Radiol Oncol 2004; 38(1): 15-9.

Rituximab affects the prognosis of patients with nonHodgkin's lymphomas

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Background. *Rituximab - the most widely used monoclonal antibody in the B cell lymphoid malignancies - has been applied successfully in the treatment of relapsed and refractory indolent CD20 positive B cell lymphomas and more recently, also in the treatment of aggressive lymphomas in combination with standard chemotherapy. Albeit the chemo-immunotherapy has a wide range of potential applications, there are still several issues that have to be resolved: (1) the optimal scheduling of antibody-chemotherapy combinations, (2) the most active of these combinations, as well as (3) the predictors of response to rituximab.*

Patients and methods. *To facilitate addressing the first two questions, we performed an analysis in 25 patients with different histological types of CD20 positive nonHodgkin's lymphomas (10 aggressive and 15 indolent). Seventeen patients were treated with chemo-immunotherapy for a relapse, and just in 8 patients rituximab was added to first line chemotherapy. Most of the responders received the CHOP regimen, but also other regimens (FC, BVCPP) were effective in combination with rituximab.*

Results. *The overall response rate was 76%, with 68% complete remissions. The median response duration has not been reached yet. The response was markedly better in the group of previously untreated patients, where the overall response rate reached 100%, with 7 patients in complete and 1 patient in partial remission. Most of the treatment failures occurred in heavily pretreated patients with aggressive lymphomas. No serious adverse effects were observed.*

Conclusion *The chemo-immunotherapy improves the treatment outcomes in patients with untreated and relapsed CD20 positive nonHodgkin's lymphomas in comparison to chemotherapy alone. The combined treatment is the most effective when used as soon as possible (preferably as the first line treatment). To optimize the use of rituximab, not only the most active antibody-chemotherapy combination will have to be determined, but also the predictors of success of such treatment will have to be identified.*

Key words: lymphoma, nonHodgkin's; rituximab

Received 27 January 2004
Accepted 03 February 2004

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Introduction

The CD20 antigen, a 35 kDa phosphoprotein, is restricted to the B cell lineage and is expressed by mature B cells and most malignant B cell lymphomas. While the exact functions of CD20 are unknown, it may play an integral role in the activation of cell cycle progression in B lymphocytes, possibly via calcium regulation. Its attributes, as its tetraspan binding in the cell membrane and the lack of internalization or downregulation upon antibody binding, make the CD20 suitable as a target for an effective antibody.[1]

Rituximab, a chimeric IgG κ monoclonal antibody that recognizes the CD20 antigen[2], is the most widely recognized and used monoclonal antibody in the B cell lymphoid malignancies. It has been applied successfully in the treatment of relapsed and refractory indolent CD20 positive B cell lymphomas and more recently, also in the treatment of aggressive lymphomas in combination with standard chemotherapy. The indications for its use are now expanding also to Hodgkin's disease and autoimmune diseases.[3]

Even though the results with rituximab as monotherapy as well as in combinations with chemotherapy have been encouraging, many questions still remain to be answered about optimizing its use in patients with malignant lymphomas. Actually, the optimal scheduling of antibody-chemotherapy combinations and the identification of the most active of these combinations have to be resolved, as have the details about its mechanisms of action and the predictors of response to this agent.

With the aim of seeking the optimal scheduling of antibody-chemotherapy combination and identifying an active combination, we performed a retrospective analysis of the results obtained from 25 patients with predominately relapsed CD20 positive nonHodgkin's lymphomas.

Patients and methods

In the year 2001, 25 patients with CD20 positive nonHodgkin's lymphomas were treated with the combination of rituximab and chemotherapy at the Institute of Oncology in Ljubljana, Slovenia. The group consisted of 10 male and 15 female patients. According to the histological type, there were 1 patient with Burkitt's lymphoma, 5 patients with diffuse large B cell lymphoma, 2 patients with unclassified CD20 positive aggressive lymphoma, 13 patients with follicular lymphoma (5 patients grade I, 3 patients grade II, 2 patients grade II/III, 3 patients grade III, and 1 patient unspecified grade), 2 patients with mantle cell lymphoma, and 2 patients with small lymphocytic lymphoma/CLL. Most of the patients were treated for a relapse - in 12 patients the combined treatment with rituximab and chemotherapy was third (or more) line treatment, in 5 patients second line treatment, and just in 8 patients rituximab was added to inadequately successful first line chemotherapy.

The patients received at least 2 and not more than 6 cycles of chemo-immunotherapy. Rituximab was applied in standard doses (375 mg/m^2) on day 1 of the chemotherapy cycle, and was combined predominately with CHOP regimen (20 patients), but also with other chemotherapy schedules (1 patient COP, 2 patients FC, 1 patient VACPE, 1 patient BVCPP) according to their previous treatments. All patients received methylprednisolone, paracetamole and clemastine prior to the application of rituximab.

Treatment response was evaluated according to Cheson's criteria.[4]

Results

In total, complete response was achieved in 17 patients, which represents 68%. The longest observed duration of complete re-

sponse until now is 19 months, and 11 patients are still in complete remission.

The partial response was observed in 2 patients (8%), with the median duration of 8 months. In 1 patient there was stable disease after rituximab and FC treatment, and the patient continued his treatment with a different chemotherapy regimen.

Five patients progressed during chemo-immunotherapy - they all received less than 6 cycles of therapy (at least 2 and at the most 4 cycles), and eventually died of lymphoma. In 3 of these patients, the chemo-immunotherapy was fifth line treatment, in 1 patient second line treatment, and in 1 patient third line treatment. Four of the 5 patients with progressive disease had aggressive histological types of lymphomas, and only 1 patient had indolent follicular lymphoma, but was heavily pretreated.

Surprisingly good results were observed in the small group of patients in whom rituximab wad added to the first line chemotherapy treatment. The overall response rate in this group was as high as 100% with 88% complete responders (7 out of 8 patients), and 1 partial responder. The patient with partial remission relapsed after 14 months, while 6 of 7 complete responders are still in remission.

The treatment outcomes according to histological subtypes are given in Table 1.

The chemo-immunotherapy was very well tolerated and no serious infusion related adverse effects were observed in more than 100 applications. The addition of rituximab to chemotherapy also had no significant influence on the hematological toxicity, and no WHO grade IV infections were observed.

Table 1. The treatment outcomes according to histological subtypes

Histological subtype	No. of patients	Chemotherapy regimen	Line of treatment	Response	Duration of complete or partial response (months)
Burkitt's lymphoma	1	CHOP (1 pt.)	Second (1 pt.)	Progressive disease (1 pt.)	
Diffuse large B cell lymphoma	5	CHOP (2 pts.) VACPE (1 pt.) FC (1 pt.) BVCPP (1 pt.)	First (1 pt.) Second (1 pt.) Third (3 pts.)	Complete response (4 pts.) Progressive disease (1 pt.)	12+
Unclassified aggressive lymphoma	2	CHOP (1 pt.) COP (1 pt.)	Third or more (2 pts.)	Progressive disease (2 pts.)	
Follicular lymphoma	13	CHOP (13 pts.)	First (5 pts.) Second (3 pts.) Third or more (5 pts.)	Complete response (11 pts.) Partial response (1 pt.) Progressive disease (1 pt.)	8,8+ 14
Mantle cell lymphoma	2	CHOP (2 pts.)	First (2 pts.)	Complete response (2 pts.)	4+
Small lymphocytic lymphoma/CLL	2	CHOP (1 pt.) FC (1 pt.)	Third or more (2 pts.)	Partial response (1 pt.) Stable disease (1 pt.)	2

Discussion

Although various standard chemotherapeutic regimes are active in the treatment of patients with nonHodgkin's lymphomas, the results of such treatments are far from optimal. The addition of rituximab to chemotherapy seems to offer an advantage to these patients both in terms of the percentage of response as well as in terms of the response duration. As to the chemotherapy regimen choice it has been namely confirmed by *in vitro* observations that monoclonal antibody exposure may sensitize tumor cells to chemotherapy, and specifically to fludarabine, cisplatin, vinblastine, and doxorubicin.[5,6] Most of the applied regimens in our study included one of the above mentioned cytotoxic drugs, while for the others it has been expected that rituximab will enhance their effect through its interference with the apoptotic processes.[7]

Our outcomes are in accordance with the clinical results of various authors stating that the addition of rituximab to different chemotherapy regimens improves the treatment results.[8-12] However, more and more data confirm the fact that rituximab should be used as soon as possible (preferably in the first line treatment) in the treatment of lymphoma patients in order to achieve maximal efficacy.[13,14] Among our patients, in only 8 patients rituximab was added to inadequately successful first line chemotherapy, while all others received immunotherapy for relapses of nonHodgkin's lymphomas. All 8 patients actually achieved a remission after the addition of the rituximab to the chemotherapy regimen that they had been receiving before (in 7 patients a complete remission, and in 1 patient a partial remission). The results with relapsed lymphomas were convincingly worse. Out of 17 patients, 10 achieved a complete remission (59%), 1 a partial remission (6%), 1 a stable disease (6%), and 5 patients progressed (29%). Certainly, the significance of these results is inestimable due to a small number of patients. However, the results speak in favor of using rituximab as a first line treatment.

Since it is becoming obvious from the numerous clinical studies that rituximab improves the treatment outcomes when it is combined with various chemotherapy regimens, the next step in the research will have to be the identification of predictors for success with chemo-immunotherapy. Not only the IPI, but also new molecular, biologic, and immunologic factors will have to be recognized, before the use of rituximab can be stated as rational. Currently, the overexpression of certain genes involved in cellular immunity has already been confirmed in nonresponders to rituximab[15], as well as the meaning of pretreatment Mcl-1/Bax ratio.[16] Also the cytogenetic abnormality as del (17p13.1) was identified as the predictor of poor response to rituximab.[17] Another predictor, the bcl-2 overexpression, that according to Mournier *et al.*[18] foretells a better outcome of first line rituximab plus CHOP treatment (compared to bcl-2 negative patients) has not been confirmed in patients with relapsed diffuse large B cell lymphoma.[19] Thus to determine more accurately the patients that will benefit at most from the chemo-immunotherapy, further studies will have to be done on a larger number of patients.

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