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BONE MARROW TRANSPLANTATION FOR HEMATOLOGICAL DISEASES

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ABSTRACT

This article is devoted to the problems of bone marrow transplantation for hematological diseases, in addition, in the article diseases of the blood system still represent one of the most complex and understudied sections of clinical medicine were discussed.

KEYWORDS: *Blood System, Bone Marrow, Transplantation, Hematology, A Plastic Anemia.*

INTRODUCTION

Diseases of the blood system still represent one of the most complex and understudied sections of clinical medicine. Since the beginning of the twentieth century, when the outstanding Russian scientist A.A. Maksimov developed a unitary theory of hematopoiesis and introduced the concept of "stem cell", many events took place in hematology associated with the rapid development of a number of fundamental disciplines: immunology, cytogenetics, molecular biology, genomics, proteomics, etc. The accuracy of diagnosing many pathological conditions has significantly increased, fundamentally new approaches to the treatment of previously absolutely fatal diseases: acute leukemia, malignant lymphomas, myelodysplastic syndromes, a plastic anemia, etc. Such high-tech methods of treatment as bone marrow and hematopoietic stem cell transplantation, immunotherapy using monoclonal antibodies and vaccines have made a great contribution to improving treatment outcomes, radio immunotherapy, gene therapy, etc.

One of the main tasks of the Clinic of Hematology and Cell Therapy. A.A. Maksimov, created at the National Medical and Surgical Center. N.I. Pirogov in 2005 is the introduction of high medical technologies into clinical practice.

A new era in the treatment of hematological and oncological diseases was opened by high-dose chemotherapy with bone marrow and hematopoietic stem cell transplantation. Let us consider in more detail the possibilities of this technology, which has found wide application in the National Medical and Surgical Center named after. N.I. Pirogov.

Types and main indications for myelotransplantation.

Myelotransplantation is a method of treatment of hematological and oncological diseases, in which the patient, after the induction of a deep depression of the immune and hematopoietic systems, caused by the use of conditioning regimens (megadoses of cytostatics, ± total body exposure), pre-prepared bone marrow or hematopoietic stem cells (HSCs) are injected. In oncohematological diseases and solid tumors, high-dose chemotherapy with myelotransplantation provides the most effective eradication of the tumor cell pool.

There are two main types of myelotransplantation:

1) allogeneic (AlTKM), in which the patient is injected with bone marrow from a related or unrelated histocompatible donor;

2) autologous (ATCM), when the recipient receives a pre-prepared own bone marrow.

A variant of ALTCM is syngeneic TCM (myelotransplantation from an identical twin). The main advantage of AltCM is the low risk of recurrence. This is due, firstly, to the fact that the bone marrow of a healthy donor is transplanted to the patient, and in case of oncological diseases, in addition, to the development of the reaction "graft against leukemia" (RTPL). The main disadvantage of the method is high mortality, reaching 20–30%.

Main indications for allogeneic BMT

1) Acute leukemia;

2) Chronic myeloid leukemia;

3) Severe aplastic anemia;

4) Hemoglobinopathies;

5) Congenital immunodeficiencies and metabolic disorders.

The main advantage of ATCM is low mortality (3-10%), and the disadvantage is the risk of recurrence due to the possible presence of tumor cells in the graft.

Main indications for autologous BMT:

1) Malignant lymphomas: non-Hodgkin's lymphomas and Hodgkin's disease;

2) Solid tumors: germ cell tumors, breast cancer, sarcomas, etc.

In general, AltCM is characterized by the best long-term results and is the method of choice for diseases accompanied by damage to the bone marrow (leukemia, aplastic anemia, etc.). ATCM is

indicated, first of all, in the absence of bone marrow damage (lymphogranulomatosis, non-Hodgkin's lymphomas, solid tumors, autoimmune diseases).

Due to the limited number of related histocompatible donors, which are available only in 20-25% of patients, in recent years, altCM from unrelated HLA-identical donors has been used. For these purposes, International registries have been created to select a potential bone marrow donor and optimize the prognosis in patients who are indicated for AltCM (acute leukemia, chronic myeloid leukemia, aplastic anemia, hemoglobinopathies, immunodeficiencies, metabolic disorders). The total number of registered donors in the world exceeds 5 million people, including about 10 thousand in Uzbekistan.

An important achievement was the introduction of HSC transplantation into practice. In recent years, it has been established that HSCs are located not only in the bone marrow, but under certain influences (appointment of CSF, "exit" from postcytostatic agranulocytosis) appear in the peripheral blood. The use of monoclonal antibodies (MABs) makes it possible to identify the population of cells with the HSC immunophenotype, and automatic blood cell separators provide the required amount of HSCs. This makes it possible to perform HSC transplantation, which has recently taken an increasing place in transplantation. The benefits of HSC transplantation include:

1) Carrying out the stem cell collection operation without general anesthesia;

2) Shorter duration of the period of cytopenia;

3) Faster recovery of the immune system;

4) The possibility of carrying out with bone marrow fibrosis (for example, after radiation therapy to the lymph nodes and abdominal organs).

Purification of the bone marrow or peripheral blood from residual tumor cells using MCA and/or physical methods reduces the frequency of relapses and allows the widespread use of ATCM/TSCC in patients with leukemia. Currently, transplantation of not only autologous, but also allogeneic HSCs (ALTSCs) is actively used.

Advantages of AlTSKK in comparison with AltKM:

1) The possibility of obtaining a larger number of CCMs;

2) Carrying out the operation without general anesthesia;

3) Shorter duration of cytopenia;

4) Faster recovery of the immune system. The main disadvantages of AltSKK:

1) The possibility of developing side effects in connection with the use of CSF to mobilize the SCM;

2) The need for repeated sessions of cytopheresis.

Another potential source of HSC is cord blood, the main advantage of which is less alloreactivity. The creation of cord blood banks expands the possibilities of performing unrelated CTBS in adult patients. The technique of myelotransplantation differs depending on its type (allogeneic or autologous), the nosological form of the disease, and a number of other factors.

Let us give a brief description of the possibilities of using high-dose chemotherapy with BM/HSC transplantation in various types of hematological and solid tumors.

Malignant lymphomas

Malignant lymphomas (ML) are a heterogeneous group of malignant tumors originating from lymphoid tissue. In general, ML accounts for about 2% of malignant tumors. In the structure of childhood malignant tumors, PLs occupy the third place.

In recent years, there has been an increase in the incidence of non-Hodgkin's lymphomas (NL). The probability of developing NL increases with age from 0.7 (10 years) to 20 cases per 100,000 populations per year (80 years). Aggressive ("blast") NL are observed in children, the prevalence of indolent forms is typical for the elderly (60–80 years). The most common and practically significant variants of NL are diffuse large B-cell lymphoma, follicular lymphoma, B-cell CLL, peripheral T-cell lymphomas, mantle cell lymphoma, marginal zone lymphomas (including extranodal MALT lymphomas), anaplastic large cell lymphomas [10].

Diffuse large B-cell lymphoma (DLCL)

- the most common type of NL (40% of patients), and an increase in the incidence of 3–4% is recorded annually. DLCL occurs primarily or as a result of the transformation of other NL (FL, LKMZ), are characterized by an aggressive course and low survival in the absence of adequate therapy.

Follicular lymphomas (FL) are the second most common form of NL (>30%). In most cases, PL proceeds indolently. At the same time, in some histological variants (a large number of centroblasts, diffuse growth), an aggressive course of the disease is noted, requiring intensive treatment. Peripheral T-cell lymphomas (PTCL) occur in 15% of patients. The most common are unspecified and angioimmunoblastic T-cell lymphomas (AICL). Previously, AITCL was called angioimmunoblastic lymphadenopathy and belonged to benign diseases. It has now been established that the median survival in AITCL does not exceed 18 months, so these patients need active treatment.

Lymphomas from cells of the mantle zone (LCMZ) are observed in 6% of patients. In recent years, the diagnosis of LCMZ means the need for aggressive therapy (including myelotransplantation), since the median survival against the background of standard chemotherapy does not exceed 2 years.

MALT lymphoma (extranodal B-cell marginal zone lymphoma) occurs in 4–14% of cases. With this type of NL, it is possible to damage any organ that contains lymphoid tissue associated with the mucous membrane. Most often, the gastrointestinal tract is involved, and in case of stomach damage, Helicobacter pylori is detected in 90% of patients. Anaplastic large cell lymphoma (ALCL) has recently been isolated due to the development of immunohistochemical techniques - this NL is characterized by the expression of the CD30 antigen. With adequate treatment, the prognosis is favorable.

Due to the heterogeneity of NL, studies have been conducted for a long time on predicting the course of this group of diseases. The following factors have been found to have a negative prognostic value:

1) More than three courses of PCT courses required to obtain a PR;

2) Accumulation of 67Ga in lymph nodes during scanning;

3) Increased expression of the Ki67 gene;

4) Increased level of CD44 expression;

5) Increased expression of the bcl-2 gene and a number of cytokines (IL-6, tumor necrosis factor receptor);

6) Mutation of the anti-oncogene p53;

7) T-cell phenotype;

8) Disorders on the part of chromosomes 7 and 17. Myelotransplantation expands the possibilities of therapy; most authors believe that in aggressive lymphomas with high MPI, ATCM/TSCC is indicated for consolidation of the first complete remission (CR). Thus, in a randomized study including 542 patients with NL younger than 55 years old, it was found that ATCM for the purpose of consolidating PR has no advantages in patients with low and "low intermediate" risk. On the contrary, at high intermediate and high risk, ATKM leads to long-term relapse-free survival in 56% of patients, with standard therapy - in 36%. In the case of aggressive NP with low MPI, ATCM/TSCC is indicated during the first relapse (with sensitivity to PCT), the second or subsequent CR.

In patients with low-grade CL with the presence of risk factors, ATCM/TSCC also improves the long-term prognosis: long-term relapse-free morbidity after transplantation during the first PR is observed in 85% of patients, during the second PR and the first chemosensitive recurrence - in 65%.

ATCM/TSCC in patients with low-grade CL is necessary in the following cases:

1) During the second PR with the duration of the first PR <18 months or during subsequent PRs with the duration of the previous PR <12 months;

2) During the first partial remission (PR) with an aggressive course of NL;

3) During the first PR in patients with LCMZ (the most unfavorable prognostic variant).

Long-term results of ATCM deteriorate sharply in patients with bone marrow damage: 5-year recurrence-free survival with intact bone marrow is 90%, in the presence of residual tumor cells (according to PCR) - 25%. In this regard, prior to autologous transplantation, purification of the bone marrow or peripheral blood HSC with the help of MCA is indicated. Indications for ALTCM in NL are much narrower than in patients with leukemia. The question of performing AltCM / TSCC from a related HLA-identical donor can be discussed:

1) If necessary, obtain a graft-versus-lymphoma reaction (for example, in patients with aggressive NL with a high risk of relapse);

2) With damage to the bone marrow;

3) In young patients.

All types of myelotransplantation in NL are contraindicated in case of primary refractoriness to adequate cytostatic therapy. In each case, the question of the advisability of myelotransplantation should be decided individually.

Lymphogranulomatosis

The most common histological types of lymphogranulomatosis (LGM) are nodular sclerosis (75%) and mixed cell variant (20–30%); lymphoid predominance and lymphoid depletion are much less common - respectively, in 3-5% and 1-2% of cases. In addition, the 2001 WHO classification additionally identifies the fifth morphological variant of LGM - classical Hodgkin's disease (HD) with a large number of lymphocytes. The basis for the treatment of patients with advanced stages of LGM is PCT, and the "gold standard:

– ABVD program. When using this scheme in patients with III-IV stages of the disease, PR is achieved in 80-85% of patients; the absence of disease progression is recorded within 5 years - in 60%.

Due to the good results of chemotherapy in patients with LGM, myelotransplantation is used only in risk groups.

Indications for ATKM/TSKK:

1) The first relapse, especially when the duration of the first CR < 1 year;

2) The second PR or the second and subsequent relapses sensitive to PCT;

3) Primary resistance to treatment, i.e. lack of PR after standard PCT.

Conducting ATKM/TSKK during the first relapse significantly improves the prognosis: the absence of disease progression within 5 years after myelotransplantation is 50-70%, after PCT - 30-35%. The results of transplantation are greatly influenced by risk factors: the duration of the first PR < 12 months, the presence of B-symptoms or extra nodal lesions in the development of recurrence.

CONCLUSION

Bone marrow and stem cell transplant. One of the fundamentally new and highly effective methods of treatment of hematological and oncological patients. In recent years, all stages of the operation have been optimized: selection of donors, harvesting of hematopoietic stem cells, conditioning regimens, prevention and treatment of post-transplant complications. The number of hematopoietic stem cell transplantations in Uzbekistan is constantly increasing, and the list of diseases for which myelotransplantation is used is expanding. There are also fundamentally new approaches that use non-myeloablative chemotherapy regimens in conditioning programs, as well as combined transplantation options using immunotherapy methods. Specialists of the National Medical and Surgical Center. N.I. Pirogov contributes to the development of the theoretical and practical foundations of HSC transplantation and bringing this high-tech method of treatment to hematological and oncological patients from various countries.

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