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Up-to-date in the hematological malignancies treatment

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BACKGROUND

The hematological diseases are a constant field of interest in many research studies regarding new therapeutic solutions, characterized by efficacy, safety and tolerability, with few adverse events, easy way of administration and even a potential curability in some cases, thus improving the patient's prognostic and life quality.

We intend to present some of the therapeutic news in hematological malignancy field, in order to better understand the on-going process of searching for the most complete line of treatment. ❑

The monoclonal antibodies therapy is part of the modern scheme of treatment; the target is a certain clone of cells, characterized by the same surface antigen, which binds the specific antibody. The monoclonal antibody RIUXIMAB- MabThera is a chimeric human/mouse antibody Ig G1 isotype against B cell CD 20 positive, obtained by genetical engineering. This monoclonal antibody against CD 20 has a reduced immunogenicity, an increased capacity of binding the complement and a long half time. The CD 20 antigen may be considered an ideal target, due to the following characteristics: it is found on the surface of all the malign B, pre B, and mature B cells, and immunoblast, but it is not seen on stem cell, B cell progenitors, early pre B cell and not even on the normal plasmocyt; CD 20 antigen does not suffer from mutations or variations, it is neither internalized in the cell, nor secreted from the cell; a segment of the antibody remains outside the cell; also, it is not modulated after binding the antibody (2,3,4).

RITUXIMAB can be successfully used in the chemotherapeutic scheme owing to the easy way of administration and the lack of additional toxicity, with no require of dose limitation (2).

RITUXIMAB-MabThera may be used in the following diseases: follicular lymphoma, marginal zone B-cell lymphoma, mantle cell lymphoma – among indolent lymphomas, diffuse large B-cell lymphoma – among aggressive lymphomas, B cell chronic lymphocytic lymphoma, all of these sharing the presence of CD 20; furthermore, the indications are extended to other autoimmune diseases, such as autoimmune hemolytic anemia and others (4).

Follicular lymphomas have a long natural evolution, with an 8-10 years mean of survival period from the onset; this particular way of evolution includes them in the indolent lymphomas category, but for the moment they are incurable using chemotherapy, they go along with important co-morbidities and have an implacable evolution to death. Due to these findings, RITUXIMAB was used in treating this type of lymphomas in combination with standard chemotherapy, like CVP, as first line therapy, and RITUXIMAB alone as maintenance treatment when remission followed. The results

achieved were a good overall response with minimal additional toxicity, with a longer progression- free survival and event- free survival, with decrease of relapse risk and a prolonged long- term survival. The adverse events that occurred were fever, chilly, headache, abdominal pain, hypotension, nausea, myalgia, bronchospasm, and rash (2,3).

The new therapeutic strategies in these types of hematological malignancies are: association between monoclonal antibodies and various protocols of chemotherapy, combinations of different types of monoclonal antibodies with numerous targets, combinations of monoclonal antibodies with anti-idiotype vaccines, or therapeutic agents that inhibit angiogenesis-Thalidomide, or kinase inhibitors, or anti-sense oligonucleotides (3,4).

ALEMTUZUMAB (MabCampath), using passive immunotherapy, is a humanized monoclonal antibody, that specifically binds CD 52 antigen, which can be found on normal and malignant B – and T – cells, but not on the progenitors hematopoietic cells. Over the past years, many clinical studies have shown that this monoclonal antibody has a significant activity in chronic lymphocytic leukemia, in T cell chronic lymphoprolypherative diseases, as well as in the prevention and therapy of GVHD (graft versus host disease) from allogenic stem cell transplant. The indications of treatment with ALEMTUZUMAB tend to extend also to autoimmune diseases (7). The most significant adverse event of the ALEMTUZUMAB therapy is the predisposition to infections, related to severe lymphopenia.

Traditionally speaking, chronic lymphocytic leukemia is well recognized as an incurable disease, the therapy only having a palliative role. Nowadays, this concept is a struggle against several studies that take the treatment of chronic lymphocytic leukemia to new levels and attitudes: chemotherapies combined with antiCD 52 monoclonal antibody, as well as consolidation therapy, in order to achieve a long survival in this hematological malignancy. ALEMTUZUMAB, a humanized anti CD 52 monoclonal antibody, is administrated subcutaneous in the first line therapy of symptomatic B cell chronic lymphocytic leukemia; but the indication for this type of therapy is also extended to the refractory or relapsed disease, previously treated with fludarabine or alkilating agents. Half of the patients with chronic lymphocytic leukemia have a p53 mutation (3); in such cases, the prognostic is unfavorable, with unsatisfactory response to conventional therapy, but successfully treated with ALEMTUZUMAB. The maintenance therapy with a monthly injection of ALEMTUZUMAB in chronic leukemia and non Hodgkin lymphoma have been proved efficient, in terms of prolonging the therapeutic response (7,8). The hematological adverse events of ALEMTUZUMAB therapy are reversible; the main one is neutropenia, which is curable and not leading to the interruption of the treatment. The increased rate of the overall response assessed and the rare complications noticed in patients previously untreated, have proved beneficial by using ALEMTUZUMAB in first line therapy (4,7).

Recent data concerning the treatment of the patient with chronic lymphocytic leukemia is related to the use of ALEMTUZUMAB as a treatment for minimal residual disease in patients responding to fludarabine. Therefore, remission without minimal residual disease leads to improvement in the overall rate response and extends the progression- free survival period.

These days, there are other indications for ALEMTUZUMAB therapy, as follows: non-myeloalative conditioning regimen for allogenic hematopoietic stem cell transplant in refractory non-Hodgkin lymphomas, as well as T cell limphoprolypherative disease- T-prolymphocytic leukemia, cutaneous T cell lymphoma, large granular cell leukemia, adult T cell leukemia/ HTLV I positive lymphoma (3,4,7,8).

New treatments in hematological malignancies also involve radioimmunotherapy. This method is a combination of both immunoglobuline and radioisotope. In this precise enumeration we also find the therapy with imunotoxine- monoclonal antibody chelated with citotoxic antitumoral antibiotic (3).

The cytokines, such as interferons, have been used in hematology for many years, but interleukines (as interleukin 2) are still under study (3,4).

The specific inhibitors of signal transduction, such as the specific inhibitor of tyrosine kinase related to BCR-ABL gene, IMATINIB MESYLAT-STI 571, have known a spectacular evolution, just in a few years. It was first given to a patient in 1998; in 2001 it was included in the treatment of chronic myeloid leukemia refractory to interferon; now, it is indicated in all the

phases of this disease- chronic, accelerated and blastic phase- and the indications extend to myelodisplastic syndrome, myelofibrosis, primar hypereosinophilic syndrome (3,4,6).

The genetic alteration in chronic myeloid leukemia – reciprocally translocation of proto-oncogene ABL on chromosome 9 near the BCR gene on chromosome 22- leads to a chimeric protein BCR-ABL which has a tyrosine kinase activity and becomes active by releasing controls on stem cell proliferation or by blocking programmed cell death in such ways that lead to accumulation of cells. IMATINIB attaches to ATP binding site of BCR-ABL oncogene and interferes with the phosphate transfer from ATP to secondary messenger. Thus, this agent shows activity against the tyrosine kinase of BCR-ABL, c-kitt and platelet derived growth factor receptor oncogenes (6,10).

Other novel therapies are THALIDOMIDE, arsenical agents – ARSENIC TRIOXIDE – that have pro-apoptosis, immunomodulatory and anti-angiogenesis roles and are indicated in multiple myeloma, Waldenstrom macroglobulinemia, myelofibrosis, myelodisplazia (1).

The multiple myeloma pathogeny offers to both of the therapeutic objects molecular targets – that is genetic anomalies of myeloma cells and receptors- signal targets, that is the interaction of multiple myeloma cells with its bone marrow microenvironment (1,3,4,5,9). The BORTEZOMIB-Velcade mechanism of action is to inhibit the proteasome function by reversible binding to chemotripsine-like protease, with consecutive blockade of proteolytic activity. All these actions lead to apoptosis of myeloma cell, because the tumor cells are more sensitive to proteasome inhibition than normal cells, and the DNA cell is destroyed (9).

BORTEZOMIB is a new therapeutic approach in multiple myeloma, it's target being myeloma cell and its environment, with toxic action on the tumor cells (1,5,9). ❑

Conclusion

There is no doubt that the review of novel therapies in hematological malignancies can not stop here; the theme is not yet exhausted, only rises questions and problems that I believe is worth to extend and complete it in the future.

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