

Observation of the Curative Effect of Mabthera in Combination with the CHOP Regimen in Treating Invasive B-Cell Lymphoma: A Report of 45 Cases

Yuerong Shuang
Daqian Ye
Jianxiang Chen
Yaohua Wu
Hui Huang
Guanghua Fan

No.1 Department of Medical Oncology, Jiangxi Cancer Hospital, Nanchang 330029, Jiangxi Province, China.

Correspondence to: Yuerong Shuang
E-mail: syr2003syr@yahoo.com.cn

Received October 27, 2007; accepted January 8, 2008.

CJCO <http://www.cjco.cn>
E-mail: 2008coccr@gmail.com
Tel (Fax):86-22-2352 2919

OBJECTIVE To observe the clinical efficacy and toxic effects of Mabthera (rituximab) in combination with the CHOP (R-CHOP) regimen for treating invasive B-cell non-Hodgkin's lymphoma.

METHODS A total of 45 patients with CD20 positive B-cell non-Hodgkin's lymphoma were randomly divided into the R-CHOP (22 cases) and CHOP groups (23 cases for controls). They received the regimens of Mabthera in combination with CHOP or single CHOP therapy respectively. An appraisalment of the curative effect could only be performed following 4 cycles of chemotherapy for the 45 patients. Follow-up was conducted to observe the conditions of survival.

RESULTS The rate of complete remission (CR) in the R-CHOP group was 68.2%, with a total effective rate of 81.8%, and in the CHOP group these rates were 34.8% and 78.3% respectively. There was a significant difference in comparing the CR rates between the two groups ($P < 0.05$). The 1, 2 and 3-year overall survival (OS) rates of the RCHOP group were 90.9%, 81.8% and 77.3%, respectively. In the CHOP group, the OS rates were respectively 91.3%, 69.5% and 47.8%. The difference in the 3-year OS between the two groups was significant ($P < 0.05$).

The toxic effects of the two groups were mainly a slight and moderate bone marrow depression and a gastrointestinal reaction, with similar tolerable toxic effects in the two groups ($P > 0.05$). Adverse effects related to the Mabthera infusions occurred in 6 cases of the R-CHOP group (27.2%). These effects lessened after symptomatic treatment.

CONCLUSION The therapeutic regimen of Mabthera, in combination with CHOP (R-CHOP) has an obvious curative effect for treating invasive B-cell non-Hodgkin's lymphoma, with a favorable tolerance. It is highly recommended as the treatment of choice.

KEY WORDS: B-cell non-Hodgkin's lymphoma, Mabthera (rituximab), chemotherapy.

Copyright © 2008 by Tianjin Medical University Cancer Institute & Hospital and Springer

Introduction

Invasive B-cell lymphoma is most frequently seen in non-Hodgkin's lymphomas. In CHOP therapeutic regimens, chemotherapy has been the standard therapy for invasive B-cell lymphoma, however the 5-year overall survival (OS) rate is only approximately 40%~50%^[1]. Mabthera (rituximab) is a CD20-specific chimeric monoclonal antibody. Since CD20 is expressed in 95% of B-cell lymphomas, Mabthera can specifically combine with CD20 of the B-cell antigen, resulting in an immunoreaction clearing the B cells by various mechanisms. Over the past few years, Mabthera has been used to treat invasive B-cell lymphoma, and it can significantly raise the efficacy of the

CHOP therapeutic regimen^[2–4]. In our study, 45 patients with invasive B-cell lymphoma were randomly divided into 2 groups. One group received only the CHOP regimen, and the other group Mabthera in combination with CHOP (RCHOP). The curative and toxic effects were then compared.

Materials and Methods

Clinical data

From January 2001 to December 2006, 45 patients who were positive CD20, and shown to have invasive B-cell non-Hodgkin's lymphoma (NHL), were admitted to our hospital. Of the total patients, 33 were males and 12 females, with ages ranging from 25 to 79 years, and a median of 45. Among these cases 36 were diffuse large B-cell lymphomas (DLCL), and 9 mantle cell lymphomas (MCL). Thirty-two patients received an initial treatment, and 13 were the patients with a recurrence after chemotherapy. The CHOP chemotherapeutic regimen was employed for all the patients with a relapse, usually 3–6 chemotherapeutic cycles with 3 the most common. Details of the 45 cases were as follows, based on Ann Arbor Staging: 15 cases with Stage II, 25 Stage III and 5 Stage IV. In our study, the Eastern Cooperative Oncology Group (ECOG) performance status score of all patients was 0 to 2. Based on the IPI scoring, there were 9 cases with low risk, 28 with moderate risk, and 8 with high risk. Routine blood examinations, liver and renal function tests and ECG results were normal, with an expected survival time of over 6 months. All of the 45 patients were randomized into two groups, and received either the RCHOP or the CHOP chemotherapeutic regimen. The general condition of patients in the two groups was similar. See Table 1 for the condition of the patients.

Treatment methods

Mabthera, in combination with the CHOP therapeutic regimen, was used for treating 22 cases in the RCHOP group, and the single CHOP regimen was employed for treatment of 23 cases of the control group. ①CHOP therapeutic regimen: cyclophosphamide 750 mg/m², i.v., d1; pirarubicin 40 mg/m² or Pharmorubicin 60 mg/m², i.v., d1; vincristine 1.4 mg/m², i.v., d 1; prednisone 100 mg, PO, d 1–d 5, a cycle every 3 weeks. ②RCHOP therapeutic regimen: Mabthera 375 mg/m², the first day of each cycle (d1), i.v. drip infusion; CHOP regimen started from d 3 of the cycle, with a cycle every 3 weeks. Slow i.v. drip infusion of Mabthera (100 mg) was conducted at d1, with addition of 500 ml of 5% glucose and saline (GS), approximately 15–20 drops/min. If no adverse reaction was noted following a half to 1 h, the infusion speed was raised up to 30 drops/min. The drip infusion was completed within about 2 h. Then 500 mg of Mabthera was added with 500 ml of 5% GS for an i.v. drip infusion which was completed in a period from

4 to 6 h. Half a hour before medication of this drug, 2 tablets of Xinguangpian was taken orally and 20 mg of diphenhydramine was injected intramuscularly.

On the day of medication, the blood pressure, heart rate and respiratory frequency were monitored, once an hour for 10 h. Assessment of the curative effects for all 45 patients was conducted at 4 to 6 cycles following the chemotherapy. The cases with a treatment period of less than 4 cycles were not included in the statistics. Before the chemotherapy, a routine 5-HT3 antagonist was administered to prevent vomiting. During the treatment, if a degree-III to IV bone marrow depression or a fever, neutrocytopenia occurred in the patients, a supportive treatment of granulocyte colony-stimulating factor (C-CSG) was immediately administered.

Table 1. Grouping and general state of health of the 45 patients (cases).

Characteristic	RCHOP	CHOP
Cases	22	23
Treated initially	15	17
Retreated	7	6
Sex		
Male	16	17
Female	6	6
Age, years		
Range	28–79	25–76
Median	46	44
Pathological types		
DLCL	15	21
MCL	7	2
Stage		
II	8	7
III	10	15
IV	4	1
IPI scoring		
Low risk	6	3
Moderate risk	13	15
High risk	3	5

Evaluation criterion

Assessment of the objective curative effects was carried out based on the WHO evaluation criterion^[5]. These effects were divided into complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD). Assessment of the adverse effects was conducted based on WHO evaluation criterion on acute and subacute toxic reaction of anticancer drugs^[5].

Statistical analysis

In comparing the data between the 2 groups, the chi-square test was used to complete a total statistical analysis.

Results

Curative effects

The CR rate of the RCHOP group was 68.2%, and the total effective rate was 81.8%. In the CHOP group, these rates were respectively 34.8% and 78.3%, resulting in a significant difference between the CR rate of two groups ($P < 0.05$). The short-term effect of the RCHOP therapeutic regimen was superior to the CHOP-only therapeutic regimen. All the cases were followed-up until December 2006, with a follow-up time of 6 to 55 months and a median time of 26.5 months. Thirteen patients of both groups died; of the total cases, 11 died of a PD, and 2 died of serious hepatitis (both received the CHOP regimen). In the RCHOP group, the 1, 2 and 3-year overall survivals (OSs) were 90.9%, 81.8%, and 77.3%, respectively. In the CHOP group, these OSs were respectively 91.3%, 69.5% and 47.8%, showing a significant difference in the 3-year OS between patients of the two groups ($P < 0.05$). The RCHOP regimen provides survival advantage with the longest survival. In the RCHOP group, the longest disease-free survival was 57 months. The patients with the longest survival were those who suffered a diffuse large-B cell lymphoma and, who had received an initial treatment, and withdrawal of the chemotherapy for 54 months. For another 1 patient with diffuse large-B cell lymphoma, a variety of salvage chemotherapeutic regimens failed to attain any remission of the recurrence after a combined chemotherapy. However CR of the symptoms occurred with 6 cycles of treatment after receiving the R-CHOP therapeutic regimen, with a disease-free survival of 55 months.

Toxic effects

The toxic effects of the two groups were mainly slight with moderate bone marrow depression and gastrointestinal reaction. There was no statistical difference between the two groups, $P > 0.05$ (Table 2). In the RCHOP group, an adverse effect related to Mabthera infusion occurred in 27.2% of the patients. No apparent problems were found in the 6 patients with a fever (27.2%), and following symptomatic treatment, the patient's condition improved. A 79-year patient developed a high fever (40°C), chills, palpitation, dyspnea, and a fall in blood pressure. The symptoms disappeared after immediate withdrawal of Mabthera infusion, with oxygen inhalation and anti-anaphylactic treatment. A drop in blood pressure occurred in 3 patients (13.6%), a skin rash in 2 (9%), and cardiac arrhythmia in another 2 (9%). A 64-year female patient developed systemic skin itching and a multiple allergic rash at the start of administering 30 mg of Mabthera i.v. The symptoms gradually vanished, after an immediate withdrawal of the Mabthera infusion, and administration of dexamethasone and promethazine. No cutaneous reaction recurred following a continuous i.v. drip of Mabthera. There were no cases of death in relation to the treatment in the two groups.

Table 2. Main toxic effects in the 2 groups after treatment.

Characteristic	R-CHOP	CHOP
Cases	22	23
WBC		
I~II	13	14
III~IV	7	7
PLT		
I~II	16	15
III~IV	3	4
N and V		
I~II	11	13
III~IV	2	2
Peripheral neuritis		
I~II	14	13
III~IV	0	0
Alopecia		
I~II	16	19
III~IV	0	0
Liver function		
I~II	5	6
III~IV	0	0

N, nausea; V, vomiting

Discussion

Mabthera (rituximab) is a human-mouse chimeric monoclonal antibody that targets the CD20 antigen. Since it reacts specifically with the CD20 antigen of B-lymphocytes, it induces a complement-dependent and antibody-dependent cell-mediated cytotoxic effect and apoptosis, allowing removal of CD20-positive B cells^[6]. In vitro experiments have shown that Mabthera directly inhibits tumor-cell growth or induces apoptosis^[7].

Mabthera was the first monoclonal antibody, approved by the FDA for clinical treatment. The total remission rate of single medication on recurrent follicular non-Hodgkin's lymphoma (NHL) was 48%, and the CR rate was 6%^[8]. Over the past few years, Mabthera in combination with the CHOP therapeutic regimen for treating invasive NHL has attained a noteworthy curative effect^[9,10]. In the GELA98-5 study by Feugier et al.^[2], Mabthera was combined with the CHOP regimen to initially treat 202 patients with invasive lymphoma (DLBCL), while in the control group 197 patients received the CHOP regimen. The CR rates were respectively 75% and 69% ($P = 0.005$), and the median event-free survival times were respectively 3.8 and 1.1 years ($P < 0.001$). The results indicated that the Mabthera plus CHOP regimen for initially treating invasive lymphoma can significantly increase the therapeutic efficacy, and can markedly improve the disease-free survival and the overall survival times. The MInT program, com-

pleted by Pfreundschuh et al.^[3] analyzed 350 young patients receiving the Mabthera-combined CHOP regimen for initially treating low-risk diffuse large-B cell lymphoma (DLBCL) patients. The CR rate was 86%, and the 3-year event-free survival was 79%, which was obviously superior to the CHOP therapeutic regimen in the control group ($P < 0.001$). The results showed that Mabthera combined with the CHOP therapeutic regimen for treating young patients with low-risk DLBCL would lengthen patient's survival.

In our study, the CR rate of the RCHOP regimen was 68.2%, and the total effective rate 81.8%. In the CHOP group, these two rates were respectively 34.8% and 78.3%. There was a significant difference in comparison of the CR rate between the two groups ($P < 0.05$). The 1, 2 and 3-year overall survival (OS) rates of the patients receiving the RCHOP therapeutic regimen were respectively 90.0%, 81.8% and 77.3%. In the CHOP group, these rates were respectively 91.3%, 69.5% and 47.8%, with a significant difference in comparing the 3-year OS rates ($P < 0.05$). Since the follow-up time was too short, the summary of a long-term (i.e. 5-year) survival rate is expected, following further follow-up.

The main side effect of Mabthera occurred at first with i.v. drip infusion. The clinical manifestations were fever, chills, nausea, vomiting, skin rash and flushing etc. Most of these effects are slight or moderate symptoms, which are tolerable for the patients. Toxic effects, such as bronchospasms or a drop in blood pressure, may occur in a few patients, therefore immediate withdrawal of Mabthera, and oxygen inhalation as well as anti-anaphylactic treatment should be conducted. Before a 30-min drip infusion of Mabthera, oral administration of diphenhydramine hydrochloride, paracetamol and preventive decrease in the infusion speed should be conducted. In our RCHOP group, 27.2% of the patients developed adverse effects relating to the Mabthera infusion. However these effects were not severe and improved after treatment. Vose et al.^[11] reported that Mabthera did not increase toxic effect of chemotherapeutics, which was in accordance with the findings of our group. There was no statistical difference in chemotherapeutic toxic effect between the two groups, $P > 0.05$, indicating that Mabthera did not aggravate the toxic effects. All patients completed the treatment, and no deaths resulted related to the treatment.

In conclusion, Mabthera combined with the CHOP (R-CHOP therapeutic regimen) for treating CD20-positive invasive B-cell lymphoma attained a marked curative effect, with a satisfactory patient tolerance. It can therefore be recommended as the optimal therapeutic regimen for invasive B-cell lymphoma.

References

- 1 Jiang WQ, Sun XF, Zhang L, et al. Ed. Practical Manual of Medical Oncology Prescription. Guangzhou: Guangdong Science Publishing House 2003; 316–317 (Chinese).
- 2 Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: A Study by the Groupe d'Etude des Lymphomes de l'Adulte. Clin Oncol 2005; 23: 4117–4126.
- 3 Pfreundschuh M, Trümper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 2006; 7: 379–391.
- 4 Glass B, Kloess M, Benter M, et al. Dose-escalated CHOP plus etoposide (Mega CHOEP) followed by repeated stem cell transplantation for primary treatment of aggressive high-risk non-Hodgkin's Lymphoma. Blood 2006; 107: 3058–3064.
- 5 Zhou JC. Ed. Practical Medical Oncology. Beijing: People's Medical Publishing House 2003; 29–47 (Chinese).
- 6 Jiang WQ, Zhang XS, Zhu XF, et al. Biotherapeutics of Oncology. Guangzhou: Guangdong Science Publishing House 2006; 13–14.
- 7 Lu YQ, He QH, Xu J, et al. In vitro induction of rituximab on apoptosis of Daudi cells. Zhonghua Xue Ye Xue Za Zhi 2002; 23: 206–207 (Chinese).
- 8 Maloney DG, Grillo-lopez A J, White CA, et al. Rituximab anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's Lymphoma. Blood 1997; 90: 2188–2195.
- 9 Jermann M, Jost LM, Taverna CH, et al. Rituximab-EPOCH, an effective salvage therapy for relapsed, refractory or transformed B-cell lymphomas: results of a phase II study. Ann Oncol 2004; 15: 511–516.
- 10 Kewalramani T, Zelenetz AD, Nimer SD, et al. Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood 2004; 103: 3684–3688.
- 11 Vose JM, Link BK, Grossbard ML, et al. Phase 1 study of Rituximab in combination with CHOP chemotherapy in patients with previously untreated aggressive non-Hodgkin's lymphoma. Clin Oncol 2001; 19: 389–397.