Cancer Chemother Pharmacol (2003) 52 (Suppl 1): S90–S96
DOI 10.1007/s00280-003-0595-y

Kensei Tobinai

Monoclonal antibodies for the treatment of hematologic malignancies: clinical trials in Japan

Published online: 18 June 2003

Abstract Of 12 patients with relapsed $CD20^+$ B-cell non-Hodgkin's lymphoma (B-NHL) enrolled in a phase I study of rituximab, 11 were eligible, and of these 2 achieved a complete response and 5 a partial response. The elimination half-life of rituximab was 445 ± 361 h, and serum rituximab levels were detectable at 3 months after the final infusion. In a phase II study, 90 patients with relapsed indolent B-NHL or mantle cell lymphoma (MCL) were treated with infusions of rituximab 375 mg/m^2 once weekly for four doses. The overall response rate 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 progression-free survival (PFS) was shorter in MCL patients, in those with extranodal disease, and in those who had received two or more prior chemotherapy regimens ($P < 0.01$). Rituximab retreatment was well tolerated in 13 patients with relapsed indolent B-NHL and there were no grade 3/4 nonhematologic toxicities. Partial response was observed in five (38%, 95% CI 14–68%) patients, and the median PFS after retreatment was 5.1 months. In a single-agent phase II study of infusions of rituximab 375 mg/m^2 once weekly for eight doses against relapsed aggressive B-NHL showed, 21 (37%, 95% CI 24–51%) of the 57 eligible patients responded. In conclusion, rituximab is a highly effective agent in relapsed indolent and aggressive B-NHL and MCL with acceptable toxicities. Yttrium-90 provides advantages over iodine-131 because it delivers higher β energy. In 2002, we initiated a feasibility study of yttrium-90-labeled ibritumomab tiuxetan for relapsed indolent B-NHL in Japan. Gemtuzumab ozogamicin (CMA-676) is a calicheamicin-conjugated humanized anti-CD33 monoclonal antibody. Of 20 patients with relapsed or refractory acute myeloid leukemia enrolled in a "bridging" phase I/II study, 7 showed an objective response. It is concluded that monoclonal antibodies will play a significant role in the treatment of hematologic malignancies in the future.

Keywords Monoclonal antibody therapy · CD20 · B-cell lymphoma · Rituximab · Hematologic malignancy

This work was presented at the 18th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium, "New Strategies for Novel Anticancer Drug Development," 8–9 November 2002, Nagoya, Japan.

K. Tobinai
Hematology Division, National Cancer Center Hospital,
5-1-1 Tsukiji, Chuo-ku, 104-0045, Tokyo, Japan
E-mail: ktobinai@ncc.go.jp
Tel.: +81-3-35422511
Fax: +81-3-35423815

Introduction

Indolent B-cell non-Hodgkin's lymphoma (B-NHL) is not curable in the majority of patients using current treatment modalities. Therefore new agents with different mechanisms of action are required. The CD20 antigen is a 35-kDa cell-surface nonglycosylated hydrophobic phosphoprotein expressed consistently on nearly all human B cells and in most B-NHLs. The CD20 antigen is not modulated by antibody binding and is not shed from the cell surface, and thus provides an ideal target for monoclonal antibody (mAb) therapy.

Rituximab is a chimeric IgG1 mAb with mouse variable and human constant regions that recognizes the CD20 antigen [14, 18]. High-level expression of the gene encoding rituximab was achieved by transfection of the relevant gene constructs into Chinese hamster ovary cells. Several mechanisms have been proposed to account for the antitumor activities of rituximab, including antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), blockade of signaling pathways, activation of apoptosis, and extended half-life [2, 17, 18, 20].

Consecutive clinical trials of rituximab have been conducted in the USA [14, 15, 16, 17]. The adverse drug reactions (ADRs) were mainly nonhematologic grade 1 or 2 episodes. Clinical responses with long-lasting

remissions were observed using infusions of rituximab 375 mg/m^2 once weekly for four doses. In the phase II part of the phase I/II study in the USA, in 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% [16]. The good response rate and relatively long time to progression (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 [17].

Radiolabeled mAbs (radioimmunoconjugates) have been regarded as attractive agents for the treatment of NHL because lymphoma cells are inherently sensitive to radiation. The aim of radioimmunotherapy (RIT) is to use the mAb to target radiation to lymphoma tissue while minimizing toxicity to healthy cells. The most common radionuclide used for RIT has been iodine-131 (^{131}I). However, ^{131}I RIT has several limitations, such as long half-life of the radioisotope, dehalogenation of iodinated antibody both in blood and at tumor sites, hypothyroidism, and γ-emission of ^{131}I, which results in irradiation to distant organs, restrictions on the patient to prevent exposure to the family and the public, and hospitalization with shielding in some cases. Yttrium-90 (^{90}Y) has advantages over ^{131}I because it delivers higher β energy (2.3 vs 0.6 MeV) to the tumor site and has a path length of 5–10 mm, resulting in an improved ability to kill both targeted and adjacent tumor cells, an advantage in bulky or poorly vascularized tumors. Because ^{90}Y is a pure β-emitting radioisotope, hospitalization with shielding is not required. Although ^{90}Y cannot be used for imaging and dosimetry, mAbs conjugated with the γ-emitter indium-111 (^{111}In) have been successfully used.

Feasibility and pharmacokinetic study of rituximab in Japan

For a full report of this study, see reference 20.

Study design, patients, and methods

Under the administration schedule of infusions once weekly for four doses, the starting dosage was selected as rituximab 250 mg/m^2 per infusion [15]. The dosage was escalated to 375 mg/m^2 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, defined as grade 4 hematologic toxicity or nonhematologic toxicity of grade 3 or more. The appearance of human anti-mouse antibody (HAMA) and human anti-chimeric antibody (HACA) was determined using an enzyme-linked immunoabsorbent assay [15, 16, 20].

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 sum of the products (SPD) of the perpendicular diameters of the indicator lesion(s) without appearance of new lesions for at least 4 weeks. Progressive disease was defined as a >25% increase in the SPD of the indicator lesion(s) or appearance of new lesions. All other categories of tumor response were defined as no change.

Drug formulation and administration

Rituximab was supplied by IDEC Pharmaceuticals Corporation (San Diego, Calif.) through Zenyaku Kogyo Company (Tokyo, Japan). The agent 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 for the rest of the infusion. Acetaminophen and diphenhydramine were administered 30 min prior to each rituximab infusion as prophylaxis for influenza-like and cutaneous symptoms.

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 of 0–2; and (5) adequate organ function. Each patient gave written informed consent prior to inclusion in the study. The study protocol was approved by the institutional review boards of all participating institutions and the trial was performed in accordance with the Declaration of Helsinki.

Four patients received the rituximab 250-mg/m^2 dosage and eight the 375-mg/m^2 dosage. One patient who was enrolled in the 250-mg/m^2 cohort was judged ineligible. All 11 eligible patients had received prior chemotherapy and all required therapy due to disease progression. The majority of patients (8/11) had lymphoma with follicular histology.

Pharmacokinetic study

During weeks 1 and 4 of treatment, serum was collected immediately before starting the infusion and at 10 min, and 24, 48 and 120 h after completion of the infusion. During weeks 2 and 3, samples were collected immediately before starting the infusion, and at 10 min and 120 h after the infusion. 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 on either a one- or a two-compartment model and the trapezoidal area under the curve (trapezoidal AUC) based on a noncompartment model.

Results

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 most common 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.

Hematologic toxicities

Seven patients developed hematologic toxicities, but none was grade 4. Three patients experienced grade 3 toxicities. All hematologic toxicities were transient.

Changes in B-cell counts in peripheral blood

In 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.

HAMA and HACA

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

Response

Of the three eligible 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 TTP was >4.5 months with a median follow-up of 4.5 months. Seven of eight patients who achieved objective responses had lymphoma of follicular histology.

Pharmacokinetics

The mean values ($\pm$SD) of the trapezoidal AUC and C_{max} in the 375-mg/m^2 dosage 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 dosage group (91,343 $\pm$ 70,267 μg/ml · h and 64.3 $\pm$ 21.4 μg/ml, respectively). 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. Rituximab was detectable in the serum 3 months after the final infusion in most patients.

Pivotal phase II study in relapsed indolent B-NHL and mantle cell lymphoma (MCL) in Japan

For a full report of this study, see reference 9.

Study design, patients, and methods

Patients with indolent B-NHL or MCL who had relapsed or were resistant to conventional chemotherapy were enrolled and divided into two groups: group I comprised patients with indolent B-NHL and group II patients with MCL. Patients had to be 15–75 years of age with at least one measurable lesion of 2 cm or more at the greatest diameter. All other eligibility criteria were the same as those in the phase I study [20].

Of the 90 enrolled patients (69 in group I and 21 in group II), 12 patients 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 >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 11 (52%) in group II. The median numbers of previous chemotherapy regimens were three in group I and two in group II. The primary endpoint was ORR. Progression-free survival (PFS) and toxicity profiles were secondary endpoints.

Central review of pathology

The pathology of biopsied specimens 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

The dosage and schedule of rituximab in the phase II study was infusions of rituximab 375 mg/m^2 once weekly for four doses.

ADRs, response rate, and PFS

Evaluation of ADRs and response rates was conducted in a manner similar to that in the phase I study [20]. 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 on biopsies from 86 patients (96%). Agreement between the diagnosis at each institution and that by the Central Pathology Review Committee was 93% (62/67) in group I and 84% (16/19) in group II. Follicular lymphoma accounted for 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. All nonhematologic toxicities were reversible.

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 in 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 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 up to 6 months or thereafter.

Monitoring of HACA development

Of the 90 patients who received rituximab infusion, four developed HACA. In three patients, HACA levels were below the quantifiable limit (3.9 ng/ml), while in one, HACA levels were 398 ± 53 ng/ml.

Response and PFS

The ORR in the 61 eligible patients in group I was 61% (95% CI 47–73%), including 14 CRs (23%) and 23 PRs (38%). The ORR in the 13 eligible patients in group II was 46% (95% CI 19–75%), and all six responders achieved a PR. The median PFS intervals in groups I and II were 245 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 patients whose histopathology was confirmed as indolent B-NHL or MCL. The ORR was significantly affected by the number of prior chemotherapy regimens. Multivariate analysis demonstrated that histopathologic diagnosis of MCL, extranodal disease, and the number of prior chemotherapy regimens were unfavorable factors significantly affecting PFS (all $P < 0.05$ by Cox's proportional hazard regression model).

Serum rituximab levels and correlations with PFS

The PFS intervals of patients with higher serum rituximab levels (≥70 μg/ml) before the third infusion were longer than those of other patients ($P < 0.05$).

Retreatment study in Japan

For a full report of this study, see reference 8.

Study design, patients, and methods

The purpose of this study was to investigate the toxicity and the efficacy of retreatment with rituximab in relapsed patients with indolent B-NHL who had responded to rituximab in the previous phase I or II study [9, 20]. A total of 13 patients with relapsed indolent B-NHL were enrolled in this retreatment study. All were retreated with rituximab at 375 mg/m^2 once weekly for four doses.

Results

Rituximab retreatment was well tolerated with no grade 3/4 nonhematologic toxicities, similar to the initial treatment. No patients developed detectable HACA. PR was observed in five of 13 patients (38%; 95% CI 14–68%), while six showed stable disease and two showed progressive disease. The median PFS after the retreatment was 5.1 months, while that after the initial treatment was 8.2 months. Although rituximab retreatment induced prolonged depletion of normal peripheral blood B cells in all patients, no significant decreases in serum immunoglobulin or complement level were observed.

Discussion

The toxicity profiles observed in Japanese phase I and II studies of rituximab infusion were consistent with those in the US trials. Most nonhematologic toxicities were grade 2 or less and mainly confined to influenza-like symptoms and skin reactions during the infusion. They were all manageable with the use of antipyretics and antihistamine. The incidence of hematologic toxicities was slightly higher in our Japanese trials [9, 20] than in the US trials [15, 17], presumably partly because blood cell counts were determined more frequently in our trial.

In the US trials, the serum levels of rituximab were significantly higher in responders than in nonresponders

[17]. In the Japanese phase I study, no significant differences in pharmacokinetic parameters were found between responders and nonresponders [20]. The marked interpatient variability in the pharmacokinetic parameters in our study 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 in serum was found to be 76.6 ± 43.7 h in the phase I/II trial [15] and 225.9 ± 102.7 h in the phase II trial [16] using infusions of rituximab of 375 mg/m^2 once weekly for four doses. The $T_{1/2}$ observed in the Japanese phase I study [20] 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 [15, 16, 17]. Compared with the US trials, the C_{max} and clearance 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 difference because the interpatient variability was large and detailed pharmacokinetic analyses were performed in only small numbers of patients.

In the Japanese phase II study, we achieved an ORR in recurrent indolent B-NHL and recurrent MCL of 61% and 46%, respectively. The ORR (61%) in group I (indolent B-NHL) was higher than that in the US pivotal trial (48% for the intent-to-treat group of all 166 patients enrolled) [17], probably because no patients with small lymphocytic lymphoma were enrolled in our study [9], whereas 30 patients (18%) with small lymphocytic lymphoma were enrolled in the USA and their ORR was only 13% [17]. The ORR in patients with follicular lymphoma in both studies was approximately 60%. Compared with the previous report on therapeutic results in MCL in Europe (ORR of 33–38%) [3, 7], the ORR in the 13 eligible patients in the Japanese phase II study (46%) was slightly higher. However, when considering the small sample size, the therapeutic results in MCL would not be different between Europe and Japan.

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, histopathologic type, bone marrow involvement, BCL-2 positivity in the peripheral blood/bone marrow, and the number of extranodal sites were significant [17]. In the Japanese phase II study, PFS was significantly associated with performance status, histopathologic diagnosis of MCL, B symptoms, extranodal disease, number of prior chemotherapy regimens, and response to the last prior chemotherapy by univariate analysis, and histopathologic diagnosis of MCL, presence of extranodal disease, and number of prior chemotherapy regimens were significant by multivariate analysis [9]. In addition, the Japanese phase II study demonstrated that the PFS of the patients with higher serum concentrations at day 15 (≥70 μg/ml) after rituximab infusion was significantly longer than those of patients with lower serum concentrations ($P < 0.05$). Several prognostic factors and serum rituximab concentrations at specific timepoints might be useful in predicting the therapeutic efficacy of rituximab.

In the Japanese retreatment study, five of 13 patients (38%) achieved PR without major toxicities [8]. It remains to be determined whether retreatment with rituximab can produce a PFS similar to that achieved by the initial treatment. In the US retreatment study, the TTP of the responders at retreatment was 17.8 months ($n = 57$) [6]. The PFS analyzed in the Japanese retreatment study is for all patients including nonresponders, whereas the US study addressed the TTP for responders alone. When we calculated the median TTP for responders ($n = 5$) in the present study, it was as short as 5.3 months, showing some difference between the two studies.

The findings of the Japanese retreatment study suggest that retreatment with rituximab did not produce either a better response rate or a longer PFS when compared with that achieved in the initial treatment. Several factors may lead to resistance to rituximab treatment, including a decrease in CD20 antigen expression, the appearance of another tumor clone resistant to rituximab, and either decreased ADCC or decreased CDC activity [19]. Some studies have suggested that a clone other than CD20-positive cells may appear during antibody treatment [12]. Despite these findings, we obtained an approximately 40% ORR and the meaningful prolongation of PFS in responders by rituximab retreatment. In addition, three patients achieved PR at every retreatment, and showed prolonged PFS, e.g. up to 4 years after the initial treatment of rituximab in the longest case. These results suggest that further evaluation of multiple treatments with rituximab is warranted.

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-NHL, 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. In the former phase II study of rituximab 375 mg/m^2 once weekly for eight doses in recurrent aggressive B-NHL, the Independent Computed Tomography Review Committee found that ORR was 35% (24/68) in enrolled patients and 37% (21/57, 95% CI 24–51%) in eligible patients [10], according to the International Workshop Criteria [1]. The complete scheme of the Japanese rituximab trials is shown in Fig. 1.

After the approval of rituximab by the Ministry of Health, Labour and Welfare of Japan in 2001, two new trials incorporating rituximab are in preparation. One is a phase II/III study of rituximab in combination with CHOP and biweekly CHOP for untreated advanced-stage indolent B-NHL. In the biweekly arm we expect to observe a synergistic action between rituximab and

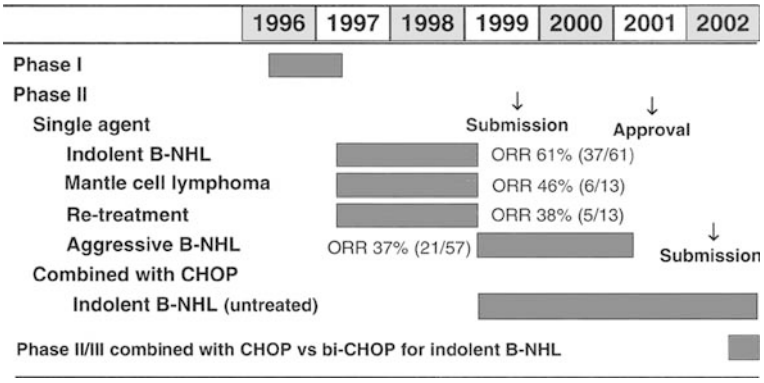

Fig. 1 Schematic representation of the clinical trials of rituximab in Japan (*B-NHL* B-cell non-Hodgkin's lymphoma, *CHOP* cyclophosphamide + doxorubicin + vincristine + prednisolone, *bi-CHOP* CHOP every 2 weeks with the prophylactic use of granulocyte colony-stimulating factor, *ORR* overall response rate). Figure slightly modified with kind permission of the Japanese Society for Hematology from Fig. 4 of Tobinai K (2002) Int J Hematol 76:411

granulocyte colony-stimulating factor. Another study is a phase II study of high-dose chemotherapy for untreated MCL, and we expect to observe an in vivo purging effect of rituximab.

Promising results have been reported for phase II and III studies of rituximab in combination with CHOP for untreated patients with indolent and aggressive B-NHL [4, 5, 21]. Murine anti-CD20 radioimmunoconjugates such as ^{90}Y-labeled ibritumomab tiuxetan and ^{131}I-tositumomab have shown encouraging therapeutic results in relapsed or refractory B-NHL [11, 22, 23]. In 2002, we initiated a feasibility study of ibritumomab tiuxetan for relapsed indolent B-NHL in Japan. In addition, new mAbs targeting CD22 such as humanized antibody *Pseudomonas* exotoxin-conjugated immunotoxin and chemoimmunoconjugate are being developed for B-cell malignancies [13].

Gemtuzumab ozogamicin (CMA-676) is a calicheamicin-conjugated humanized anti-CD33 mAb. In a "bridging" phase I/II study, 20 patients with relapsed or refractory acute myelogenous leukemia were enrolled, and seven showed objective responses. It is concluded that monoclonal antibodies will play a significant role in the treatment of hematologic malignancies in the future.

Acknowledgements Clinical studies of rituximab were supported in part by Zenyaku Kogyo Company Ltd., Tokyo, Japan. We thank all the investigators, including the physicians and nurses in the institutions participating in Japanese multicenter trials. We thank the members of the Central Pathology Review Committee, the Independent Computed Tomography Review Committee, and the Independent Data Monitoring Committee.

References

1. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, Lister TA, Vose J, Grillo-López A, Hagenbeek A, Cabanillas F, Klippenstein D, Hiddemann W, Castellino R, Harris NL, Armitage JO, Carter W, Hoppe R, Canellos GP (1999) Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. J Clin Oncol 17:1244
2. Clynes RA, Towers TL, Presta LG, Ravetch JV (2000) Inhibitory Fc receptors modulate in vivo cytotoxicity against tumor targets. Nat Med 6:443
3. Coiffier B, Haioun C, Ketterer N, Engert A, Tilly H, Ma D, Johnson P, Lister A, Feuring-Buske M, Radford JA, Capdeville R, Diehl V, Reyes F (1998) Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. Blood 92:1927
4. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, Morel P, Van Den Neste E, Salles G, Gaulard P, Reyes F, Lederlin P, Gisselbrecht C (2002) CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 346:235
5. Czuczman MS, Grillo-López AJ, White CA, Saleh M, Gordon L, LoBuglio AF, Jonas C, Klippenstein D, Dallaire B, Varns C (1999) Treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy. J Clin Oncol 17:268
6. Davis TA, Grillo-López AJ, White CA, McLaughlin P, Czuczman MS, Link BK, Maloney DG, Weaver RL, Rosenberg J, Levy R (2000) Rituximab anti-CD20 monoclonal antibody therapy in non-Hodgkin's lymphoma: safety and efficacy of re-treatment. J Clin Oncol 18:3135
7. Foran JM, Rohatiner AZ, Cunningham D, Popescu RA, Solal-Celigny P, Ghielmini M, Coiffier B, Johnson PW, Gisselbrecht C, Reyes F, Radford JA, Bessel EM, Souleau B, Benzohra A, Lister TA (2000) European phase II study of rituximab (chimeric anti-CD20 monoclonal antibody) for patients with newly diagnosed mantle-cell lymphoma and previously treated mantle-cell lymphoma, immunocytoma, and small B-cell lymphocytic lymphoma. J Clin Oncol 18:317
8. Igarashi T, Ohtsu T, Fujii H, Sasaki Y, Morishima Y, Ogura M, Kagami Y, Kinoshita T, Kasai M, Kiyama Y, Kobayashi Y, Tobinai K (2001) Re-treatment of relapsed indolent B-cell lymphoma with rituximab. Int J Hematol 73:213
9. Igarashi T, Kobayashi Y, Ogura M, Kinoshita T, Ohtsu T, Sasaki Y, Morishima Y, Murate T, Kasai M, Uike N, Taniwaki M, Kano Y, Ohnishi K, Matsuno Y, Nakamura S, Mori S, Ohashi Y, Tobinai K (2002) Factors affecting toxicity, response and progression-free survival in relapsed patients with indolent B-cell lymphoma and mantle cell lymphoma treated with rituximab: Japanese phase II study. Ann Oncol 13:928
10. Igarashi T, Itoh K, Kobayashi Y, Ogura M, Kinoshita T, Taniwaki M, Hiraoka A, Hotta T, Aikawa K, Tsushita K, Tobinai K (2002) Phase II and pharmacokinetic study of rituximab with eight weekly infusions in relapsed aggressive B-cell non-Hodgkin's lymphoma (B-NHL). Proc Am Soc Clin Oncol Abstract 1142

11. Kaminski MS, Zelenetz AD, Press OW, Saleh M, Leonard J, Fehrenbacher L, Lister TA, Stagg RJ, Tidmarsh GF, Kroll S, Wahl RL, Knox SJ, Vose JM (2001) Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 19:3918
12. Kinoshita T, Nagai H, Murate T, Saito H (1998) CD20-negative relapse in B-cell lymphoma after treatment with rituximab. J Clin Oncol 16:3916
13. Kreitman RJ, Wilson WH, Bergeron K, Raggio M, Stetler-Stevenson M, FitzGerald DJ, Pastan I (2001) Efficacy of the anti-CD22 recombinant immunotoxin BL22 in chemotherapy-resistant hairy cell leukemia. N Engl J Med 345:241
14. Maloney DG, Liles TM, Czerwinski DK, Waldichuk C, Rosenberg J, Grillo-López A, Levy R (1994) Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. Blood 84:2457
15. Maloney DG, Grillo-López AJ, Bodkin DJ, White CA, Liles T-M, Royston I, Varns C, Rosenberg J, Levy R (1997) IDEC-C2B8: results of a phase I multiple-dose trial in patients with relapsed non-Hodgkin's lymphoma. J Clin Oncol 15:3266
16. Maloney DG, Grillo-López AJ, White CA, Bodkin D, Schilder RJ, Neidhart JA, Janakiraman N, Foon KA, Liles T-M, Dallaire BK, Wey K, Royston I, Davis T, Levy R (1997) IDEC-C2B8 (rituximab) anti-CD20 antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. Blood 90:2188
17. McLaughlin P, Grillo-López AJ, Link BK, Levy R, Czuczman MS, Williams ME, Heyman MR, Bence-Bruckler I, White CA, Cabanillas F, Jain V, Ho AD, Lister J, Wey K, Shen D, Dallaire BK (1998) Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 16:2825
18. Reff ME, Carner K, Chambers KS, Chinn PC, Leonard JE, Raab R, Newman RA, Hanna N, Anderson DR (1994) Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood 83:435
19. Schmitz K, Brugger W, Weiss B, Kaiserling E, Kanz L (1999) Clonal selection of CD20-negative non-Hodgkin's lymphoma cells after treatment with anti-CD20 antibody rituximab. Br J Haematol 106:571
20. Tobinai K, Kobayashi Y, Narabayashi M, Ogura M, Kagami Y, Morishima Y, Ohtsu T, Igarashi T, Sasaki Y, Kinoshita T, Murate T (1998) Feasibility and pharmacokinetic study of a chimeric anti-CD20 monoclonal antibody (IDEC-C2B8, rituximab) in relapsed B-cell lymphoma. Ann Oncol 9:527
21. Vose JM, Link BK, Grossbard ML, Czuczman M, Grillo-López A, Gilman P, Lowe A, Kunkel LA, Fisher RI (2001) Phase II study of rituximab in combination with CHOP chemotherapy in patients with previously untreated, aggressive non-Hodgkin's lymphoma. J Clin Oncol 19:389
22. Witzig TE, White CA, Wiseman GA, Gordon LI, Emmanouilides C, Raubitschek A, Janakiraman N, Gutheil J, Schilder RJ, Spies S, Silverman DH, Parker E, Grillo-López AJ (1999) Phase I/II trial of IDEC-Y2B8 radioimmunotherapy for treatment of relapsed or refractory $CD20^+$ B-cell non-Hodgkin's lymphoma. J Clin Oncol 17:3793
23. Witzig TE, Gordon LI, Cabanillas F, Czuczman MS, Emmanouilides C, Joyce R, Pohlman BL, Bartlett NL, Wiseman GA, Padre N, Grillo-López AJ, Multani P, White CA (2002) Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 20:2453