Semi-extended, six weekly rituximab infusions in pre-treated advanced low-grade B cell non-Hodgkin's lymphoma: a phase II study

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Either four or eight weekly rituximab infusions in relapsed or refractory low-grade or follicular B cell non-Hodgkin's lymphoma (NHL) are well tolerated and efficacious. This phase II trial investigated the safety and efficacy of six weekly rituximab doses in chemotherapeutically pre-treated relapsed or refractory low-grade NHL patients. Sixty-eight patients (median age 64 years) received six i.v. rituximab infusions 375 mg/m^2 weekly. All patients had received one or more prior therapies (median 2; range 1–18). Forty-two patients had progressive disease and were evaluated for toxicity and efficacy; 12 of these required re-treatment with six weekly rituximab infusions. Twenty-six patients received rituximab as remission consolidation therapy and were assessed for toxicity only. No patients discontinued because of adverse events. Most adverse events were National Cancer Institute grade 1 (2–9%) or 2 (3–5%) and usually occurred during the first infusion. No hematological abnormalities were observed. Overall response rate was 59% (median time to response 2 weeks) and 10 of 12 re-treated patients responded. Median time to progression for all patients was 14 months and for responders 21 months. More than half the 42 patients evaluated for efficacy and more than 70% of the 25 responding patients still survived longer than 3 years after treatment. The safety profile and efficacy achieved in this study compare favorably with those seen with four or eight weekly doses in pre-treated low-grade NHL. *Anti-Cancer Drugs* 14:809–815 © 2003 Lippincott Williams & Wilkins.

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Introduction

The pathophysiology of low-grade B cell non-Hodgkin's lymphoma (NHL) appears to be based on defects in cell death, as opposed to cell proliferation, resulting in the accumulation of monoclonal, long-living B lymphocytes. The majority of these are G_0 phase quiescent cells with defects in the normal pathways of apoptosis [1]. Such lymphomas are initially sensitive to a variety of chemotherapeutic agents, including alkylating drugs, anthracyclines, purine analogs and combination regimes, and treatment results in a high rate of remission. However, remission is rarely complete or of long duration and remission rates decrease with subsequent therapy [2,3]. Furthermore, high-dose myeloablative chemotherapy with autologous or allogeneic stem cell rescue is curative in only a limited number of patients [4–6].

Since the clinical course of the vast majority of low-grade NHL patients is characterized by continuing relapses, alternative treatment options are urgently needed. Recent immunological studies have shown that during differentiation, B cells undergo a series of genetic and phenotypic changes, including sequential acquisition or loss of surface antigens [7]. The CD20 antigen is acquired during the transition from pro-B cell to pre-B cell. CD20 surface expression increases during differentiation, reaching maximum levels on mature cells. CD20 expression then decreases during further B cell differentiation and may be absent in mature plasma cells [7]. The surface expression of the CD20 antigen varies among the different NHL subtypes [7].

Rituximab (Genentech, South San Francisco, CA and Hoffmann-La Roche, Grenzach-Wyhlen, Germany), a chimeric monoclonal anti-CD20 antibody, has recently been developed as the first targeted monoclonal antibody therapy for NHL [8]. The mechanisms of rituximab-mediated killing of CD20$^+$ tumor cells are likely to include a combination of immune-mediated effects with complement-mediated lysis and antibody-dependent cell-mediated cytotoxicity, as well as direct effects induced by CD20 ligation, including growth inhibition and apoptosis [9].

Initial clinical trials in patients with previously treated indolent NHL demonstrated that weekly infusions of

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rituximab over 4 weeks were well tolerated and had significant clinical activity, with overall response rates of 30–50% [8,10–14]. In an extended treatment with weekly rituximab infusions over 8 weeks in 37 patients, the overall response rate was 60% [15]. Here, we report the results of a phase II study of the safety and efficacy of a semi-extended rituximab treatment administered as weekly infusions of 375 mg/m^2 for 6 weeks in pre-treated patients with low-grade or follicular NHL.

Methods

Study design

Between February 1998 and July 2000, 68 patients entered this open-label, single-arm, single-center phase II safety and clinical efficacy study of six weekly infusions of rituximab 375 mg/m^2 (Table 1). In total, 42 NHL patients with relapsed or refractory progressive diseases were evaluable for safety and clinical efficacy. Of these patients, 12 were re-treated with weekly rituximab infusions over 6 weeks after disease relapses. Toxicity was studied in 26 patients with chemotherapy-induced complete or partial remissions, who received rituximab as remission consolidation therapy. Informed consent was obtained from all patients before receiving study drug.

Patients

Eligibility criteria included: adults (age range 40–79 years), a histologic diagnosis according to standard Kiel criteria [16] for lymphoma and demonstrated CD20-positivity of the NHL B cell population in pathologic lymph nodes or a bone marrow specimen. In the Kiel classification, the immunocytic (IMC) subtype of low-grade B cell NHL includes patients with lymphoplasmacytoid lymphomas (B cell chronic lymphocytic leukemia [B-CLL] with plasmacytoid differentiation in the REAL classification [17]) and lymphoplasmacytic lymphoma (lymphoplasmacytoid IMC in the REAL classification), including those with Waldenström's macroglobulinemia. The diagnosis of mantle cell lymphoma (MCL) and follicular NHL were made in accordance with the REAL classification.

Clinical characteristics at the time of study entry are listed in Table 1. All patients had a WHO performance status of $\leqslant 2$. The median age of all patients was 64 years. Most patients (96%) had stage III or IV disease and nine patients (13%) had systemic symptoms.

Any prior therapy must have been completed at least 1 month before initiation of rituximab treatment. Each patient received at least one (median 2) cytostatic chemotherapy regimes prior to this study (Table 2). Patients with blood lymphocytosis were not excluded, but those with central nervous system involvement or severe lymphoma-related symptoms requiring a rapid response to therapy were excluded from the study. Additional eligibility criteria for relapsed or refractory patients included: measurable or evaluable disease, WBC count $\geqslant 3000/\mu l$ and platelets $\geqslant 100\,000/\mu l$, and adequate liver and kidney function.

Before beginning therapy, all patients underwent staging procedures, including: history, physical examination, complete blood counts, chemistry profile, computerized tomography of the chest and abdomen, and bone marrow aspiration/biopsy.

Treatment

Rituximab (MabThera; Hoffmann-La Roche, Grenzach-Wyhlen, Germany) was administered once weekly on an outpatient basis for 6 weeks as an i.v. infusion of 375 mg/m^2. The drug was given in 500 ml of normal saline over several hours and vital signs were regularly monitored

Table 1. Patient characteristics

Characteristic	Number of patients (%)
Evaluable for toxicity	68 (100)
Evaluable for toxicity and efficacy	42 (62)
Median age (years)	64
Age range (years)	40–79
Female	29 (43)
Male	39 (57)
Histological type	
CLL	13 (19)
IMC	29 (43)
follicular	22 (32)
MCL	3 (4)
other	1 (2)
Disease stage (except CLL)	55 (81)
I	1 (2)
II	2 (4)
III	5 (9)
IV	48 (87)
B symptoms present	9 (13)
B symptoms not present	59 (87)
Years from diagnosis	
median	4
range	0.2–19
ECOG performance status	
0	42 (62)
1	21 (31)
2	5 (7)

Table 2. Prior treatment for lymphoma in the study population

Prior therapy[a]	Previous treatments ($n=227$, median 2, range 1–18)
Alkylating agents[b]	115
Anthracyclines[c]	45
Interferon-α	40
Fludarabine	9
Other ($\geqslant 1$)[d]	18

[a]Some patients have received a treatment (e.g. chlorambucil) on more than one occasion.
[b]Chlorambucil ± prednisolone or cyclophosphamide, vincristine and prednisolone or bendamustine or trofosfamide.
[c]Doxorubicine, epirubicine, mitoxantrone or idarubicine alone or as a component of a combination chemotherapy regime (e.g. CHOP [cyclophosphamide, hydroxydaunomycin, oncovin (vincristine) and prednisone]).
[d]Other single agents (e.g. vinblastine, etoposide, bleomycin) or combination chemotherapy regime.

during infusion. Oral pre-medication with an antipyretic (e.g. 500 mg paracetamol) was given routinely.

Monitoring

Patients underwent a weekly clinical review during treatment, including physical examination, to assess for evidence of toxicity or progressive disease. Toxicities were graded according to National Cancer Institute (NCI) criteria [18]. Laboratory testing, including hematology (hemoglobin, WBC count and platelet count) and serum chemistry (electrolytes, creatinine, uric acid and liver function tests), was performed at baseline, then weekly prior to therapy and at follow-up. Evaluations for disease assessment included: physical examination, chest radiography, computed tomography and bone marrow aspiration/biopsy (if positive at baseline). Evaluations were carried out at 1 and 3 months after treatment, every 3 months for 2 years, and every 6 months thereafter.

Response criteria

Strict response criteria as recommended by an international workshop to standardize response criteria for NHL have been used, including regular bone marrow examinations [19].

Statistical methods

Time-to-progression (TTP) was measured from the first infusion until disease progression. The Kaplan–Meier product-limit method [20] was used to analyze TTP and overall survival (OS). Differences in TTP and OS between subgroups of patients were tested for statistical significance using the log-rank test [21]; the exact Mantel–Haenszel test was applied to test for differences in response rates.

Results

Patient features

All patients had received at least one prior cytostatic chemotherapy regime (median 2; range 1–18) (Table 2). The median time interval from the first prior treatment to the beginning of rituximab infusions was 33 months (range 2–216 months).

Of the 68 NHL patients, 62 received all six rituximab doses. Rituximab treatment had to be terminated after three to five infusions in three patients due to continuous disease progression and subsequent death. Three patients received only four of six infusions due to protocol violation.

Clinical adverse events

All 68 patients were included in the evaluation of toxicity (Table 3). The rituximab infusions were generally well tolerated. Infusional side effects occurred most frequently during the first treatment (20 events of NCI grade 1 and 2 toxicity), declining with subsequent infusions (seven events of NCI grade 1 and 2 toxicity due to second infusion).

Table 3. Non-hematologic toxicity in the safety population (maximum per patient, $n=68$)

	NCI grade [*n* (%)]		
	0	1	2
Fever	64 (94)	4 (6)	–
Chills	60 (88)	6 (9)	2 (3)
Pain ($n=67$)	65 (97)	2 (3)	–
Nausea	64 (94)	1 (1)	3 (4)
Vomiting	66 (97)	2 (3)	–
Diarrhea	65 (96)	1 (1)	2 (3)
Obstipation	68 (100)	–	–
Hypotension	68 (100)	–	–
Epidermis	66 (97)	2 (3)	–
Sensorium	66 (97)	2 (3)	–
Dyspnea	68 (100)	–	–
Allergic symptoms	66 (97)	2 (3)	–
Sweating	68 (100)	–	–

– = no events recorded.

Most clinical adverse events were mild to moderate (NCI grade 1 or 2) during the 6-week treatment period and no toxicity occurred thereafter. The most frequently occurring adverse events consisted of transient chills (12%), fever or nausea/vomiting (6%), diarrhea (4%) and pain, dizziness or rush/urticaria (each 3%) (Table 3). No patient discontinued treatment because of an adverse event. Tumor lysis syndrome was not observed and no significant abnormalities in serum chemistry were recorded in the study population. In particular, no hepatic or renal toxicity was noted.

A median of 14 months (range 6–24 months) following first rituximab treatment period, 12 patients again presented with disease progression and received a second course of weekly rituximab infusions over 6 weeks. Only four non-hematologic adverse events were observed, all of which were NCI grade 1, including fever, chills and allergic skin reactions.

Hematologic abnormalities did not occur. During the 6-week treatment period and the subsequent 6 months, the median hemoglobin values varied between 12.8 and 14.0 g/dl. Median leucocyte, neutrophil and lymphocyte counts varied over the ranges 4.6–5.3, 2.5–3.6 and 1.0–1.8/nl, respectively. Platelet counts remained stable, with median counts recorded to be between 164 and 179/nl.

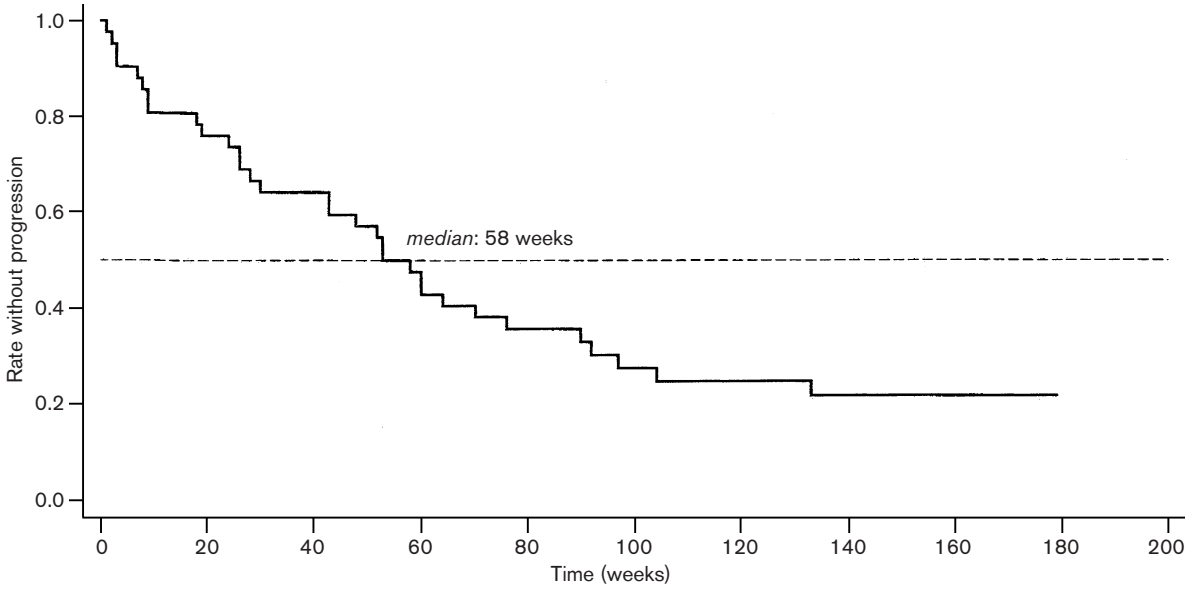
Response to treatment

The 26 patients in complete or partial remission received rituximab infusions as consolidation therapy and were not assessed for efficacy (Table 1). In the 42 patients who were evaluated for efficacy, the response rate was 59%, including 11 (26%) patients in complete remission (Table 4). Subgroup analyses revealed no difference in response by sex or histology, but significantly higher remission rates in patients with a normal performance status and

Table 4. Clinical responses to treatment

Patient group	Total (*n*)	Complete remission [*n* (%)]	Partial remission [*n* (%)]	No change [*n* (%)]	Progressive disease [*n* (%)]	*p*
Evaluable	42	11 (26)	14 (33)	9 (21)	8 (19)	
Male	26	5 (19)	10 (38)	5 (19)	6 (23)	NS
Female	16	6 (38)	4 (25)	4 (24)	2 (12)	
CLL	9	3 (33)	3 (33)	1 (11)	2 (22)	NS
NHL	33	8 (24)	11 (33)	8 (24)	6 (18)	
Follicular	8	2 (25)	3 (38)	3 (38)	–	NS
Immunocytic	22	6 (27)	8 (36)	4 (18)	4 (18)	
ECOG 0	23	10 (43)	7 (30)	5 (22)	1 (4)	0.0019
ECOG $\geqslant 1$	19	1 (5)	7 (37)	4 (21)	7 (37)	
Two or less pre-treatments	19	7 (37)	9 (47)	2 (11)	1 (5)	0.0082
More than two regimes	23	4 (17)	5 (22)	7 (30)	7 (30)	

Fig. 1



Progression-free survival in 42 relapsed NHL patients after six weekly rituximab infusions (32 events, 10 censored).

who had received a lower number of pre-treatments (Table 4). Fully-active patients who were able to carry out normal activities of daily living (ECOG performance score 0) or who had received no more than two pre-treatments experienced response rates of 73 and 84%, respectively, compared to those with an ECOG score of 1 (42%) or more than two prior lymphoma treatments (39%) ($p = 0.0019$ and 0.0082, respectively) (Table 4). No site-specific clustering of responses was apparent.

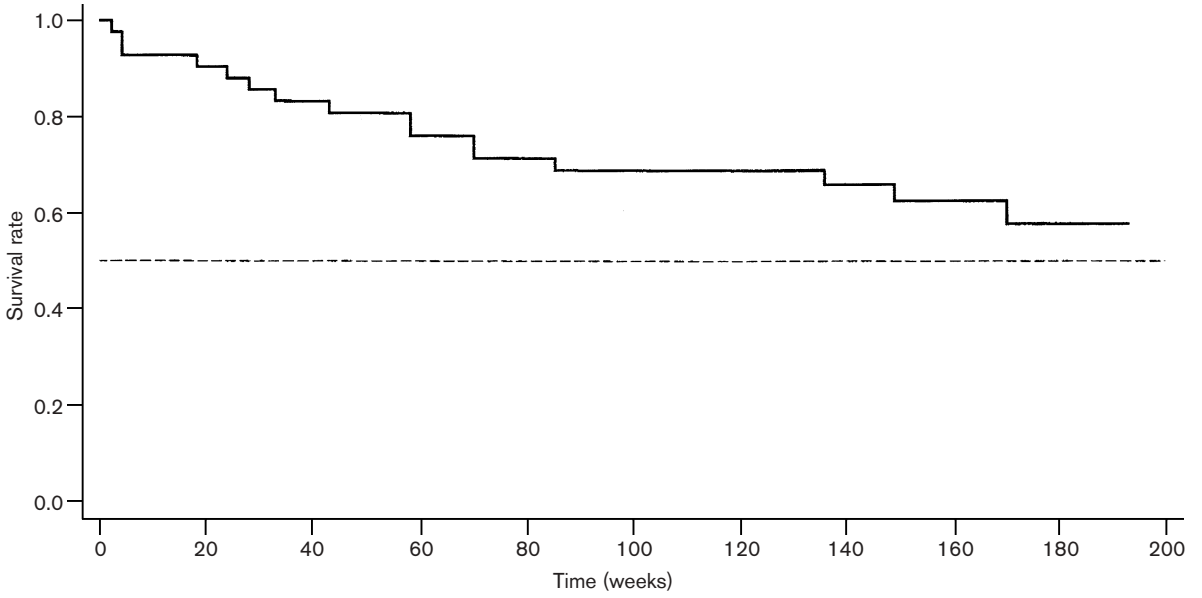
Ten patients (24%) presented with an initial blood lymphocytosis ($\geqslant 5.0$/nl) and eight patients showed a decrease of more than 50% in blood lymphocyte count 2 weeks after the start of the rituximab infusion period. Therefore, a median time to response of 2 weeks has been determined in these lymphocytosis patients.

Re-treatment with six weekly rituximab infusions was performed in 12 patients. Three of these patients achieved a complete and seven a partial remission with an overall response rate of 83%. Two patients showed no change performance status.

Median and mean follow-up periods were 34 and 28 months, respectively, in the 42 patients evaluated for efficacy. Median TTP for these patients was 13.5 months (Fig. 1) and 13 months for the 12 re-treated patients. The 25 responding patients showed a median TTP of 21 months and those with stable or progressive disease of 4 months.

Subgroup analysis for gender, histological subtype or performance status resulted in similar TTPs, but the 17 patients with two pre-treatments or fewer exhibited a significantly longer TTP of 21 months than those 23 patients more heavily pre-treated (TTP 6.5 months, $p = 0.0082$). A similar TTP of 21 months was observed in

Fig. 2



Overall survival in 42 relapsed NHL patients after six weekly rituximab infusions (16 events, 26 censored).

the 26 patients who perceived rituximab infusions as remission consolidation therapy.

More than half of the 42 evaluable patients survived for more than 3 years after treatment (Fig. 2). In particular, more than 70% of the 25 responding patients are alive after a 3-year follow-up period, whereas the non-responding patients showed a median OS of 13.5 months. Subgroup analyses exhibited no correlation of OS with gender or histology, but a correlation was observed with ECOG performance score and number of pre-treatments. Median OS was significantly shorter with each 16 months for patients with reduced performance status (ECOG scale $\geqslant 1$) or more than two pre-treatment regimes, whereas median OS has not been reached in patients with an ECOG score of 0 or fewer pre-treatments ($p = 0.024$ and 0.0005, respectively).

Discussion

The toxicity of the 6-week rituximab infusion program was notably mild; in particular, no myelosuppressive toxicities were observed. This is consistent with the observations of other studies [11,13,15,22,23]. Only B lymphocytes were rapidly depleted and levels recovered after 9–12 months following treatment [11,13–15,23].

Most adverse events associated with the study treatment were mild and comparable to those seen in other recent trials [11,13,15,22–26]. Adverse events mainly occurred during the first infusion, and the majority of patients experienced no further infusion-related toxicities with second and subsequent infusions. Although rituximab destroys normal as well as malignant NHL B cells, no increased incidence of infection was observed.

The 6-week rituximab treatment regime for patients with low-grade NHL who had relapsed or failed primary therapy resulted in a favorable 59% response rate in 42 evaluable patients. Most of the responses were partial, which is typical of single-agent therapy in relapsed or refractory low-grade NHL. Median TTP for all patients was 13.5 months and that of the responding patients was 21 months. The clinical responses compare favorably with a previous 8-week phase II trial of weekly rituximab therapy, which achieved the same response rate in 37 patients with recurrent or relapsed low-grade or follicular NHL and similar median TTPs for all as well as responding patients [15].

Previous studies with four weekly infusions of rituximab in pre-treated indolent NHL patients reported overall response rates of 30–60% [8,10–14] and median TTP in responders of 10–13 months [10,11,23]. In a study by Davis *et al.*, patients with bulky relapsed or refractory low-grade or follicular NHL had an overall response rate of 43%, with a median TTP of 8.1 months [22]. These response data are apparently lower than those after six or eight rituximab infusions, which may be due to different histologic subtypes of study populations, differences in rituximab antibody serum levels [15,22] and different

densities of CD20 antigen expressed on the cell surfaces of malignant NHL cells of low-grade histology subtypes [27]. However, randomized trials would be necessary to clarify whether eight or six rituximab infusions result in increased response data compared with a four-infusion program.

Due to multiple mechanisms of action of rituximab [9], $CD20^+$ NHL cells are killed within short time intervals. The median time to response of 2 weeks observed in this study is the fastest to be reported so far. In previously reported trials, intervals of 1–2 months have been determined [24,25,28,29].

Subgroup analyses of the current study revealed ECOG performance status as a prognostic factor, which is consistent with the findings of Igarashi *et al.* [23]. Furthermore, this Japanese study showed that the absence of B symptoms and of extranodal disease are factors for an increased likelihood of response to rituximab therapy. Age, sex, lactate dehydrogenase and tumor size have been found to be without prognostic influence [22,23].

Recently, rituximab has been applied as first-line treatment in patients with newly-diagnosed indolent NHL. Compared with pre-treated low-grade NHL patients, increased response rates of 47 [26], 60 [14] and 73% [25] have been observed. In addition, two trials evaluated the feasibility of administering repeated courses of rituximab as periodic maintenance treatment. They achieved an increase of the major response rates and prolonged TTP, as well as median response duration [14,26]. Furthermore, rituximab has been studied as re-treatment at the time of progression in NHL patients who previously responded to rituximab. In agreement with data reported by Davis *et al.* [24], our re-treated patients exhibited no differences in toxicity, response rate or TTP compared with the patients after initial rituximab exposure.

In this 6-week rituximab study, the response data appear inferior to the most encouraging recent chemotherapy results for relapsed indolent NHL. Treatment with the potentially bifunctional agent, bendamustine, has been shown to yield high remission rates of 73–92% [30–32]. However, in the current study, remission data are comparable to those reported in single-agent studies with the purine analogs, fludarabine [33] and 2-CdA [34,35]. Both fludarabine and 2-CdA induced remission rates of 30–70% in pre-treated low-grade NHL.

Use of rituximab prior to and during treatment with fludarabine, bendamustine, or CHOP [cyclophosphamide, hydroxydaunomycin, oncovin (vincristine) and prednisone] for patients with low-grade or follicular NHL has been reported [36–39]. Up to 100% of these patients achieved a partial or complete response and 75% of the patient population remained in remission after 3 years of follow-up [36]. It remains to be determined if this approach is superior to standard chemotherapy alone.

The optimal role of rituximab in the treatment of low-grade NHL continues to be defined. Rituximab produces high response rates with minimal toxicity in refractory diseases and in previously untreated patients. In patients who are elderly, who have poor performance status, who may have difficulty in tolerating chemotherapy or in whom myelosuppressive toxicities appear clinically contraindicated, monotherapy with rituximab may provide an attractive treatment option. Additional indications for use of rituximab are likely to be defined in the future.

References

1 Reed JC, Kitada S, Kim Y, Byrd J. Modulating apoptosis pathways in low-grade B cell malignancies using biological response modifiers. *Semin Oncol* 2002; **29**(**1 suppl 2**):10–24.

2 Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. *J Clin Oncol* 1998; **16**:2780–2795.

3 Vose JM. Current approaches to the management of non-Hodgkin's lymphoma. *Semin Oncol* 1998; **25**:483–491.

4 Gutierrez-Delgado F, Golden J, Maloney DG, Holmberg L, Hooper H, Storb R, *et al.* High-dose chemotherapy (HDC) and autologous stem cell transplantation (AST) for non-Hodgkin's lymphoma. Five-year follow up. *Proc Am Soc Clin Oncol* 2000; **19**:14a (abstr 46).

5 Laport GF, Williams SF. The role of high-dose chemotherapy in patients with Hodgkin's disease and non-Hodgkin's lymphoma. *Semin Oncol* 1998; **25**:503–517.

6 Toze CL, Shepherd JD, Connors JM, Voss NJ, Gascoyne RD, Hogge DE, *et al.* Allografting for indolent lymphoid neoplasms. *Ann Oncol* 2000; **11**(**suppl 1**):59–61.

7 Kipps TJ. Advances in classification and therapy of indolent B cell malignancies. *Semin Oncol* 2002; **29**(**1 suppl 2**):98–104.

8 Grillo-Lopez AJ, White CA, Varns C, Shen D, Wei A, McClure A, *et al.* Overview of the clinical development of rituximab: first monoclonal antibody approved for the treatment of lymphoma. *Semin Oncol* 1999; **26**(**5 suppl. 14**):66–73.

9 Maloney DG, Smith B, Rose A. Rituximab: mechanism of action and resistance. *Semin Oncol* 2002; **29**(**1 suppl 2**):2–9.

10 Maloney DG, Grillo-Lopez AJ, Bodkin DJ, White CA, Liles TM, Royston I, *et al.* IDEC-C2B8: results of a phase I multiple-dose trial in patients with relapsed non-Hodgkin's lymphoma. *J Clin Oncol* 1997; **15**:3266–3274.

11 McLaughlin P, Grillo-Lopez AJ, Link BK, Levy R, Czuczman MS, Williams ME, *et al.* Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol* 1998; **16**:2825–2833.

12 Feuring-Buske M, Kneba M, Unterhalt M, Engert A, Gramatzki M, Hiller E, *et al.* IDEC-C2B8 (Rituximab) anti-CD20 antibody treatment in relapsed advanced-stage follicular lymphomas: results of a phase-II study of the German Low-Grade Lymphoma Study Group. *Ann Hematol* 2000; **79**:493–500.

13 Foran JM, Rohatiner AZ, Cunningham D, Popescu RA, Solal-Celigny P, Ghielmini M, *et al.* 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* 2000; **18**:317–324.

14 Ghielmini M, Hsu Schmitz SF, Cogliatti SB, Pichert G, Fey M, Betticher D, *et al.* Maintenance treatment with 2-monthly rituximab after standard weekly $\times 4$ rituximab induction significantly improves event-free survival in patients with follicular lymphoma. *Ann Oncol* 2002;**13**(**suppl 2**): 38 (abstr 112).

15 Piro LD, White CA, Grillo-Lopez AJ, Janakiraman N, Saven A, Beck TM, *et al.* Extended Rituximab (anti-CD20 monoclonal antibody) therapy for relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma. *Ann Oncol* 1999; **10**:655–661.

16 Stansfeld AG, Diebold J, Kapanci Y, Kelenyi G, Lennart K, Mioduszewska O, *et al.* Updated Kiel classification for lymphomas. *Lancet* 1998; **1**:292–293.
17 Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, *et al.* A revised European–American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994; **84**:1361–1392.
18 Cancer Therapy Evaluation Program. *Investigator's Handbook: A Manual for Participants in Clinical Trials of Investigational Agents*. Bethesda, MD: CTEP, National Cancer Institute; 1993.
19 Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, *et al.* Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. *J Clin Oncol* 1999; **17**:1244–1253.
20 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Ass* 1958; **53**:457–481.
21 Peto R, Peto J. Asymptomatically efficient rank invariation test procedures (with discussion). *J R Stat Soc Ass* 1972; **135**:185–206.
22 Davis TA, White CA, Grillo-Lopez AJ, Velasquez WS, Link B, Maloney DG, *et al.* Single-agent monoclonal antibody efficacy in bulky non-Hodgkin's lymphoma: results of a phase II trial of rituximab. *J Clin Oncol* 1999; **17**:1851–1857.
23 Igarashi T, Kobayashi Y, Ogura M, Kinoshita T, Ohtsu T, Sasaki Y, *et al.* Factors affecting toxicity, response and progression-free survival in relapsed patients with indolent B cell lymphoma and mantle cell lymphoma treated with rituximab: a Japanese phase II study. *Ann Oncol* 2002; **13**:928–943.
24 Davis TA, Grillo-Lopez AJ, White CA, McLaughlin P, Czuczman MS, Link BK, *et al.* Rituximab anti-CD20 monoclonal antibody therapy in non-Hodgkin's lymphoma: safety and efficacy of re-treatment. *J Clin Oncol* 2000; **18**:3135–3143.
25 Colombat P, Salles G, Brousse N, Eftekhari P, Soubeyran P, Delwail V, *et al.* Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: clinical and molecular evaluation. *Blood* 2001; **97**:101–106.
26 Hainsworth JD, Litchy S, Burris III HA, Scullin DC, Corso SW, Yardley DA, *et al.* Rituximab as first-line and maintenance therapy for patients with indolent non-Hodgkin's lymphoma. *J Clin Oncol* 2002; **20**:4261–4267.
27 Molica S, Levato D, Dattilo A, Mannella A. Clinico-prognostic relevance of quantitative immunophenotyping in B cell chronic lymphocytic leukemia with emphasis on the expression of CD20 antigen and surface immunoglobulins. *Eur J Haematol* 1998; **60**:47–52.
28 Huhn D, von Schilling C, Wilhelm M, Ho AD, Hallek M, Kuse R, *et al.* Rituximab therapy of patients with B cell chronic lymphocytic leukemia. *Blood* 2001; **98**:1326–1331.
29 Conconi A, Thieblemont C, Martinelli F, Ferreri AJ, Devizzi L, Peccatori F, *et al.* IELSG phase II study of rituximab in MALT-lymphomas. *Ann Oncol* 2002; **13**(**suppl 2**):81(abstr 272).
30 Heider A, Niederle N. Efficacy and toxicity of bendamustine in patients with relapsed low-grade non-Hodgkin's lymphomas. *Anticancer Drugs* 2001; **12**:725–729.
31 Kath R, Blumenstengel K, Fricke HJ, Hoffken K. Bendamustine monotherapy in advanced and refractory chronic lymphocytic leukemia. *J Cancer Res Clin Oncol* 2001; **127**:48–54.
32 Bremer K. High rates of long-lasting remissions after 5-day bendamustine chemotherapy cycles in pre-treated low-grade non-Hodgkin's-lymphomas. *J Cancer Res Clin Oncol* 2002; **128**:603–609.
33 Bergmann L. Purine analogues in the therapy of chronic leukemia and indolent lymphomas. *Onkologie* 1997; **20**:278–286.
34 Tulpule A, Schiller G, Harvey-Buchanan LA, Lee M, Espina BM, Khan AU, *et al.* Cladribine in the treatment of advanced relapsed or refractory low and intermediate grade non-Hodgkin's lymphoma. *Cancer* 1998; **83**:2370–2376.
35 Tondini C, Balzarotti M, Rampinelli I, Valagussa P, Luoni M, De Paoli A, *et al.* Fludarabine and cladribine in relapsed/refractory low-grade non-Hodgkin's lymphoma: a phase II randomized study. *Ann Oncol* 2000; **11**:231–233.
36 Czuczman MS, Grillo-Lopez AJ, White CA, Saleh M, Gordon L, LoBuglio AF, *et al.* Treatment of patients with low-grade B cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy. *J Clin Oncol* 1999; **17**:268–276.
37 Czuczman MS, Fallon A, Mohr A, Stewart C, Bernstein ZP, McCarthy P, *et al.* Rituximab in combination with CHOP or fludarabine in low-grade lymphoma. *Semin Oncol* 2002; **29**(**1 suppl 2**):36–40.
38 Hainsworth JD, Buris III HA, Yardley DA, Litchy S, Morrissey L, Grimaldi M, *et al.* Rituximab plus short duration chemotherapy as first-line treatment for follicular non-Hodgkin's lymphoma (NHL): a Minnie Pearl Cancer Research Network phase III trial. *Proc Am Soc Clin Oncol* 2002; **21** (abstr 1070).
39 Rummel MJ, Kim SZ, Chow KU, Weidmann E, Hoelzer D, Mitrou PS. Bendamustine and rituximab act synergistically *in vitro* and are effective in the treatment of indolent and mantle-cell lymphomas pre-treated with purine analogues. *Ann Oncol* 2002; **13**(**suppl 2**):58 (abstr 187).