = 0.006$ and $P = 0.0001$, respectively).

Discussion

The ADRs observed in our phase I and II studies of rituximab infusion were consistent with those in the US

trials. Most nonhematologic toxicities were of grade 2 or less, and they were mainly confined to 'flu-like symptoms and skin reactions during the infusion. They were all manageable with the use of antipyretics and antihistamine. In the phase I study, no dose-limiting toxicities were identified and the maximum tolerated dose was not reached [10]. The incidence of hematologic toxicities was slightly higher in the Japanese trials of rituximab [10, 11] than in the US trials [6, 8], presumably because blood cell counts were determined more frequently in Japan.

In the US trials, the serum levels of rituximab were significantly higher in responders than in nonresponders [8]. In the Japanese phase I study, the pharmacokinetic parameters fluctuated widely from patient to patient, and no significant differences in pharmacokinetic parameters were found between responders and nonresponders [10]. The marked interpatient variability in the pharmacokinetic parameters might be explained in part by the difference in total tumor volume or total number of CD20 molecules expressed on B lymphoma cells.

In the US trials, the $T_{1/2}$ of rituximab was found to be 33.2 ± 21.1 h in the phase I/II trial [6] and 225.9 ± 102.7 h in the phase II trial [7] using four weekly infusions of rituximab 375 mg/m^2. The $T_{1/2}$ observed in the Japanese phase I study was somewhat longer (387.7 ± 188.9 h at 375 mg/m^2 and 445.4 ± 361.4 h overall) than in the US trials [6, 7, 8, 10]. Compared with the US trials, the C_{max} and Cl rate values were lower in the Japanese phase I study. However, it remains unclear whether these differences in the pharmacokinetic parameters were due to racial or ethnic differences in the pharmacokinetics of rituximab, because the interpatient variability was large and detailed pharmacokinetic analyses were performed in only small numbers of patients.

The dose of four weekly infusions of rituximab 375 mg/m^2 established as the phase II dose in the previous US clinical trials was found to be safe and effective in Japanese patients with relapsed B cell lymphoma. The long $T_{1/2}$ of rituximab observed in the present study suggests that an effective concentration of the agent is maintained by this dosage and schedule for several months in most patients.

In the Japanese phase II study, we obtained an ORR in recurrent indolent B-NHL and recurrent MCL of 61% (95% CI 47–73%) and 46% (95% CI 19–75%), respectively. The ORR (61%) in group I (indolent B-NHL) was somewhat higher than in the US pivotal trial (48% for the intent-to-treat group of all 166 patients enrolled) [8], probably because no patients with small lymphocytic lymphoma (SLL) were enrolled in the Japanese phase II study, whereas 30 patients (18%) with SLL were enrolled in the USA and their ORR was only 13% [8]. The ORR in patients with follicular lymphoma in both studies was approximately 60%. Compared with the previously reported therapeutic results in MCL (ORR of 33–38%) [2, 3], the ORR in the 13 eligible patients in the Japanese phase II study (46%) was slightly higher, although when considering the wide range of 95% CI (19–75%) due to the small sample size, the therapeutic results in patients with MCL did not differ.

The only significant factor affecting the ORR in the Japanese phase II study was the number of prior chemotherapy regimens by both univariate and multivariate analyses, while in the US pivotal trial, histologic type, bone marrow involvement, bcl-2 positivity in the peripheral blood/bone marrow, and number of extranodal sites were significant [8]. In the Japanese phase II study, PFS was significantly associated with PS, disease type (indolent B-NHL vs MCL), B-symptom, extranodal disease, number of prior chemotherapy regimens, and response to the final prior chemotherapy by univariate analysis, and disease type, presence of extranodal disease, and number of prior chemotherapy regimens were significant by multivariate analysis. In

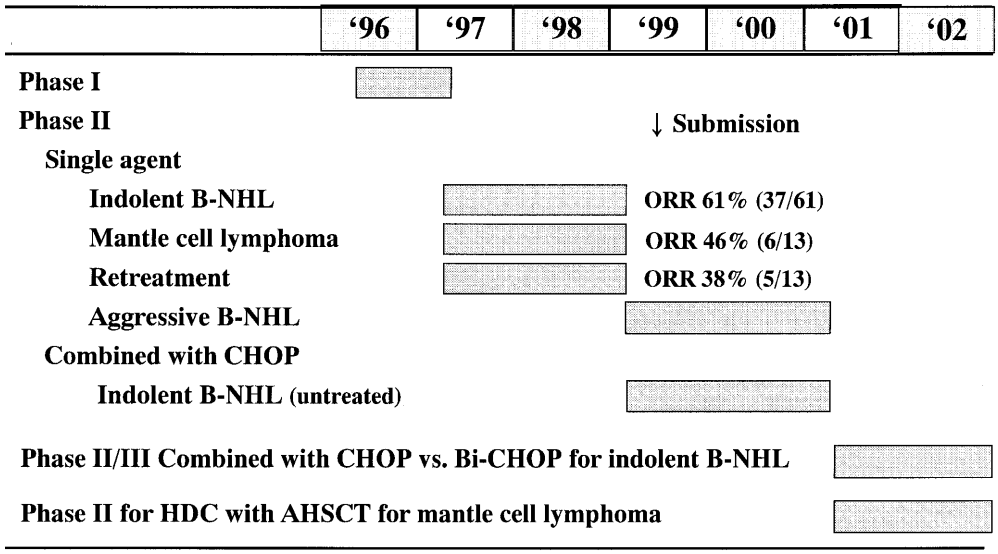

Fig. 3 Schematic representation of the clinical trials of rituximab in Japan (*CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisolone; *Bi-CHOP* CHOP every 2 weeks with the prophylactic use of granulocyte colony-stimulating factor, *HDC* high-dose chemotherapy, *AHSCT* autologous hematopoietic stem cell transplantation)

addition, the Japanese phase II study demonstrated that the PFS of the patients with higher serum concentration at day 15 (≥70 μg/ml) and at 3 months after (≥10 μg/ml) rituximab infusion was significantly longer than those of patients with lower serum concentrations. Therefore several prognostic factors and serum rituximab concentrations at specific time points might be useful in predicting the therapeutic efficacy of rituximab.

In the Japanese retreatment study in patients who had previously shown objective responses to rituximab, 5 of 13 patients (38%) achieved PR without major toxicities [4]. In 1999, two multicenter phase II studies were initiated in Japan: a single-agent phase II study of rituximab in relapsed or refractory aggressive B cell lymphoma, and a randomized phase II study of cyclophosphamide + doxorubicin + vincristine + prednisolone (CHOP) combined with rituximab comparing concurrent and sequential administration in previously untreated patients with advanced indolent B-NHL. Patient enrollment in both studies was completed in 2000. The complete scheme of the Japanese rituximab trials is shown in Fig. 3.

In conclusion, rituximab is a highly effective agent in relapsed indolent B-NHL and MCL with acceptable toxicities. Further studies of rituximab are warranted as single-agent therapy for aggressive B-NHL and in combination with other agents and hematopoietic stem cell transplantation.

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