

## MONOCLONAL ANTIBODIES IN THE TREATMENT OF NON-HODGKIN'S LYMPHOMAS

IVO RADMAN<sup>1</sup> and BRANKA PETRIČEVIĆ<sup>2</sup>

<sup>1</sup>Division of Hematology, Department of Internal Medicine, Zagreb University Hospital Center,  
<sup>2</sup>Department of Pathophysiology, Zagreb University Medical School

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### Summary

Monoclonal antibodies are an exciting advance in the treatment of lymphoma. They are safe and well-tolerated, and exhibit little cross-resistance with conventional chemotherapeutic agents. In indolent lymphomas, antibody has shown useful response rates both as first line therapy and in relapsed disease. Follicular lymphomas appear to be particularly sensitive to rituximab, and chronic lymphocytic leukaemia to alemtuzumab. In aggressive lymphomas, the addition of rituximab to CHOP chemotherapy significantly prolongs disease-free and overall survival compared to CHOP alone as first-line therapy. Novel agents, including radiolabelled antibodies are showing promise in phase I and II trials in a variety of clinical settings.

KEY WORDS: *monoclonal antibodies, lymphoma, immunotherapy*

### MONOKLONSKA PROTUTIJELA U LIJEČENJU NE-HODGKINOVIH LIMFOMA

#### Sažetak

Monoklonska protutijela su velik korak naprijed u liječenju limfoma. Sigurna su i dobro se podnose, a s konvencionalnim kemoterapijskim lijekovima izazivaju vrlo malu unakrsnu rezistenciju. Kod indolentnih limfoma protutijela su pokazala korisnu stopu odgovora kad su primjenjivani kao terapija prvoga reda i kao terapija kod relapsa bolesti. Folikularni limfomi su osobito osjetljivi na rituksimab, a kronična limfocitna leukemija na alemtuzumab. Dodavanjem rituksimaba kemoterapiji po shemi CHOP u liječenju agresivnih limfoma znatno se produljuje razdoblje bez bolesti i sveukupno preživljenje usporedimo li rezultate primjene samo kemoterapije CHOP kao terapije prvoga reda. Novi lijekovi među kojima su radioaktivno obilježena protutijela u kliničkim ispitivanjima I. i II. faze pokazuju obećavajuće rezultate u različitim kliničkim situacijama.

KLJUČNE RIJEČI: *monoklonska protutijela, limfom, imunoterapija*

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### INTRODUCTION

Monoclonal antibodies represent the new approach for the treatment of lymphoma. This review summarizes their impact on the management of patients with lymphoma, beginning with an overview of the scientific background to their synthesis, mechanism of action and choice of target antigen. The agents currently in routine clinical

use and those in advanced clinical trials are then briefly reviewed including rituximab, ibritumomab, tositumomab and alemtuzumab.

### RITUXIMAB, IBRITUMOMAB, TOSITUMOMAB

Rituximab is a human-mouse chimeric monoclonal antibody targeted at CD20 – surface

antigen of healthy and malignant B lymphocytes. The antibody is produced by genetic engineering combining of murine variable regions of heavy and light chains with human constant regions of heavy and kappa light chains IgG1 targeted at CD20 antigen. The mechanism of action includes several pathways. The murine portion of the antibody, the Fab variable region, binds CD20 on the surface of the lymphoma cell with a high degree of specificity. The human portion of the antibody, the Fc region of the IgG1 immunoglobulin isotype, is then responsible for invoking the patients' immune pathways. First, antibody-dependent cell-mediated cytotoxicity (ADCC) occurs through binding of Fc receptors on natural killer cells, monocytes and macrophages to the opsonized tumor cells. Second, complement-mediated cytotoxicity occurs through binding and activation of C1q on the Fc region of rituximab, leading to formation of the membrane attack complex on the lymphoma cells, as well as further opsonization of the lymphoma cell, augmenting the ADCC response. Third, rituximab probably also blocks proliferation and promotes apoptosis of lymphoma cells through intracellular second messenger pathways initiated by its binding to surface CD20.

A phase I clinical trial of rituximab began in 1993, and preliminary data suggested activity against B-cell lymphoma (1, 2). A multicentric study tested rituximab in 166 patients with follicular or low-grade non-Hodgkin's lymphoma that had progressed after a median of two chemotherapy regimens. Half the patients had a response, the response lasted approximately one year, and the antibody was extremely well tolerated (3). On the basis of these data, on November 26, 1997, rituximab became the first monoclonal antibody to be approved by the US Food and Drug Administration for the treatment of human cancer, thereby shifting the course of lymphoma therapy in a new direction.

Since *in vitro* experiments suggested that rituximab sensitizes lymphoma cells to the cytotoxic effects of the chemotherapeutic agents (4), the antibody was rapidly incorporated into numerous chemotherapy regimens, with encouraging results. The response rates within CHOP (cyclophosphamide, doxorubicine, vincristine, prednison) plus rituximab in patients with indo-

lent or aggressive non-Hodgkin's lymphoma were higher than would be expected with chemotherapy or antibody alone (5,6). These data were confirmed by a randomized trial of Coiffier et al. (7), where patients aged 60 to 80 with diffuse large B-cell lymphoma were randomly assigned to receive CHOP or CHOP plus rituximab in initial therapy. The combined therapy resulted in a higher rate of complete remission (76%, as compared to 63% with CHOP alone); in addition, for the first time in the initial treatment of diffuse large-B-cell lymphoma, a statistically significant prolongation of survival was observed. The rate of survival was 70% with CHOP plus rituximab and 57% with CHOP at a median follow up of two years. Extending the trial follow up to 5 years the following results were achieved: median disease-free survival was not reached for R-CHOP (rituximab- CHOP) patients compared to 2.45 years for CHOP patients. Median overall survival was not reached for R-CHOP patients compared to 3.1 years for CHOP patients. The 5-year overall survival was 58% in R-CHOP arm compared to 45% in CHOP arm. Stratified analysis according to aIPI showed significant superiority of R-CHOP over CHOP in terms of overall survival (OS) in low risk patients (5 year OS in low risk patients R-CHOP- 80%, CHOP 62%). However, the difference in high-risk patients was only of borderline significance (5 year OS in high risk patients R-CHOP- 48%, CHOP 39%) (8).

In the RICOVER-60 trial (9) CHOP was compared to R-CHOP regimen in patients 61 to 80 years of age with diffuse large B-cell lymphoma (DLBCL) of all stages; involved field radiation therapy could be added at the physician's discretion. The trial was 2x2 design, with patients randomized by regimen as well as cycle number (6 vs 8). There was no significant difference when the entire population was analyzed by 6 vs 8 cycles. However, in the analysis by treatment regimen, R-CHOP vs CHOP, patients randomized to receive rituximab demonstrated a superior complete response, 81% versus 73%, and time to treatment failure at 26 months of 70% vs 57%. In this interim analysis, there was no demonstrated survival advantage of R-CHOP vs CHOP. There was adequate power to perform a 4-arm analysis, allowing a comparison of 6-8 cycles of CHOP and R-CHOP. A small advantage was observed with

CHOP in time to treatment failure for 8 cycles (58 vs 53 months), but there was no advantage for 8 vs 6 cycles after rituximab was added.

The ECOG 4494 US Intergroup trial (10) used 6-8 cycles of CHOP or 2 cycles after best response. The majority of these patients received 6 cycles, and there was a trend toward better survival in those patients who received 6 cycles. Taken together with the RICOVER-60 trial, it appears that R-CHOP $\times$ 6 is the adequate therapy. Patients not in complete response after 6 cycles have a greater tendency to fail and are candidates for second line therapy.

Pfreundschuh and colleagues (9) presented an update of MinT (Mabthera International Trial) in which patients  $\leq$  60 years of age with DLBCL and IPI (International Prognostic Factor Index) scores 0-1 reviewed results with chemotherapy plus rituximab (R-chemotherapy) vs chemotherapy alone. For this analysis, they chose to evaluate results with CHOP and CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone), and performed subset analyses on patients according to 2 adverse risk factors: IPI score and bulky disease (mass  $>$ 5 cm). With a median follow up of 22 months, time to treatment failure (TTF) and overall survival (OS) results were significantly better with R-chemotherapy than with chemotherapy alone, and complete response and TTF results with CHOEP were better than with CHOP, although OS results are not significantly better to date. However, results with R-CHOEP were not better than with R-CHOP: those with IPI 0 and nonbulky disease had 2-year TTF and OS results of 97% and 100%, respectively, compared with 89% and 95% with R-CHOEP. Patients with IPI 1 or bulky disease had worse results than did the favorable group, but results were not affected by treatment with R-CHOP or R-CHOEP. This study established that, for young patients with favorable presentations of DLBCL, R-CHOP is currently the regimen of choice.

While the initial clinical trials and licensing of rituximab in follicular lymphoma were in relapsed patients, there has been increased interest in using it in first line therapy. There was also evidence from trials in relapsed patients that it is more effective when used earlier in a patient's treatment program. Numerous trials compared

the combination of rituximab with standard chemotherapy to chemotherapy alone in initial treatment (CVP (cyclophosphamide, vincristine, prednisone) vs R-CVP, CHOP vs R-CHOP, MCP (mitoxantrone, cyclophosphamide, prednisone) vs R-MCP, CHVP IFN (cyclophosphamide, doxorubicin, temiposide, prednisone plus interferon) vs R-CHVP IFN). Thus, according to the results of FL2000 trial comparing R-CHVP/IFN and CHVP/IFN, after 31 months of follow up survival rates reached 78% for R-CHVP/IFN arm and 63% for CHVP/IFN arm (11). Similar results with favorable outcome for patients with follicular lymphoma treated with rituximab were achieved in our center (12). Concluding the results of the mentioned trials it became clear that rituximab in initial therapy of low-grade lymphomas increases remission rates and disease-free survival, and concomitant application with chemotherapy is more efficient than sequential.

Relapsed follicular lymphoma is the most extensively studied indication for the use of monoclonal antibody therapy. Rituximab in monotherapy has overall response of 50%, complete response in 5-10% of patients, and median response duration of 12 months (2,13). In the following trials rituximab was incorporated in conventional chemotherapy regimens for low-grade relapsed lymphomas (CHOP; FND (fludarabine, mitoxantrone, dexamethasone); FC (fludarabine, cyclophosphamide) (14-16). The results were similar – response to therapy rates were over 80%, with a high proportion of complete responses and median disease-free survival of 13 months. The addition of rituximab to chemotherapy did not increase toxicity.

The other approach for augmenting the activity of single agent monoclonal CD20 antibodies in lymphoma is the conjugation of the antibody to a radioisotope, and two of these radio-labelled antibodies have been well studied in relapsed or refractory low-grade lymphoma: iodine-131 tositumomab (I-131) and yttrium-90 (Y-90) ibritumomab tiuxetan. Their additional effect over rituximab is delivering a dose of radiation to the cell the antibody binds. Lymphomas are generally radiosensitive, but often widespread at diagnosis, limiting the value of external beam radiotherapy in their management. These

antibodies thus represent a means of targeting a radiation dose. The results of clinical studies have shown that by applying these antibodies in relapse/refractory low-grade non-Hodgkin's lymphomas higher response rates are achieved than by using rituximab (57%-80%), but the median time to progression does not appear to be any longer (6-11 months) (17,18). Toxicity is slightly greater, with reversible myelosuppression a common adverse event, and ongoing concerns about the long-term safety of radiation exposure.

A final question of management of relapsed low-grade lymphoma is whether treatment with rituximab, or cross-over to radiolabelled antibody therapy, after a first dose of antibody therapy is feasible. One study treated patients who have previously responded to rituximab with a second course of rituximab on relapse. There was an overall response rate of 40% with a median duration of response of 16 months, at least as good as and possibly better than the duration of response with the first course of rituximab (19). In groups of patients with indolent lymphoma considered refractory to rituximab therapy, both I-131 tositumomab and Y-90 ibritumomab tiuxetan induced overall response rates of 70-74% with median duration of response 15 months and more than 7.7 months respectively (20,21).

## ALEMTUZUMAB

Alemtuzumab is another monoclonal antibody used in lymphoma treatment. It is a humanized antibody directed against the CD52 antigen, which is abundantly expressed on all normal and most malignant T lymphocytes, making alemtuzumab a good candidate for novel therapy in T-cell malignancies. It proved efficient in patients with relapsed or refractory T prolymphocytic leukaemia (22). Response to therapy rates were 76% (60% complete remissions, 16% partial). The median disease-free interval of patients who achieved complete response was 10 months (up to 45 months) which was significantly prolonged. Alemtuzumab proved effective also in refractory cutaneous T cell lymphomas – Sezary syndrome, with response to therapy rate of 50% (23). Also in individual cases of adult T-cell leukaemia/lymphoma complete response over 12

months was achieved using alemtuzumab (24,25). Pretreated and refractory T-peripherally lymphomas respond to alemtuzumab, with response rate of 35%, and response duration from 2 to 12 months (26). Apart from first-dose reactions, which are common, treatment is well tolerated, the main complication being infection and viral reactivation associated with prolonged lymphopaenia.

## CONCLUSION

Monoclonal antibodies have transformed the treatment of non-Hodgkin's lymphoma. Rituximab as the first monoclonal antibody approved in cancer therapy has shown high efficacy in both first line and relapsed indolent lymphoma treatment, as well as in induction therapy of aggressive lymphomas. Alemtuzumab treatment, on the other hand, may offer new hope to patients who otherwise have a poor prognosis including the patients with clinically aggressive, mature, post-thymic T-cell malignancies.

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*Author's address: Ivo Radman, MD, Zagreb University Hospital Center, Division of Hematology, Department of Internal Medicine, Kišpatičeva 12, 10 000 Zagreb, Croatia*