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

Ivica Pejčić, Svetislav Vrbić

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

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 NHL
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 mono-therapy 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 LNHL-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 immunochemochemotherapy is not a mandatory option for this entity with poor prognosis (10). The European MCL Network has stressed that immunochemochemotherapy resulted in high RR 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/m² 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/m² 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). Ofatumumab is a subject of numerous clinical trials. One of the segments of is a phase VII 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 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 (90Y)-labeled IBUTUMOMAB TIUXETAN (Zevalin, Cell Therapeutics) and Iodine-131 (131I)-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.

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