Efficacy and Safety of Monoclonal Anti-CD20 Antibody (Rituximab) for the Treatment of Patients with Recurrent Low-Grade Non-Hodgkin’s Lymphoma after High-Dose Chemotherapy and Autologous Hematopoietic Cell Transplantation

Hakan Kaya, Yi-Kong Keung, Douglas Case, Julia M. Cruz, James J. Perry, James E. Radford, David D. Hurd

Comprehensive Cancer Center of Wake Forest University School of Medicine, Winston-Salem, North Carolina

Correspondence and reprint requests: David D. Hurd, MD, Section of Hematology and Oncology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, North Carolina 27157 (e-mail: dhurd@wfubmc.edu).

ABSTRACT

The major cause of treatment failure following high-dose therapy with autologous hematopoietic cell transplantation (AHCT) for low-grade lymphomas (non-Hodgkin’s lymphoma [NHL]) is persistent disease or recurrence. Most patients whose disease progresses following AHCT have resistant disease and limited bone marrow reserve. In this setting, treatment options are limited and responses to conventional chemotherapy are generally poor. Rituximab is a chimeric immunoglobulin G1κ monoclonal antibody that recognizes the CD20 antigen on B-cells. Published data on the use of rituximab for the treatment of recurrent NHL after autologous transplantation are limited. We present a detailed report of anti-CD20 antibody treatment for 8 patients with recurrent follicular low-grade NHL after high-dose therapy and autologous transplantation. Rituximab was administered at 375 mg/m² intravenously once weekly for a total of 4 infusions. Median follow-up for this study was 23.4 months. Six (75%) of 8 patients responded to rituximab (2 complete response, 4 partial response). The Kaplan-Meier estimated median time to progression was 17.8 months. Rituximab was generally well tolerated. One patient developed delayed neutropenia. Other side effects were infusion related and transient. Two patients were re-treated with rituximab for progressive disease and achieved partial response. In summary, this retrospective study suggests that anti-CD20 antibody treatment is feasible in the treatment of patients who relapse or progress with low-grade NHL after autologous transplantation. There appears to be a high proportion of patients who benefit and have durable responses. Anti-CD20 antibody should be considered as a first-line salvage treatment for patients with CD20⁺ recurrent low-grade NHL in whom high-dose therapy has failed.

KEY WORDS

Treatment failure • B-lymphocytes • Low-grade lymphoma • Monoclonal antibody therapy • Rituximab

INTRODUCTION

Rituximab is a chimeric immunoglobulin G1κ monoclonal antibody that recognizes the CD20 antigen [1]. CD20 antigen is present on the surface of malignant and normal B-lymphocytes but not on other tissues. This specificity makes CD20 antigen a suitable target for lymphoma (non-Hodgkin’s lymphoma [NHL]) treatment. In a multicenter phase II trial, rituximab was used to treat 37 patients with low-grade or follicular NHL [2]. The overall response rate was 50%, and the time to tumor progression for the responders was approximately 1 year. Rituximab was well tolerated, with serious side effects occurring in less than 10% of the patients. A multicenter pivotal trial involving 166 patients with relapsed low-grade or follicular NHL showed an overall response rate of 50% (6% complete response [CR] and 44% partial response [PR]) [3]. Median time to progression for
responders was 13.2 months. In this trial and in other single-agent trials, most adverse events were grades 1 and 2 and occurred mainly during the first infusion [3]. Follicular small cleaved and follicular mixed smallcleaved and large cell NHL account for 15% to 30% of newly diagnosed lymphomas [4]. Most patients with low-grade lymphomas cannot be cured with conventional chemotherapy [5, 6]. High-dose therapy with autologous hematopoietic cell transplantation (AHCT) has been investigated as a treatment modality for low-grade lymphomas [7-10]. The major cause of failure following transplantation remains disease progression or recurrence. Most patients who progress following AHCT have resistant disease and limited bone marrow reserve. In this setting, treatment options are limited and responses to conventional chemotherapy are generally poor. Second autologous transplantations have been tried without significant benefit [11]. Only anecdotal accounts of experience with allogeneic hematopoietic cell transplantation for recurrent low-grade lymphomas following autologous transplantation have been available [12]. Although selected patients may benefit from this approach, early mortality remains unacceptably high.

Published reports of experience using anti-CD20 antibody (rituximab) for the treatment of recurrent NHL after autologous transplantation are very limited. Subset analysis of the rituximab pivotal trial reveals that 23 patients had been given rituximab for a recurrence after an autologous transplantation [3]. Although no specific details were provided for this subset of patients, response rate in patients treated with rituximab was higher than that of all other patients (78% versus 48%). A multicenter phase II study using anti-CD20 antibody for treatment of patients with relapsing or refractory aggressive lymphomas included 6 patients with prior history of transplantation [13]. Two of 6 patients responded to rituximab. There is only one report in the literature addressing the efficacy of anti-CD20 antibody therapy for progressive NHL after high-dose therapy and autologous stem cell transplantation [14]. This retrospective study involves 7 patients with progressive intermediate-grade NHL, who were treated with rituximab at the time of relapse after AHCT. Overall response rate was 86%, with 1 patient achieving a CR, 5 achieving PR, and 1 patient having stable disease (SD).

To our knowledge, there have been no published reports specifically addressing the efficacy of anti-CD20 antibody for treatment of recurrent follicular low-grade lymphomas after high-dose therapy and AHCT. We present a detailed report of our first 8 patients who underwent high-dose therapy with autologous hematopoietic stem cell transplantation for follicular low-grade NHL lymphoma and subsequently received treatment with rituximab for recurrent disease.

### PATIENTS AND METHODS

#### Patient Characteristics

We reviewed the medical records of patients at Wake Forest University Baptist Medical Center who had low-grade NHL and were treated between February 1998 and September 1999 with rituximab for relapsed/progressive disease following AHCT. Patients with a history of low-grade NHL that had transformed to a more aggressive histologic subtype were excluded from this analysis. Treatment with other agents before rituximab for progressive disease following transplantation was permitted. Patients who were treated with additional agents during rituximab therapy were not included. No other specific exclusion criteria were used. This retrospective review identified 8 patients with a history of either follicular small-cleaved cell or follicular mixed small-cleaved and large cell NHL. Median age at the time of rituximab therapy was 56 years (range, 50-67 years). None of the patients had bulky (>5 cm) disease. Three patients had splenomegaly (nos. 2, 6, and 8); 1 patient (no. 4) had a prior splenectomy. Only 2 patients (nos. 4 and 7) had their bone marrow evaluated at the time of rituximab therapy; 1 of these patients (no. 7) was found to have minimal lymphoma involvement. None of the patients had morphologic evidence of circulating lymphoma cells. Median number of treatments before transplantation was 3 (range, 2-4). Six patients were treated with 1, 2, or 3 (Table 2) posttransplantation therapies prior to rituximab; 1 of the 6 (no. 5, Table 2) underwent a second autologous transplantation for progressive disease following her initial transplantation. Rituximab was the initial treatment for 2 patients following postransplantation relapse. Details of patient characteristics and prior treatments are given in Tables 1 and 2.

#### Therapy

Rituximab was administered at 375 mg/m² intravenously once weekly for a total of 4 infusions (days 1, 8, 15, and 22) on an outpatient basis. Premedication with acetaminophen and diphenhydramine was given to all patients. Some patients also received cimetidine. The initial infusion rate for rituximab was 50 mg/hour with subsequent infusion.
Table 2. Prior Treatments and Responses*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dx, mo/yr</th>
<th>Tx 1</th>
<th>Tx 2</th>
<th>Tx 3</th>
<th>Tx 4</th>
<th>AHCT</th>
<th>Post-AHCT</th>
<th>Tx I</th>
<th>Tx II</th>
<th>Tx III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>1/91 ProMACE-</td>
<td>CABV</td>
<td>ICE</td>
<td>Dex</td>
<td>BU/CY</td>
<td>6/94 CR</td>
<td>10/95 Surgery</td>
<td>10/95 CR</td>
<td>Rad Tx</td>
<td>8/96 CR</td>
</tr>
<tr>
<td>Patient 2</td>
<td>3/92 CVP</td>
<td>12/92 CR</td>
<td>CNOP</td>
<td>BU/CY</td>
<td>7/95 CR</td>
<td>8/97 Rad Tx</td>
<td>8/97 CR</td>
<td>Cbl</td>
<td>12/97 SD</td>
<td>R</td>
</tr>
<tr>
<td>Patient 3</td>
<td>10/92 CHOPE</td>
<td>11/92 PR</td>
<td>Rad Tx</td>
<td>11/93 CR</td>
<td>BU/CY</td>
<td>9/95 CCR</td>
<td>7/97 Oral VP18</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 6</td>
<td>1/92 CVP</td>
<td>1/92 PR</td>
<td>CHOP</td>
<td>12/92 PR</td>
<td>CY/TBI</td>
<td>1/94 PR</td>
<td>6/94 Pred</td>
<td>9/94 SD</td>
<td>VAD</td>
<td>1/95 SD</td>
</tr>
<tr>
<td>Patient 7</td>
<td>9/92 CHOP</td>
<td>10/92 CR</td>
<td>MINE</td>
<td>8/93 PR</td>
<td>CY/TBI</td>
<td>12/93 CR</td>
<td>12/95 R</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Dx indicates diagnosis; Tx, treatment; Res, response; ProMACE-CytaBOM, cyclophosphamide, doxorubicin, etoposide, prednisone, cytarabine, bleomycin, vincristine, methotrexate, leucovorin; IT Mtx, intrathecal methotrexate; CABV, cyclophosphamide, doxorubicin, bleomycin, vincristine; ICE, ifosfamide, carboplatin, etoposide, mesna; Dex, dexamethosone; BU, busulfan; CY, cyclophosphamide; Rad Tx, radiation therapy; CVP, cyclophosphamide, vincristine, prednisone; CNOP, cyclophosphamide, mitoxantrone, vincristine, prednisone; CNOPE, CNOP and etoposide; Cbl, chlorambucil; CHOPE, cyclophosphamide, doxorubicin, vincristine, prednisone; DHAP, dexamethasone, cytarabine, cisplatin; DHA, dexamethasone, cytarabine; VP16, etoposide; BCNU, carmustine; TBI, total body irradiation; Pred, prednisone; VAD, vincristine, doxorubicin, dexamethasone; MINE, mesna, ifosfamide, mitoxantrone, etoposide; Flu, fludarabine; R, rituximab.
Rituximab for Low-Grade NHL after High-Dose Chemotherapy and AHCT

rates increased according to package insert instructions if no toxicity was seen.

**Evaluation of Response**

Response to rituximab treatment was evaluated with serial physical examinations, computed tomographic (CT) scans, and laboratory studies. All patients had comparison CT scans, which were done shortly before initiation of rituximab treatment. Bone marrow examinations were not routinely done, but in the 1 patient (no. 7) with documented marrow involvement prior to rituximab, examination of subsequent bone marrow showed it to be without morphologic evidence of disease. Complete response (CR) was defined as the disappearance of all evidence of disease and no appearance of new disease for at least 4 weeks. More than a 50% reduction in the product of the bidimensional tumor measurements without appearance of new disease was defined as partial response (PR). Less than a 50% reduction in tumor size was defined as SD and was not considered a response. Any evidence of progression discovered by CT scan and/or physical examination results was defined as progressive disease (PD).

**Statistical Methods**

Descriptive statistics (medians and ranges or means and standard deviations for continuous variables and frequencies and percentages for categorical variables) were used to summarize the results of this retrospective follow-up study. Outcomes observed were white blood cell counts, platelet counts, and hemoglobin levels (calculated as the change in values from baseline to nadir); adverse effects of treatment; response to rituximab; and time to progression. Wilcoxon signed-rank tests were used to assess the significance of the hematologic changes. Kaplan-Meier methods were used to estimate the time to progression distribution, and methods described by Korn were used to estimate median follow-up [15]. Approximate (for continuous variables) and exact (for binary outcomes) 95% confidence intervals (CIs) were calculated to estimate the possible magnitude of some of the treatment effects.

**RESULTS**

**Response**

CT scans were repeated following the completion of the last rituximab infusion at a median time of 76 days (range, 21-105 days) and compared with the pretreatment scans for evaluation of objective responses. Two patients experienced CR (nos. 1 and 7), 4 had PR (nos. 2, 3, 5, and 6), 1 had SD (no. 8), and 1 patient had PD (no. 4). Overall, 6 of 8 patients (75% CI, 24%-91%) responded (CR + PR) to rituximab.

Median follow-up time for this study was 23.4 months. The Kaplan-Meier estimated median time to disease progression was 17.8 months (Figure). Two partially responding patients (nos. 5 and 6) developed PD at 6.4 months and 18.6 months, respectively. The latter patient was re-treated with 6 weekly infusions of rituximab at the time of progression and achieved a second PR. Patient no. 8, who had SD, was re-treated with 6 weekly infusions of rituximab at the time of progression, approximately 6 months after completion of the initial rituximab treatment, and achieved a PR. Only 1 patient (patient no. 4, who initially had PD following rituximab) died, at day 172 from complications of subsequent chemotherapy. At the time of this report, 4 of 8 patients were in either PR or CR following therapy with only rituximab. Follow-up for 2 patients (nos. 1 and 7) was approaching 3 years and they continued to be in CR without any evidence of recurrent/progressive lymphoma. Response to rituximab for all patients and their status at the time of this report are summarized in Table 3.

**Toxicities**

Rituximab was generally well tolerated in this series. During the first infusion, 1 patient (no. 6) experienced an

<table>
<thead>
<tr>
<th>Table 3. Response to Rituximab and Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient No.</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
</tbody>
</table>

*Progressed initially.
anaphylactoid reaction, which did not recur during subsequent infusions. The same patient also developed delayed neutropenia 1 month after the last rituximab infusion. She required hospitalization for neutropenic fever and promptly responded to treatment with granulocyte colony-stimulating factor and intravenous antibiotics. When rechallenged with rituximab 19 months later, she did not develop neutropenia. Another patient (no. 5) experienced transient hypotension during the first infusion. No other significant side effects were observed. There was no treatment-related mortality in our patients.

Six of the 8 patients had decreasing white blood cell counts during therapy, 1 patient had stable counts, and 1 had increasing counts. The mean ± SD change in white blood cell count was 1010 ± 1950/µL (95% CI, −340 to 2360). Five patients experienced decreases in their platelet counts, and 3 had increases. The mean ± SD change in platelets was 18,100 ± 30,600/µL (95% CI, −3100 to 39,300). Four patients experienced decreases in hemoglobin levels, 1 patient had stable levels, and 3 had increases in hemoglobin levels. Most of the changes in the hematologic parameters were not clinically significant, except for development of neutropenia requiring hospitalization in 1 patient.

**DISCUSSION**

Most patients with low-grade lymphomas cannot be cured with conventional chemotherapy. For this group of patients, high-dose therapy and AHCT appear to provide a significant progression-free survival benefit compared to that provided by conventional chemotherapy [16]. The major cause of treatment failure following transplantation, however, is disease progression/recurrence. Most patients who progress following transplantation have resistant disease and limited bone marrow reserve. Rituximab has been shown to be an effective agent for the treatment of recurrent low-grade lymphomas in the nontransplantation setting. There are few published reports of using this antibody to treat patients with low-grade lymphomas who have suffered a posttransplantation relapse. We have presented our initial experience with 8 patients who were treated with rituximab for progressive/recurrent low-grade lymphomas after high-dose therapy and AHCT.

Our patients were heavily pretreated before transplantation. Additional chemotherapy treatment following posttransplantation relapse had failed in most of these patients before they were considered for rituximab therapy. Six (75%) of 8 patients responded to rituximab, and most responses were durable. Two patients were still in complete remission close to 3 years after rituximab treatment. Our results are comparable to those reported for previous limited experience using rituximab for treatment of posttransplantation relapse [3] and appear superior to results of conventional chemotherapy [17,18]. Half of our patients (nos. 1, 3, 6, and 7) had a response duration greater with rituximab than they did with transplantation, but the other 4 patients (nos. 2, 4, 5, and 8) did not. Between the 2 groups of patients there were no apparent differences that would have enabled us to predict this outcome.

Rituximab was well tolerated in this study. One patient developed delayed neutropenia, which promptly responded to growth factor. This patient had a normal white blood cell count before rituximab treatment was initiated. No specific pretreatment factors that might have predisposed this patient to neutropenia were identified. Her platelet count and hemoglobin did not decrease after rituximab treatment. When this patient was re-treated with 6 cycles of rituximab for progressive disease, no neutropenia was observed. The incidence of neutropenia in our study was comparable to that reported in previous articles [2,19]. In our study, other side effects occurred mainly during the first infusion and were transient. This report suggests that the toxicity profile of rituximab does not differ in patients with prior history of transplantation. This observation is important because most patients who have undergone high-dose therapy poorly tolerate subsequent cytotoxic chemotherapy. Rituximab, with its favorable toxicity profile, appears to be a feasible option for this group of patients.

A recent study reported a 40% response rate in patients re-treated with rituximab, with a longer duration of response compared to that obtained with their prior course of treatment [20]. Most side effects were mild, and none of the patients developed human antichimeric antibody. Two of our patients were re-treated with rituximab for progressive disease. One patient, who did not respond to the initial 4-week regimen, achieved a PR 6 months later when he was re-treated with 6 weekly infusions of rituximab. Another patient, who had a partial response to the initial 4-week treatment, achieved a second PR when re-treated with 6 weekly infusions of rituximab. No significant side effects were observed during retreatment with rituximab in these 2 patients.

In conclusion, this retrospective study indicates that anti-CD20 antibody (rituximab) treatment is feasible in patients with relapsed/progressive low-grade NHL following high-dose therapy and autologous transplantation. High responses with durability can be achieved. Rituximab is generally well tolerated by the patients. It is a practical therapy that can be given on an outpatient basis and completed in a very short period (22 days). Anti-CD20 antibody (rituximab) should be considered as a first-line salvage treatment for patients with recurrent low-grade NHL in whom high-dose therapy and autologous transplantation have failed.

**REFERENCES**


