Journal of BUON 7: 309-310, 2002
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EDITORIAL

Rituximab (MabThera): A magic bullet in the therapy of non-Hodgkin's lymphomas

In this issue of J BUON, J. Marinković et al. present their experience with rituximab administered to patients with low-grade non-Hodgkin's lymphoma (NHL). The authors studied the alterations of serum immunoglobulins and the T/B lymphocytes ratio following treatment with rituximab and chlorambucil.

Monoclonal antibodies (Mabs) offer the potential for highly specific, targeted therapy of tumors. Often described as "magic bullets", a term first used by Paul Ehrlich 100 years ago, Mabs were perceived as the wonder drugs and great hope was invested in these new biotherapeutic agents as a way of revolutionising the treatment of malignant diseases [1].

NHL encompass a heterogenous group of malignancies which predominantly originate from B-lymphocytes. In contrast to the declining rates of many other cancers, the incidence of NHL is increasing rapidly and NHL is the fifth most common malignancy in the USA and Europe. Recent advances in immunochemical and molecular genetic techniques have allowed the development of the more precise REAL classification and a modified version by WHO. These classification systems divide NHL into three clinical groups according to prognosis: indolent, intermediate and aggressive [2]. Follicular lymphoma (FL) is the most common form of indolent (low grade) NHL. Unfortunately, primary chemotherapy does not appear to improve overall survival of FL, relapse is almost universal and more than 50% of patients die within 5 years of first relapse; more aggressive chemotherapy regimens are associated with significant toxicity and there is little evidence of any real impact on survival. Diffuse large B-cell lymphoma (DLCL) is the most common form of intermediate and aggressive NHL and the patients generally respond well to anthracycline-containing induction chemotherapy: CHOP is curative in up to 50% of the cases. It is thus evident that improved effective and well-tolerated treatment options are required to increase response and survival in both indolent and aggressive NHL.

The use of murine Mabs in cancer therapy is hampered by anti-mouse immune responses and lack of interaction with human effector mechanisms. However, the development of genetic engineering has allowed the creation of antibodies incorporating selected human and murine characteristics. So, efforts to improve the efficacy of murine Mabs have resulted to the creation of chimeric human/mouse antibodies which can bind effectively to the target antigen and also interact with human effector mechanisms to kill the target cells [3].

Rituximab (MabThera: F. Hoffmann-La Roche Ltd) is a chimeric human/mouse antibody that recognizes the CD20 antigen expressed by B-cells, which is present in more than 85% of cases of NHL. The CD20 antigen has characteristics that make it an ideal target in B-lymphomas. It is not expressed in stem cells, B-cell precursors, or plasma cells, but is expressed in normal B-cells and is generally present in all lymphoma cells. It is stable in the cell membrane, has no known variant, is not shed into the extracellular tissue matrix, nor is it subject to modulation after binding by antibody. MabThera as a chimeric Mab has murine variable region sequences and human constant region sequences that binds specifically to the CD20 antigen, expressed in cells of the B-cell lineage. MabThera, with its unique mechanism of action, offers a flexible treatment and kills B-cells by a variety of mechanisms, different from those of conventional chemotherapeutic agents. It has a direct effect on B-cell death by induction of apoptosis and can synergize with chemotherapeutic agents to kill target cells *in vitro*. MabThera can be used both as a single agent or in combination with a variety of other therapies.

MabThera was the first Mab approved for the treatment of patients with relapsed or refractory low-grade or follicular lymphoma. MabThera monotherapy induces a durable response rate (RR) in 50% of these patients, and as single agent has achieved a RR of 43% in bulky disease. In patients with FL and low tumor burden, a RR of 73% was obtained with monotherapy as first-line treatment (clearance of bcl-2-positive cells from the blood was achieved in 57% of patients). This Mab in combination with CHOP chemotherapy has achieved RR approaching 100%, with median duration of response more than 4 years. Patients can be retreated with MabThera without loss of efficacy, and without compromising subsequent treatment options [4].

MabThera plus CHOP in DLCL (GELA study) has yielded the first survival benefit in aggressive lymphomas compared with CHOP alone in a randomized

study in more than 20 years! This new immunochemotherapy for aggressive lymphomas confirmed, for the first time, superiority in event-free survival, overall survival and response rate over CHOP, and without serious adverse events which did not differ significantly from CHOP alone. The GELA study was expected to confirm that MabThera plus CHOP is the new standard therapy for this type of lymphoma [5].

MabThera can be used in patients receiving autologous stem cell transplantation either to prevent lymphoma cell contamination of the stem cell harvest by *in vivo* purging, or to eliminate minimal residual disease in posttransplant maintenance therapy (MabThera eliminates bcl-2 positive cells from > 90 % of stem cell harvest) [6].

This Mab has shown efficacy in a variety of CD20+ disorders other than lymphomas, including chronic lymphocytic leukemia, hairy-cell leukemia, HIV-associated lymphoma and post-transplant lymphoproliferative disorders. In addition, non-malignant hematologic disorders including immune thrombocytopenia, cold agglutinin hemolytic anemia and autoimmune hemolytic anemia are also potential targets for MabThera treatment.

MabThera is well-tolerated and safe treatment option, and is not associated with the severe hematologic or other adverse events seen with conventional chemotherapy. Hematologic abnormalities occur in a minority of patients and are ususally mild and reversible.

Peripheral B-lymphocyte count is reduced by approximetely 90% within 3 days of a single infusion of MabThera and its half-life increases in the circulation following multiple infusions. Although MabThera treatment results in rapid and profound depletion of B-cells, the incidence of systemic infections in randomized studies was not increased. A pivotal study has shown that serum immunoglobulin levels are maintained in the majority of patients. Time to recovery of B-cells was variable, with partial recovery most commonly occurring after 4-8 weeks and recovery to baseline levels requiring a minimum of approximately 3 months. In 253 patients treated with MabThera, reductions in total serum immunoglobulins occured in only 14% of patients, and these reductions were not considered clinically significant [7].

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