Two Retroperitoneal Low-Grade B-Cell Lymphoma Successfully Treated With a Combination of Chimeric Anti-CD20 Monoclonal Antibody and CHOP Chemotherapy

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ABSTRACT

Advanced low-grade B-cell lymphomas have been treated by various modalities such as alkylating-agent monotherapy, combination chemotherapy with anthracycline and other drugs. However, these modalities of therapy have not been reflected in survival, and no standard therapy has been established.

Recently, chimeric anti-CD20 IgG1 monoclonal antibody (rituximab) has found clinical application, and we performed CHOP-rituximab combination therapy for 2 patients with advanced retroperitoneal low-grade B-cell lymphoma. Rituximab at 375 mg/m^2 on day 1, cyclophosphamide at 750 mg/m^2 on day 3, adriamycin at 50 mg/m^2 on day 3, vincristine at 1.4 mg/m^2 on day 3, and prednisolone at 100 mg/m^2 on days 3-7 were administered, followed by a 2-week period of no treatment. Toxicities are acceptable, and both patients achieved complete remission after six and five courses respectively.

INTRODUCTION

Among the non-Hodgkin's lymphomas (NHL), low-grade B-cell lymphomas refer to small lymphocytic lymphoma, follicular lymphoma, marginal-zone B-cell lymphoma, and lymphoplasmacytic lymphoma. In Europe and the United States, low-grade B-cell lymphomas account for 25 to 40% of NHL. Recent studies of Japanese patients with lymphoma have reported that low-grade B-cell lymphomas, follicular lymphomas, and marginal-zone B-cell lymphomas account for 15 to 25%, 7 of 15%, and 10 of 12% of the total NHL, respectively.[1,2]

The main characteristics of low-

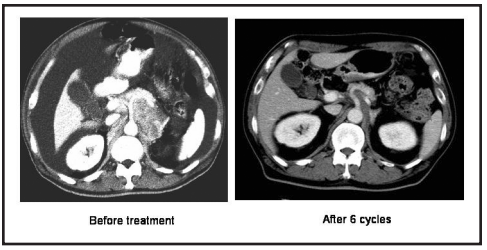

Figure 1. CT imaging of case 1 during the treatment.

grade B-cell lymphomas at the time of diagnosis are that they relatively frequently affect a middle-aged group (median age 55-60 years), and are often advanced. In American whites, 75 to 90% of patients were found to be in advanced Ann Arbor clinical stage (CS) III-IV, with a high frequency of bone marrow invasion.[3] Follicular lymphomas account for the majority of advanced low-grade B-cell lymphomas.

To date, CS III and IV advanced low-grade B-cell lymphomas have been treated by various modalities such as alkylating-agent monotherapy, combination chemotherapy with anthracycline and other drugs, chemotherapy in combination with interferon-α, and massive chemotherapy in combination with autologous or allogeneic hematopoietic stem-cell transplantation. However, these modalities of therapy have not been reflected in survival, and no standard therapy has been established.

Recently, chimeric anti-CD20 IgG1 monoclonal antibody (rituximab) has found clinical application. It has an action mechanism different from those of conventional chemotherapeutic agents, and adverse reactions or mechanisms of resistance to it do not overlap with those to chemotherapeutic agents.[4,5] Therefore, the clinical introduction of rituximab has expanded the potential for combination use with other chemotherapeutic agents, and holds promise for not only increasing the response rate but also prolonging survival.

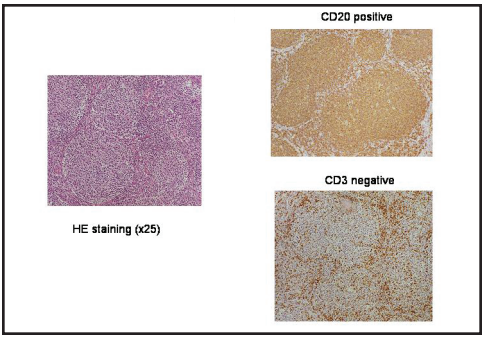

Figure 2. Histopathological finding.

In this study, we performed CHOP-rituximab combination therapy for 2 advanced retroperitoneal low-grade B-cell lymphomas, and achieved complete response in 2 patients.

CASE REPORTS

Case 1

Patient: 65-year-old man.
Chief complaint: Sensation of abdominal fullness and back pain.
Present illness: He had a sensation of abdominal fullness and left back pain in March 2003, and visited a local clinic, where an intraperitoneal, child-head-sized tumor and cervical and inguinal lymphadenopathies were pointed out, and he was referred to our hospital. Laboratory studies, including hemogram and liver and kidney function tests, were all within normal limits. CT scans showed ascites and a solid, irregular tumor, 18×12 cm in size, invading the celiac and superior mesenteric arteries (Figure 1).

The cytology of chylous ascites was class 2. Inguinal lymph node biopsy led to a histologic diagnosis of non-Hodgkin's lymphoma, follicular mixed B-cell type according to the WHO classification, and immunostaining showed the lesion to be CD20-positive (Figure 2).
Treatment and clinical course: Six courses of CHOP-rituximab combination therapy (rituximab at 375 mg/m^2 on day

Figure 3. CT imaging of case 2 during the treatment.

1, cyclophosphamide at 750 mg/m^2 on day 3, adriamycin at 50 mg/m^2 on day 3, vincristine at 1.4 mg/m^2 on day 3, prednisolone at 100 mg/m^2 on days 3-7) were administered. Grade 3 neutropenea was observed in every course, but using 2 g/kg of G-CSF (colony stimulating factor; lenograstim) the treatment was well tolerated. The 6 courses of this therapy caused a complete reduction of the abdominal tumor and the ascites. The swelling of the cervical and inguinal lymph nodes also disappeared (Figure 1). This patient is still alive with no evidence of disease after 8 cycles of the treatment.

Case 2

Patient: 57-year-old woman.
Chief complaint: General fatigue.
Present illness: She had general fatigue in September 2003, and visited a local clinic. Intraperitoneal and inguinal lymphadenopathies were pointed out, and she was referred to our hospital. Laboratory studies, including hemogram and liver and kidney function tests, were all within normal limits. CT scans showed multiple enlarged lymph nodes around the abdominal aorta, one of which measured 6.0 cm in diameter, causing hydronephrosis (Figure 3). Inguinal lymph node biopsy led to a histological diagnosis of non-Hodgkin's lymphoma, follicular mixed B-cell type according to the WHO classification, and immunostaining showed the lesion to be CD20-positive.

Treatment and clinical course: Five courses of CHOP-rituximab combination therapy were administered as in Case 1. Grade 3 neutropenea was observed in course 1, 2, 4, and 5, but with the use of 2 g/kg/day of lenograstim, the treatment was also well tolerated. The 5 courses of this therapy caused a complete reduction in the periaortic swollen lymph nodes. The swelling of the inguinal lymph nodes also disappeared (Figure 3). This patient is also alive with no evidence of disease after 8 cycles of the treatment.

DISCUSSION

Low-grade B-cell lymphomas, as typified by follicular lymphoma, are intractable diseases that have a slow course with a long median survival of 7 to 10 years and, in most patients, undergo histologic transformation to higher-grade histologic types, mainly diffuse large B-cell lymphoma (DLBCL), and ultimately cause neoplastic death. It has been reported that the histologic transformation rate of follicular lymphoma is as high as 40 to 70%, and that the median of the period between diagnosis and histologic transformation is 4 to 5 and a half years, and that the median survival after histologic transformation is less than 1 to 2 years.[6,7] Since a permanent cure is difficult to achieve, the long-term prognosis is poorer than that of intermediate- and high-grade lymphomas. Rosenberg et al reported that in the patients at all stages of disease treated by various modalities, the remission rate was approximately 80%, but the relapse late was also high with a mean remission period of 24 months, 5-year survival rate of 60 to 80%, 10-year survival rate of 50 to 60%, 5-year exacerbation-free survival rate of 30 to 40%, and 10-year exacerbation-free survival rate of 25%.[8] The 10-year survival rate of low-grade B-cell lymphomas compared with that of intermediate- and high-grade NHL is better at 60% vs 35%, but the 15-year survival

rate is poorer at 26% vs 33%.[8] The difficulty?maintaining remission, and the occurrence of relapse and exacerbation over a long period are due to the fact that low-grade B-cell lymphoma cells are resistant to chemotherapeutic agents and thus intractable.

Rituximab is a chimeric anti-CD20 IgG1 monoclonal antibody that has recently found clinical application. It has been confirmed that rituximab binds to the human B-cell surface antigen CD20, and selectively exerts a cytotoxic effect on B-cell tumors by antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) or by directly acting on cells with bcl-2 gene rearrangement (a molecular biological characteristic of CD20-positive B cells), thereby inducing apoptosis.[9,10] Cross-resistance to conventional chemotherapeutic agents and rituximab does not occur, and rituximab has a completely different mechanism of action. It has been reported that the response rate and CR rate of rituximab monotherapy are 48% (80/166) and 6% (10/166), respectively, and that it is safe, with low toxicity as indicated by a rate of toxicity over grade 3 of only 12% in spite of fever (43%), chills (28%), and headache (14%).[11]

Rituximab has an action mechanism different from those of conventional chemotherapeutic agents, and adverse reactions or mechanisms of resistance to it do not overlap with those to chemotherapeutic agents.[4,5] Therefore, the clinical introduction of rituximab has been expanding the potential for combination use with various chemotherapeutic agents.

Although CHOP is a standard therapy for intermediate- and high-degree lymphomas, the CR rate for untreated follicular lymphomas has been reported to be 36%.[12] In addition, amazing response and CR rates of 55% and 95%, respectively, have been reported for CHOP-rituximab combination therapy for untreated follicular lymphomas. Thus, this combination therapy has increasingly become a powerful candidate for the standard therapy for low-grade B-cell lymphomas.

Clinical trials of CHOP-rituximab combination therapy are in progress as an attempt at therapy for low-grade B-cell lymphomas. Six courses of CHOP therapy in combination with 6 doses of rituximab (375 mg/m^2) achieved an ORR of 95% (38/40) and a CR rate of 55% (22/40).

Retroperitoneal malignant lymphoma is relatively rare, and often found at advanced disease. The key problem is whether prolonged survival or prolonged relapse-free survival in patients in CR will be achieved. In the 2 patients reported here, CHOP-rituximab combination therapy achieved CR, making follow-up evaluation of survival important.

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