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The role of immunoglobulins in supportive treatment for patients with lymphoid neoplasms

Rola immunoglobulin w leczeniu wspomagającym nowotworów układu chłonnego

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S u m m a r y

Lymphomas are derived from lymphoid cells at different levels of maturation. The cells of this system are the basic elements of immune responses, both cellular and humoral immune response. All these neoplasms are accompanied by immune disorders, often with hypogammaglobulinemia. Immunoglobulin affect all immune effector cells. Infection complications remain a major problem in this group of patients. Regular substitution in primary as well as secondary immunodeficiency is designed to reduce the incidence of infections, particularly bacterial and mitigate their clinical course. Immunomodulatory properties of immunoglobulins are used to treat the autoimmune process of Lymphoid Malignancies. Currently, new drugs allow the prolongation of survival in many cases of patients with lymphoma. Special attention should be paid to supportive care with immunoglobulin as substitution therapy, as well as immunomodulatory effects.

Key words: intravenous immunoglobulin, secondary immunodeficiencies, lymphoma

S t r e s z c z e n i e

Nowotwory układu chłonnego wywodzą się z komórek limfoidalnych na różnym szczeblu ich dojrzewania. Komórki tego układu są podstawowym elementem odpowiedzi immunologicznej, zarówno komórkowej, jak i humoralnej. Wszystkim tym nowotworom towarzyszą zaburzenia odporności, często z hypogammaglobulinemią. Immunoglobuliny wpływają na wszystkie komórki efektorowe układu odpornościowego. Niedobór immunoglobulin upośledza przede wszystkim humoralną odpowiedź immunologiczną, ale również nie pozostaje bez wpływu na odpowiedź komórkową. To sprawia, że powikłania infekcyjne nadal stanowią duży problem w grupie chorych leczonych z powodu chłoniaków. Regularna substytucja immunoglobulin w pierwotnych, jak i wtórnych niedoborach odporności ma na celu zmniejszenie częstości występowania zakażeń, zwłaszcza bakteryjnych, jak i złagodzenie ich przebiegu klinicznego. Właściwości immunomodulacyjne immunoglobulin wykorzystywane są również w leczeniu procesów autoimmunologicznych nowotworów układu chłonnego. Nowe leki pozwalają na wydłużenie czasu przeżycia, a w wielu wypadkach na wyleczenie chorych z chłoniaków.Dlatego szczególną uwagę należy poświęcić leczeniu wspomagającemu, na które składa się nie tylko substytucyjne podawanie immunoglobulin ale również ich działanie immunomodulujące.

Słowa kluczowe: immunoglobuliny dożylne, wtórne niedobory odporności, chłoniaki

INTRODUCTION

Cancers of the lymphatic system are derived from lymphoid cells at different levels of maturation. The cells of this system are the basic elements of immune responses, both cellular and humoral immune response. The product of a properly functioning immune system are considered to be the most important molecules of the humoral immune system, whose main feature is the ability to connect to a specific antigen. Also called immunoglobulin, antibodies are secreted by plasma cells, or activated B cells in the course of humoral immune responses (1).

An immunoglobulin molecule is composed of four polypeptide chains:

two light and two heavy disulfide bonded. Depending on differences in the construction of heavy chains: α, β, ε, γ, μ, immunoglobulins can be divided accordingly into five classes: IgA, IgD, IgE, IgG, IgM. Light chains can occur in two variants: type κ and λ. Interaction of immunoglobulins with other elements of the immune

system is via the Fc domain or the F(ab')2, so that immunoglobulins affect the entire immune response system. All of the immune effector cells have receptors on their surface for the Fc region of immunoglobulin. It is the interaction of the Fc fragment to specific receptors which are mainly responsible for the impact on the functioning of immunoglobulin T and B lymphocytes, monocytes, macrophages or dendritic cells (1, 2). Antigen binding on the surface of certain cells, such as those infected with viruses or cancer, enables immunoglobulins to induce their destruction (i.e. the cells). This is done by various mechanisms, such as complement activation, induction immunophagocytosis, induction of cellular cytotoxicity and antibody-dependent.

In addition, antigen-binding immunoglobulin on the surface of microorganisms can block their penetration, e.g. intestinal epithelium, as well as the ability to neutralize the action of toxins through their bonding. They are also responsible for agglutination, clumping of cells or molecules binding to their surface antigens. Some antibodies also play the role of enzymes in relation to the antigen bound by them. IgG and IgM antibodies initiate the classical complement pathway that leads to the lytic target cell death. The auto-aggressive effect of complement activation products on the host organism limits the proper functioning of many regulators (2, 3).

INDICATION FOR INTRAVENOUS IMMUNOGLOBULINS

Human IgG preparations isolated from several donors have their established place in medicine. **It uses the properties of their broad anti-infectives, as well as immunomodulatory, anti-inflammatory and immunosuppressive effects.** They are used among others in primary and secondary immunodeficiency with impaired antibody production and in some autoimmune diseases. Regular substitution in primary immunodeficiency is designed to reduce the incidence of infections, particularly bacterial and mitigate their clinical course. Immunoglobulin is used to affect the cellular immune response, affecting the activity of dendritic cells, monocytes, macrophages, NK cells, T lymphocytes and the regulatory B cells.

Immunoglobulin treatment inhibits differentiation and maturation of dendritic cells and the expression of determinants of co-stimulatory (CD80, CD86), which reduces the ability of these cells to process and present autoantigen. This mechanism explains the inhibitory effect on autoimmune and inflammatory processes (4, 5).

SECONDARY IMMUNODEFICIENCY IN THE CLINICAL COURSE OF LYMPHOID MALIGNANCIES

Lymphoid Malignancies causing profound secondary immunodeficiency that results from the dysfunction of lymphocytes. These disorders can affect all subpopulations of lymphocytes or a selected cell line. Frequent problems in patients with a diagnosis of lymphoma are recurrent infections which are often severe, with a life-threatening course. Less frequent problems are observed in the autoimmune process, which will further worsen the prognosis of the patient, and is expressed in profound thrombocytopenia, neutropenia or hemolytic anemia, often limiting the treatment options.

Immunoglobulins are widely used as supportive care in many haematological diseases with secondary immunodeficiencies, as substitution of the missing antibodies.

This especially applies to chronic lymphocytic leukemia (CLL), multiple myeloma (MM) and other non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL), lymphoblastic leukemia, and patients in the period after hematopoietic cell transplantation (6).

Antiviral activity of immunoglobulin is used in the prevention and treatment of CMV infection, especially in patients after bone marrow transplantation for the treatment of pure red cell aplasia caused by parvovirus B19, EBV, or hepatotropic viruses, as well as a hemophagocytosis syndrome of viral etiology (6-10).

Immunomodulatory properties of immunoglobulins are used to treat the autoimmune process of Lymphoid Malignancies which usually causes immune thrombocytopenia in the course of CLL, NHL, HL, autoimmune hemolytic anemia in patients refractory to glucocorticoids or no improvement after splenectomy, autoimmune neutropenia, dependent transfusion haemorrhagic diathesis and coagulation disorders caused by the presence of inhibitors of coagulation factors (11-15).

Immunoglobulins in high doses, including 0.5-2 g/kg mc within 1-2 days are used in the treatment of immune thrombocytopenia and raises the platelet count above 50 G/L in about 80% of patients, allowing for a delay in the inclusion of steroids, which may hinder the correct diagnosis in patients during diagnosis (11, 12, 16, 17). They also allow you to avoid the transfusion of platelet concentrates and of all complications that are involved.

Depending on the damage to the cell line and the level at which there was a pathology we observe various clinical symptoms.

Patients with antibody deficiencies are particularly susceptible to encapsulated bacteria, such as *Haemophilus influenzae*, *Staphylococcus aureus* and *Streptococcus pneumoniae* which cause pyogenic infections as recurrent infections of the sinuses and lungs. Elimination from the body of the bacteria living extracellularly depends on the immune phagocytosis for which, in addition to granulocytes and macrophages, immunoglobulin is needed (1).

The characteristic clinical course is the occurrence of childhood infections in adults, such as acute or chronic otitis media or diarrhea caused by *Giardia lamblia* carrier state. Often this leads to repeated infections by the same herpes viruses especially VZV and takes the form

of chicken pox or shingles, in spite of correct responses to viral infections, which take place in these patients as in healthy subjects. An example of secondary immunodeficiency with a predominance of humoral immunodeficiency is Multiple Myeloma. More than one fourth of patients have recurrent bacterial infections, most often taking the clinical form of pneumonia caused by *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Klebsiella pneumoniae* and urinary tract infections caused by *Escherichia coli* and other Gram negative bacteria, due to large amounts of monoclonal protein in urine. Impaired humoral immunity mainly due to reduced secretion of normal polyclonal immunoglobulins and their increased degradation (18, 19). Secondary complex immunodeficiency characterized by the appearance of recurrent or prolonged infections, bacterial, fungal, viral and parasitic. We face these kinds of problems in chronic lymphocytic leukemia B cell. Humoral immunity disorders are caused by hypogammaglobulinemia, which deepens with the development of disease. Impaired cellular immunity is associated with impaired function of T cells, and observed in this case, autoimmune disorders, can often lead to cytopenias (20-22). Profound disturbances of combined immunodeficiency is also observed in patients with acute lymphoblastic leukemia during treatment and up to a year after its completion. Published results of prospective studies, especially in children, show a deep depression of the immune system especially humoral response with profound hypogammaglobulinemia during treatment, slowly recovering function after chemotherapy and radiation therapy, indicating a high risk of infectious complications with the recommendation of immunoglobulins in their prevention. The authors pointed to the critical period at the end of the therapy, where the humoral deficiency was accompanied by impairment of the cellular response (23-27).

Replacement therapy with intravenous IgG preparations used especially in primary immunodeficiency disorders with hypo- or agammaglobulinaemia. The serum half-life of IgG is about 21 days so it is recommended that the administration of intravenous immunoglobulin is every 21-28 days to obtain protective IgG concentration assessed at a level of at least 500 mg/dl (28-30). Due to secondary immunodeficiency in patients after allogeneic hematopoietic stem cell transplantation, administration of intravenous immunoglobulin is often necessary for a minimum of one year after surgery, which is the time required for B lymphocytes to regain full function which takes longer than normalization of the number and function of T cells. Immunoglobulin substitution is clearly indicated in case of chronic lymphocytic leukemia B cell hyperplasia or other clonal B cell disorders with hypogammaglobulinemia or impaired production of antibodies against specific classes of antigens, especially with recurrent infections. Many randomized studies have confirmed the benefits of regular administration of intravenous immunoglobulin in patients with CLL and MM, who are particularly vulnerable to severe bacterial infections (13, 18-22). They showed a significantly lower rate of life-threatening infectious complications of patients who received immunoglobulin prophylaxis regularly for a minimum period of 1 year. These recommendations concerning the adjunctive treatment of myeloma patients were included in the guidelines NCCN (National Comprehensive Cancer Network) in 2007.

Gamma globulin preparations obtained from the sera of donors with high titres of antibodies to CMV are used in the prevention of CMV infections in patients who are immunocompromised recipients of allogeneic transplants and specifically recommended by the EBMT (30).

SUMMARY

The observed immune disorders associated with lymphoid malignancies are often permanent and result from a lack of a durable remission. Therefore, patients with a diagnosis of CLL or MM are the biggest problem. Chronic treatment with anticancer drugs, including monoclonal antibodies results in enhanced immunosuppression. Apart from lymphopenia, neutropenia is also observed during treatment. In the era of new anticancer drugs offering patients the chance to survive for a few years longer, as is the case of multiple myeloma patients, supportive therapy is of great importance. To do this, we need to monitor the status of the immune system and possibly correct problems by protecting the patient from life-threatening infections.

We are able to permanently cure many of the lymphomas. However, many patients in the radically treated group die due to infectious complications in the long-term, resulting from the biology of these tumors to immunosuppression, as well as emerging antibiotic-resistant bacteria.

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