Application of anti-CD20 monoclonal antibodies in the treatment of lymphoproliferative diseases

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SUMMARY

Out of numerous studied monoclonal antibodies, only a few reached the stage of clinical application. The CD20 molecule, non-glycolysed phospholipoprotein (usually termed B1), belonging to the tetraspan (TM4SF) family, 35-37 kD, is characteristic for all mature B lymphocytes, including CLL cells. The CD20 receptors, characteristic for „B" lymphoproliferative diseases, have been demonstrated to be a good target for therapeutic effects to be achieved. Rituximab is a chimeric anti-CD20 IgG1 monoclonal antibody, with the sequences of the human constant region and sequences of the murine variable region. It is specifically bound to the B-lymphocyte CD20 antigen. The mechanism of all rituximab antitumor activity has not been established, but ADCC and CDC are believed to be the principal, with possible complementary effects. Therapeutic use of anti-CD20 monoclonal antibodies has demonstrated a significant benefit in the patients with "B" CD20 positive lymphoproliferative diseases. Rituximab is today a golden standard for the comparation with other treatment modalities, increasingly in combination with chemotherapy.

Key words: *Lymphoproliferative Disorders; Antibodies, Monoclonal; Antigens, CD20*

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INTRODUCTION

Tumor cells can express specific antigens, which are different or denser than those on normal cells. These specific antigens can be appropriate targets for immunotherapy, and can also be used for the production of specific monoclonal antibodies (mAbs) capable of destroying tumor cells. Tumor cell destruction occurs via multiple mechanisms, different from those encountered with conventional chemotherapy.

Out of numerous studied monoclonal antibodies, only a few reached the stage of clinical application. The mechanism of action of non-conjugated antibodies is not entirely clear, but what has been discovered is that a significant part of their activity they effectuate through the increase of antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), or through direct cell death. Conjugated antibodies (radio- and chemo-immunoconjugated), popularly termed „magic bullets", are designed in a way that their toxic content precisely targets tumor cells.

The CD20 molecule, non-glycolysed phospholipoprotein (usually termed B1), belonging to the tetraspan (TM4SF) family, 35-37 kD, is characteristic for all mature B lymphocytes, including CLL cells (1). We still do not know all the aspects of function of these molecules. It is supposed that they are involved in the activation or regulation of B cells, and in the function of cell membrane calcium ion channels.

Lymphoproliferative diseases (LPD) are the conditions in which monoclonal antibodies have been first therapeutically applied. The CD20 receptors, characteristic for "B" LPDs, have been demonstrated to be a good target for therapeutic effects to be achieved.

RITUXIMAB IN THE TREATMENT OF LPDS

Rituximab (MabThera, Roche) (Figure 1) is a chimeric anti-CD20 IgG1 monoclonal antibody, with the sequences of the human constant region and sequences of the murine variable region. It is specifically bound to the B-lymphocyte CD20 antigen. In addition to the specific mechanisms of reduction of the malignant B-clone (antibody dependent cellular cytotoxicity – ADCC, complement-dependent cytotoxicity – CDC, induction of apoptosis), rituximab sensitizes tumor cells to cytotoxic agents, therefore acting synergistically with chemotherapy (2). The relative significance of all these mechanisms has not been established, but ADCC and CDC are believed to be the principal mechanisms of antitumor activity, with possible complementary effects (3).

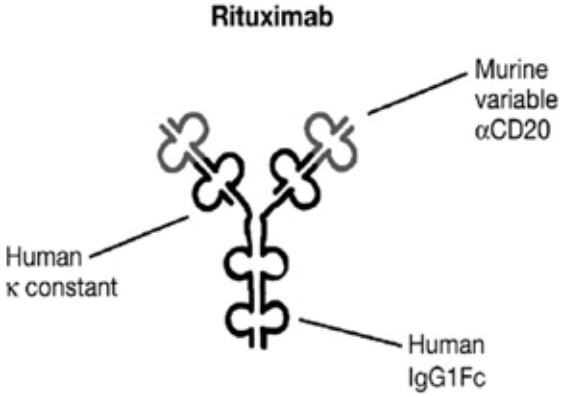

Figure 1. Rituximab structure

RITUXIMAB FOR INDOLENT NHLS

The standard first line NHL therapy involves eight cycles of rituximab, plus chemotherapy. Two large-scale studies have demonstrated that rituximab plus chemotherapy approach prolong RR, TTF interval, and PFS, compared to chemotherapy alone (4,5). The addition of rituximab to chemotherapy improves the outcome of relapse or refractory disease. In patients with indolent NHL responding to therapy or with stable disease after the induction with rituximab plus chemotherapy, maintenance with rituximab prolongs remission and delays relapse. In cases of intolerance of chemotherapy, rituximab monotherapy can be the treatment of choice. Re-treatment with rituximab does not demonstrate any loss of efficacy.

RITUXIMAB FOR AGGRESSIVE NHLS

Aggressive NHLs require, which is the current standard, eight cycles of rituximab plus CHOP chemotherapy. The improvement of overall survival in the GELA LNH-98.5 study was of such a magnitude that statistical significance was achieved after only 12 months of follow-up (6). The benefit was maintained for as long as 4 years, which confirmed the superiority of the combined treatment. These results were later confirmed by the MinT study (7). The results compelled many to try to investigate the significance of rituximab addition to chemotherapy in the second line approach. Numerous studies have demonstrated that rituximab is able to potentiate the response to therapy and, thus, disease outcome as well, especially for the patients suitable for HDT/ASCT. Studies are on the way aiming to define the role of rituximab for aggressive NHL relapses.

RITUXIMAB FOR MANTLE CELL LYMPHOMA (MCL)

Patients with MCL on conventional therapy have poor prognosis. The role of rituximab and chemotherapy combination remains controversial in that regard. However, the combination of rituximab and chemotherapy and/or HDT/ASCT demonstrates a certain progress. In some randomized trials, the combination of CHOP and rituximab (R-CHOP) was significantly better regarding the OR ($p=0.0054$) and CR ($p=0.00024$). However, the impact on TTF was much smaller ($P=0.0131$), while regarding PFS and OS there was no progress (8). However, the data produced by functional imaging (FI) suggest that the quality of early remission is significant, recommending a new strategy of HDT/ASCR therapy (9). In the study *OSHO#39*, the combination of R-MCP (mitoxantrone, chlorambucil, prednisolone) was not superior to MCP chemotherapy alone. The conclusion can be drawn that immunochemotherapy is not a mandatory option for this entity with poor prognosis (10). *The European MCL Network* has stressed that immunochemotherapy resulted in high RRs in two prospective international trials (MCL elderly and MCL younger). Further investigation will determine the role of rituximab in the maintenance therapy (11).

RITUXIMAB FOR CLL

In recent years, none of the clinical trials has demonstrated any survival advantage of various chemotherapy regimens. Nevertheless, some new agents possess the potential to overcome this barrier. First, it has been shown that rituximab 500 mg/m^2 added to chemotherapy improves overall survival compared to chemotherapy alone (serving as a history control) (12). The best results were observed in a group of patients demonstrating molecular remission of the disease (MRD). Then, a phase III study CLL8 was designed, which demonstrated that rituximab 500 mg/m^2 plus chemotherapy significantly improves PFS compared to chemotherapy alone as the first line of treatment (13). PFS was improved in patients with 17p deletion and unmutated IgVH as well, otherwise being the groups with very poor prognosis (14). The studies of alternative combinations such as rituximab plus bendamustine as the first line approach are on the way, and the results of first interim analysis of the CLL 208 study, with chlorambucil added to rituximab, are eagerly awaited for.

NEW ANTI-CD20 ANTIBODIES

A group of new anti-CD20 monoclonal „second generation" antibodies, is in the phase of pre-clinical and clinical investigation. *Atumubab* is a IgG1 antibody with some characteristics of type I antibodies, meaning that when it binds to CD20 it induces its own translocation into a detergent-insoluble layer, which is associated with complement activation and CDC type of elimination of tumor cells. In contrast to rituximab, it has a full human sequence and it binds to the epitope, which is in a more compact way bound to the cell membrane with prolonged action (15). *Ofatumomab* is a subject of numerous clinical trials. One of the segments is a phase I/II study of the patients with recurrent follicular lymphomas (16). Its toxicity is similar to the toxicity of rituximab, and responses have been achieved even in patients on rituximab treatment. The CDC effect has been observed in CLL too in phase I/II studies. In other studies, the patients with disease progression on fludarabine and alemtuzumab have been analyzed. *Veltuzumab* (hA20) is a humanized IgG1 monoclonal antibody targeting the identical epitope as rituximab (17). The results are similar to the ones rituximab achieves, but with lower dosage than rituximab. *GA101* is a type II antibody, generated, similar to many others, in the Chinese hamster ovary (CHO) cells. This antibody, in addition to the ADCC mechanism, has the properties increasing the apoptosis-induced activity (18). *AME-133* is a human IgG1 antibody with high affinity for CD20 and the ability to bind to CD16 via its Fc region, effectuating 5 to 10 times higher affinity than rituximab (19). Preclinical investigations have demonstrated also a larger effect upon the NK-cell activation. Special benefit from this will perhaps have the patients with a suboptimal status of immune effector cells. The common elements of this new group of monoclonal antibodies (including PRO 131921 as well) are that these are all human/humanized anti-CD20 monoclonal antibodies designed to bind to new epitopes, that they increase ADCC, CDC, binding to CD20, or apoptosis activation.

RADIOIMMUNOTHERAPY

Radioimmunotherapy involves the administration of antibodies labeled with a radioisotope, enabling the destruction of cells presenting the target antigen, but also the adjacent cells, which do not express enough antigens to bind the antibody. The concept was introduced by De Nardo et al. HLA antigens on the cells of aggressive non-Hodgkin lymphomas were the first target, utilizing radio-labeled antibodies against Lym-1 and achieving sporadic complete remissions (20). Nowadays, two radioconjugates targeting CD20 are available, Yttrium-90 (^{90}Y)-labeled IBRUTUMOMAB TIUXETAN (Zevalin, Cell Therapeutics) and Iodine-131 (^{131}J)-labeled TOZITUMOMAB (Bexxar, GlaxoSmithKline). They are approved for the patients with relapsed/recurrent follicular or low-evolutionary lymphomas (21).

CONCLUSION

Therapeutic use of anti-CD20 monoclonal antibodies has demonstrated a significant benefit in the patients with lymphoproliferative diseases. Rituximab is today a golden standard for the comparison with other treatment modalities, increasingly in combination with chemotherapy. New anti-CD20 agents provide both potentially higher activity characteristic for rituximab and different targets, creating the possibility to be combined with rituximab. New prospective clinical studies, especially with patients refractory to rituximab, will provide appropriate answers to these questions. Radiolabeled antibodies can prove to be useful in patients resistant to rituximab.

Conflict of interest

We declare no conflicts of interest.

REFERENCES

1 Matutes E, Polliack A. Morphological and immunophenotypic features of chronic lymphocytic leukemia. *Rev Clin Exp Hematol.* 2000;4:22-47.

2 Alas S, Emmanouilides C, Bonavida B. Inhibition of interleukin 10 by rituximab results in downregulation of bcl-2 and sensitization of B-cell non-Hodgkin´s lymphoma to apoptosis. *Clin Cancer Res*. 2001;7:709-23.

3 Zhou X, Qin X. The role of complement in the mechanism of action of rituximab for B-cell lymphoma: implications for therapy. *Oncologist*. 2008;13:954-66.

4 Marcus R, Imrie K, Belch A. M39021-an international multicentre, randomized, open-label phase III trial comparing rituximab added to CVP chemotherapy to chemotherapy alone in untreated stage III/IV follicular non-Hodgkin's lymphoma: final analysis. *Blood*. 2003;102:28a.

5 Hiddemann W, Dreyling MH, Forstpointer R. Combined immunochemotherapy (R-CHOP) significantly improves time to treatment failure in first-line therapy of follicular lymphoma: results of a prospective randomized trial of the German LowGrade Lymphoma Study Group (GLSG). *Blood*. 2003;102:104a.

6 Coffier B, Herbrecht R, Morel P. GELLA study comparing CHOP and R-CHOP in elderly patients with DLCL: 3-year median follow up with an analysis according to co-morbidity factors. *Hematol J*. 2003;Suppl 2:111.

7 Pfreundschuh M, Trümper L, Österborg A, Pettengell R, Trneny M, Shepherd L, et al. Randomized intergroup trial of first line treatment for patients <60 years with diffuse large B-cell non Hodgkin's lymphoma (DLBCL) with a CHOP-like regimen with or without the anti-CD20 antibody rituximab - early stopping after first interim analysis. *J Clin Oncol*. (Abstr. 6500). 2004;22.

8 Lenz G, Dreyling M, Hoster E. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome on patients with previously untreated mantle cell lymphoma: results of prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). *J Clin Oncol*. 2005;23:1984-992.

9 Zelenetz AD, Persky D, Rice RD, Maragulia J, Weaver SA, Portlock CS, Moskowitz CH. Results of sequential chemotherapy followed by high dose therapy and autologous stem cell rescue for mantle cell lymphoma: role of rituximab and functional imaging (Abstr. 013). *Ann Oncol*. 2008;19 Suppl 4.

10 Herold M, Haas A, Doerken B, Neser S, Al Ali KH, Neubauer A, Doelken G. Immunochemotherapy (R-MCP) in advanced mantle cell lymphoma is not superior to chemotherapy (MCP) alone-50 months up date of the OSHO phase III study (OSHO#39) (Abstr. 012). *Ann Oncol*. 2008;19 Suppl 4.

11 Dreyling M, Hoster E, Hermine O, Kluin-Nelemans H, Walevski J, Trneny M, et al. European mantle cell lymphoma network: an update on current first line trials. (Abstr. 300) *Ann Oncol*. 2008;19 Suppl 4.

12 Tam CS, O´Brien S, Wierda W. Long term results of the fludarabine, cyclophosphamide & rituximab regimen as initial therapy of chronic lymphocytic leukemia. *Blood*. 2008;112:975-80.

13 Roche. Data on file. 2008

14 Dohner H, Stilgenbauer S, Benner A. Genomic aberrations and survival in chronic lymphocytic leukemia. *New Engl J Med*. 2000;343:1910-6.

15 Teeling JL, French RR, Ceagg MS. Characterization of new human CD20 monoclonal antibodies with potent cytolytic activity against non-Hodgkin lymphomas. *Blood*. 2004;104:1793-800.

16 Hagenbeek A, Plesner T, Johnson P. Hu Max-CD20, a novel fully human anti-CD20 monoclonal antibody: results of a phase I/II trial in relapsed or refractory follicular non-Hodgkin's lymphoma. *ASH Annual Meeting Abstracts*. 2005;106:4760.

17 Stein R, Qu Z, Chen S. Characterization of a new humanized anti-CD20 monoclonal antibody, IMMU-106, and its use in combination with the humanized anti-CD22 antibody, epratuzumab, for the therapy of non-Hodgkin's lymphoma. *Clin Cancer Res*. 2004;10:2868-78.

18 Umana P, Moessner E, Bruenker P. Novel 3rd generation humanized type II CD20 antibody with glycoengineered Fc and modified elbow hinge for enhanced ADCC and superior apoptosis induction. *ASH Annual Meeting Abstracts.* 2006;108:229.

19 Weiner GJ, Bowles JA, Link BK, Campbell, Wooldridge JE, Breitmeyer JB. Anti-CD20 monoclonal antibody (mAb) with enhanced affinity for CD16 activates NK cells at lower concentrations and more effectively than rituximab (R). *ASH Annual Meeting Abstracts*. 2005;106:348.

20 De Nordo GL, De Nordo SJ, Goldstein DS. Maximum-tolerated dose, toxicity, and efficacy of ^{131}J-Lym-1 antibody for fractionated radioimmunotherapy of non-Hodgkin´s lymphoma. *J Clin Oncol*. 1998;16:3246-56.

21 Cheson BD, Leonard JP. Monoclonal Antibody Therapy for B-Cell Non-Hodgkin´s Lymphoma. *New Engl J Med*. 2008;359:613-26.