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The Use of Mabthera in Combination with the Chop for the Treatment of Cd20 Positive Non-Hodgkin's Lymphoma

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Abstract: ***Besides traditional cytostatic drugs the introduction of monoclonal antibodies has substantially influenced current treatment concepts of non-Hodgkin's lymphoma (NHL). Rituximab, a monoclonal anti-CD20 chimeric antibody, now has been widely evaluated in the various B-cell lymphatic neoplasms. The ai of the study was to evaluate the clinical efficacy and toxic effects of Mabthera (rituximab) in combination with the CHOP (R-CHOP) regimen for treating non-Hodgkin's lymphoma. A total of 60 patients with CD20 positive non-Hodgkin's lymphoma were compared into the R-CHOP and CHOP groups. They received the regimens of Mabthera in combination with CHOP or single CHOP therapy respectively. Curative effect and survival rate in both groups was evaluated following 6-8 cycles of chemotherapy. The overall survival rate in the R-CHOP group was 90% and in to control group was 54% with a significant difference between them (p<0.01) The addition of rituximab to the CHOP regimen increases the complete response rate and prolongs event-free and overall survival in patients in non-Hodgkin's lymphoma, without a clinically significant increase in toxicity. It is highly recommended as the treatment of choice.***

Keywords: Non-Hodgkin's lymphoma, Mabthera (rituximab), chemotherapy anti-CD20

1. Introduction

Non-Hodgkin's lymphoma (NHL) is the most common hematological malignancy in adults. Invasive B-cell lymphoma is most frequently seen in non-Hodgkin's lymphomas. In CHOP therapeutic regimens, chemotherapy has been the standard therapy NHL, however the 5-year overall survival rate is only approximately 40%-50%[1]. Mabthera is a anti-CD20-specific monoclonal antibody and it is effective when given as a single agent in the treatment both indolent and aggressive lymphomas [1-4]. The last few years, Mabthera has been used to treat invasive NHL, and it can significantly raise the efficacy of the CHOP therapeutic regimen [5-7]. In this study, 60 patients with invasive B-cell lymphoma were randomly divided into two groups. One group received only the CHOP regimen, and the other group Mabthera in combination with CHOP (R-CHOP). The curative and toxic effects were then compared.

2. Patients and Method

From January 2010 to December 2014, 60 patients who were CD20 positive, with invasive B-cell non-Hodgkin's lymphoma (NHL), were admitted to our hospital. Forty three patients received an initial treatment, and 17 were the patients with a recurrence after chemotherapy. The CHOP chemotherapeutic regimen was applied for all the patients with a relapse, usually 6-8 chemotherapeutic cycles. 15 cases were in the stage II, 32 cases were stage III and 11 Stage IV. 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 60 patients were compared into two groups, receiving mabthera with CHOP and CHOP chemotherapeutic regimen.

Treatment Methods

Mabthera, in combination with the CHOP therapeutic regimen, was used for treating 30 cases in the RCHOP group, and only CHOP was used for treatment of 30 cases of the control group. CHOP therapeutic regimen consisted of: cyclophosphamide 750 mg/m^2, i.v., d1; doxorubicin 60 mg/m^2, i.v., d1; vincristine 1.4 mg/m^2, i.v., d 1; prednisone 100 mg, PO, d 1-d 5, a cycle every 3 weeks. RCHOP therapeutic regimen: Mabthera 375 mg/m^2, the first day of each cycle (d1), i.v. drip infusion; CHOP regimen started from the first day of the cycle, with a cycle every 3 weeks. Vital signs of patients were monitored regularly and assessment of the response to treatment for all patients was carried out at 3 - 4 cycles following the chemotherapy. The effects of treatment were divided into complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD). The adverse effects were divided on acute and subacute toxic reaction of anticancer drugs.

Statistical analysis

Data analysis was carried out using the SPSS software. Independent samples t test was used to compare the age of patients between two groups. Chi-square and Fisher's exact test was used to compare the proportion between variables. Kaplan Meier analysis was used to compare the survival between the groups. A p value ≤ 0.05 was considered statistically significant. All tests are two tailed.

3. Results and Discussion

44 (73%) of the total patients, were males and 16 (27%) females, with ages ranging from 25 to 79 years, and a median of 45 year. 48 (60%) patients had were diffuse large

B-cell lymphomas (DLCL), and 12 (20%) of them mantle cell lymphomas (MCL). (table 1). There was no significant difference between the two groups in any clinical or pathological characteristic, p>0.05. The complete remission rate of the R-CHOP group was 69.5%, and the total effective rate was 82.3% whereas in the CHOP group, the complete remission rate 35.7% and the total effective rate was 77.1% with a significant difference between the two groups ($p < 0.05$). The short-term effect of the R-CHOP therapeutic regimen yielded better results compared to the CHOP-only therapy regimen. All the cases were followed-up from 6 to 40 months and a median time of 20 months. 17 (28%) patients of both groups did not survive. 14 cases who belonged to control died of progressive disease, renal and hepatic complication whereas 3 cases who belonged to R-CHOP group died of hepatic complication. The overall survival rate in the R-CHOP group was 90% and in to control group was 54% with a significant difference between them, (Kaplan Meier Logrank test = 7.1 , $p<0.01$ (figure 1). The survival with R-CHOP therapy was longer than CHOP alone. The longest disease-free survival was 52 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 one patient with diffuse large-B cell lymphoma, chemotherapy did not result in remission of the disease. The complete remission of the symptoms occurred with 8 cycles of treatment after receiving the R-CHOP therapy, with a disease-free survival of 52 months.

Toxic Effects

The toxic effects among the two groups were mild with moderate bone marrow depression and gastrointestinal reaction without statistical difference between them $p > 0.05$ (Table 2). Fever occurred in 8 (27%) of the patients in the R-CHOP group whose condition improved after the treatment. A decrease in blood pressure occurred in 4 patients (13%), a skin rash in 3 (10%), and cardiac arrhythmia in another 2 (7%). A 64-year female patient developed systemic skin itching and a multiple allergic rash at the start of administering of Mabthera i.v. The symptoms gradually wiped out, after the immediate withdrawal of the Mabthera and administration of anti-anaphylactic treatment. No cutaneous reaction recurred following a continuous i.v. administration of Mabthera. There were no cases of death in relation to the treatment in the two groups. Mabthera (rituximab) is a monoclonal antibody that targets the CD20 antigen. Over the past few years, Mabthera in combination with the CHOP therapeutic regimen for treating invasive NHL has shown remarkable curative effect [8,9]. This study compared the efficacy and safety of rituximab in combination with CHOP chemotherapy with that of CHOP chemotherapy alone in patients with NHL. A higher response rate, improved event-free and overall survival among patients treated with the combination of rituximab and CHOP. The longer survival in the CHOP-plus-rituximab group was due to a lower rate of disease progression during therapy and fewer relapses among patients who had a complete response. Treatment with CHOP plus rituximab was well tolerated, and the incidence of severe or serious adverse events was no different from that in the CHOP group. The CHOP was chosen for use in this study because it is as effective as, and less toxic than, other, more recently developed chemotherapeutic regimens [10-13]. 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. 28% of the patients in the R-CHOP group, developed adverse effects relating to the Mabthera infusion. However these effects were not severe and improved after treatment. Vose et.al. reported that Mabthera did not increase toxic effect of chemotherapeutics, which was in accordance with the findings of our group [14]. The results with CHOP alone in this study were similar to those previously reported in other studies [15]. For this reason, we believe that the better results with CHOP plus rituximab are not attributable to an unusually poor outcome among patients in the CHOP group.

4. Conclusion

Our study complements the randomized prospective comparisons by demonstrating that the addition of rituximab to CHOP improves the outcome in patient population. Mabthera combined with the CHOP for treating CD20-positive invasive B-cell lymphoma produced better curative effect, with a satisfactory patient tolerance. It can be recommended as the optimal therapeutic regimen for NHL.

References

[1] Maloney DG, Grillo-López AJ, White CA, et al. IDEC-C2B8 (rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. Blood 1997;90:2188-95.
[2] McLaughlin P, Grillo-Lopez AJ, Link BK, 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;16:2825-33.
[3] Coiffier B, Haioun C, Ketterer N, et al. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. Blood 1998;92:1927-32.
[4] Foran JM, Rohatiner AZS, Cunningham D, et al. European phase II study of rituximab (chimeric anti-CD20 monoclonal antibody) for patients with newly diagnosed mantle-cell lymphoma and previously treated mantlecell lymphoma, immunocytoma, and small B-cell lymphocytic lymphoma. J Clin Oncol 2000;18:317-24. [Erratum, J Clin Oncol 2000;18:2006.]
[5] 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.
[6] Pfreundschuh M, Trümper L, Osterborq A, et al. CHOPlike chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with goodprognosis diffuse large-B-cell lymphoma: a randomized controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 2006; 7: 379-391.

[7] Glass B, Kloess M, Benter M, et al. Dose-escalted 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.
[8] 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.
[9] Kewalramani T, Zelenetz AD, Nimer SD, et al. Rituximab and ICE assecond-line therapy before autologous stem cell transplantion for relapsed or primary refractory diffuse large B-cell lymphoma. Blood 2004; 103: 3684-3688.
[10] Jerkeman M, Anderson H, Cavallin-Stahl E, et al. CHOP versus MACOP-B in aggressive lymphoma — a Nordic Lymphoma Group randomized trial. Ann Oncol 1999;10:1079-86.
[11] Tirelli U, Errante D, Van Glabbeke M, et al. CHOP is the standard regimen in patients > or = 70 years of age with intermediate-grade and high-grade non-Hodgkin's lymphoma: results of randomized study of the European Organization for Research and Treatment of Cancer LymphomaCooperative Study Group. J Clin Oncol 1998;16:27-34.
[12] Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 1993;328:1002-6.
[13] Sonneveld P, de Ridder M, van der Lelie H, et al. Comparison of doxorubicin and mitoxantrone in the treatment of elderly patients with advanced diffuse non-Hodgkin's lymphoma using CHOP versus CNOP chemotherapy. J Clin Oncol 1995;13:2530-9.
[14] 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.
[15] Tilly H, Lepage E, Coiffier B, et al. A randomized comparison of ACVBP and CHOP in the treatment of advanced aggressive non-Hodgkin's lymphoma: the LNH93-5 study. Blood 2000;96:832a

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Table 1: Characteristics of study patients

Variable	R-CHOP	CHOP
	n (%)	n (%)
Patients	30 (50)	30 (50)
Treated initially	20 (67)	23 (77)
Retreated	10 (33)	7 (23)
Gender		
Male	21 (70)	23 (77)
Female	9 (30)	7 (33)
Age,years		
Range	28 -79	25 - 76
Median	46	44
Pathological types		
DLCL	20 (67)	28 (93)
MCL	10 (33)	2 (7)
Stage		
II	10 (33)	8 (27)
III	12 (40)	20 (67)
IV	8 (27)	2 (6)

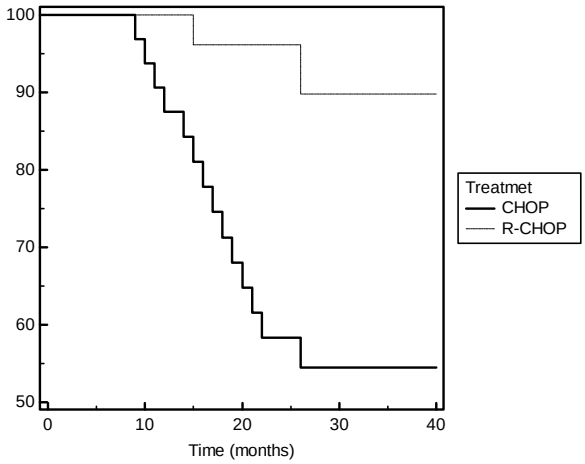

Figure 1: Kaplan Meier analysis of the survival for R-CHOP and CHOP

Table 2: Main toxic effects and their grade in the two groups after treatment

Characteristic	R-CHOP	CHOP
Patients	30 (50)	30 (50)
WBC		
I-II	18 (60)	18 (60)
III-IV	10 (33)	7 (23)
PLT		
I-II	22 (73)	15 (50)
III-IV	4 (13)	9 (30)
Nausea and Vomiting		
I-II	15 (50)	17 (57)
III-IV	3 (10)	3 (10)
Peripheral neuritis		
I-II	19 (63)	17 (57)
III-IV	0	0
Liver function		
I-II	7 (23)	8 (27)
III-IV	0	0
Alopecia		
I-II	22 (73)	25 (83)
III-IV	0	0