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СОДЕРЖАНИЕ

CONTENT

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ISSUES OF AUTOLOGICAL TRANSPLANTATION AND HEMOPOETIC CELLS IN MULTIPLE MYELOMA (LITERATURE REVIEW)

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XULOSA

Ma'lumki, myeloma kasalliginini davolashda gemopoetik hujayralarning autologik transplantasiyadan foydalanish to'liq remissiyalar sonini ko'paytiradi, shuningdek residivsiz va bemorlarning umumiy yashashini uzaytiradi. Binobarin, bemorlarning hayot sifatini oshirish uchun butun dunyoda ustuvor ahamiyatga ega bo'lgan davolashning yuqori texnologiyali zamonaviy usullarini amalga oshirish zarur. Shu munosabat bilan mielomada autotransplantatsiya qilish uchun mo'ljallangan GH olish, tashish va saqlashga tayyorlash bo'yicha aniq uslubiy yondashuvlarni ishlab chiqish muhim va zarurdir.

Kalit so'zlar: *ko'p miqdordagi miyeloma, autologik transplantatsiya, gemopoetik ildiz hujayralari, safarbarlik, muzlash.*

РЕЗЮМЕ

Известно, что применение аутоТГСК в лечении ММ увеличивает количество полных ремиссий, а также показатель без рецидивной и общей выживаемости больных. Следовательно, для увеличения продолжительности качественной жизни больных необходимо проведение высокотехнологичных современных методов лечения, что является приоритетным направлением во всем мире. В этой связи, разработка чётких методологических подходов к получению, транспортировке и подготовке к хранению ГСК, предназначенных для аутотрансплантации при ММ является важным и необходимым.

Ключевые слова: *множественная миелома, аутологичная трансплантация, гемопоэтические стволовые клетки, мобилизация, заморозка*

INTRODUCTION

Despite the long period of study of multiple myeloma (MM), the mechanisms of the emergence and development of resistance to the therapy are still unclear [1,3]. In this regard, worldwide attention of researchers is involved in the search for new informative markers that determine the individual risk of development and prognosis of the disease [2,10,13,25,28], which is undoubtedly a justified and promising direction of modern medical science.

Undoubtedly, a real breakthrough in the treatment of MM was the use of hematopoietic stem cells (HSCs) of the bone marrow, serving as the "starting point" of the complex process of hematopoiesis, which as a result of their differentiation and maturation give rise to all types of blood cells (red blood cells, platelets and various forms of white blood cells) [2,9,16]. When HSCs are injected into the organism where their own hematopoiesis is destroyed, the injected cells are able to populate the bone marrow of the patient with their generations and restore hematopoiesis [8,15]. It is on this ability of HSCs that hematopoietic stem cell transplantation is based.

One of the varieties of HSCs widely used for transplantation is autologous peripheral blood stem cells. However, under normal conditions there are very few stem cells in the peripheral blood, so their release into the blood is enhanced under the action of granulocyte colony stimulating factor (G-CFS) (neupogen, granocyte, leukostim) and some other drugs (HSCs mobilization stage), injected into the patient for several days with their subsequent isolation from the blood by apheresis until their sufficient quantity is obtained [4,7,11].

According to the European Society for Blood and Marrow Transplantation (EBMT), in 2011 peripheral blood served as a source of HSCs in 99% of autologous and 73% of allogeneic transplants [5,6,10]. Nevertheless important criteria for successful autologous HSCs transplantation (autologous HSCs) are the number and functional status of the HSCs previously harvested from the patient.

The main factor negatively affecting the number and functional state of the harvested HSCs is their freezing for the period required for pre-transplantation high-dose chemotherapy. In particular, the freezing process is accompanied by formation of intracellular ice crystals leading to HSCs damage [4,8]. And also, as the cooling process changes the nature of metabolic processes in cells, and vital processes are disrupted. Movement of various molecules and organelles in cells slows down, viscosity and physical and chemical properties of solutions, protein and other complexes change, the rate of biochemical reactions decreases, enzyme activity is disturbed, regulation of intracellular exchange changes [13].

Moreover, a special cryoprotectant used for prevention and reduction of cell damage during freezing, when mixed with HSCs, can also destroy them [12,14]. Moreover, the results of foreign specialists show that introduction of the cryoprotectant into the graft with a high concentration of leukocytes reduces the preservation and viability of HSCs [3,8]. Consequently, the dose of HSCs for transplantation after thawing can be significantly lower than the harvested one [17]. In its turn, the reduced dose of transplant HSCs can be accompanied by prolongation of the hem

topoiesis recovery period, which leads to the development of severe infectious and hemorrhagic complications, often leading to fatal outcome. Therefore, one of the conditions for effective auto-HSCs is laboratory control of the number and functional properties of HSCs both at the stages of their preparation and cryopreservation, as well as at the stages of their transplantation to the patient.

Ways to preserve cell viability during freezing are optimal cooling management and the use of cryoprotectants [3,18].

Apheresis systems are widely used for peripheral blood auto-HSCs, sparing donors from traumatic procedures of bone marrow acquisition and allowing a more rapid recovery of hematopoiesis and immunity [2,18]. It is one of the methods of apheresis - leukocytapheresis (isolation of cellular blood components in order to modify them and return to the patient) at early mobilization terms with selection of its optimal duration and multiplicity according to a number of authors is one of the important conditions of transplant quality preservation and HSCs quantity at the required level for successful auto-HSCs [1,5].

Despite the compliance with the conditions at the stages of HSCs mobilization, according to foreign researchers, in 10-30% of patients it is not possible to obtain a sufficient number of cells for transplantation. In this regard, in a significant group of patients, the optimal cellularity of the transplant can be obtained only by using different mobilization regimens and multiple apheresis sessions [10].

These difficulties are related to the kinetics of HSCs mobilization - very individual, due to specific changes in the bone marrow, as a result of the disease and polychemotherapy [5].

Granulocyte colony-stimulating factor (G-CSF) has proved to be an effective agent stimulating HSCs output into the peripheral blood [1, 2]. Along with this, the researchers note its most effective use in combination with cytostatic drugs [6]. Namely, after cytostatic drug administration, HSCF is started daily subcutaneously, and HSCs concentration in peripheral blood usually begins to increase on the third day, with a peak on the fifth - sixth day. When the maximum HSCs concentration is reached, a leukocytapheresis operation should be performed [7,6,19,21].

The time for leukocytapheresis operation is determined based on the data of peripheral blood cell composition monitoring. The minimum concentration of HSCs in the peripheral blood, at which a sufficient transplantation dose can be collected, is considered to be from 10 to 18 HSCs/μL [8,20,24]. This recommendation is largely conditional, because each patient requires an individual transplantation dose of HSCs, determined by his/her body weight and treatment plan, for example - the need for double transplantation.

According to N.L. Watts et al. (2019), every subsequent day HSCs concentration in the blood can increase, and it will turn out that leukocytapheresis was performed prematurely, or vice versa, at the same time there is a risk of HSCs concentration decrease in the following days, in which case postponing leukocytapheresis operation will not allow to collect a sufficient transplantation dose [27].

According to other specialists, monitoring of HSCs number should be started only after the increase of peripheral blood leukocytosis over 1*109/l, because until then the HSCs concentration in peripheral blood is insufficient and will increase [21,23,28], which does not always happen. There is also an opinion that absence of deep leukopenia after cytostatic injection is an indicator of ineffective mobilization, which is also not indisputable. Moreover, there are data confirming that the dynamics of leukocyte number recovery during mobilization does not correlate with HSCs release into the peripheral bloodstream [18,20,25,27].

The amount of HSCs obtained by leukocytapheresis depends on the duration of the procedure, initial concentration of HSCs in peripheral blood and kinetics of this concentration during the procedure itself [27]. If the cytapheresis machine gives stable results of HSCs production, then knowing their initial amount in the peripheral blood and kinetics of production during the operation, we can count on obtaining predictable amount of transplant material by controlling the duration of the procedure. Cell separators from different manufacturers have specific protocols for leukocytapheresis operation, sometimes not allowing to adjust their operation parameters - for example, to increase the limit amount of processed blood. At the same time, the end of the operation protocol does not always coincide with the recruitment of a sufficient dose of HSCs. In this case, F.Z. Chen, Y.M. Luo, Q. Hong (2018) recommend to repeat leukocytapheresis on the next day against the background of ongoing drug mobilization. But, as it was mentioned above, possible drop of HSCs concentration in the peripheral blood on the next day can make the repeated operation senseless [16].

On the other hand, obtaining the amount of HSCs significantly exceeding the dose sufficient for transplantation should not be the goal. There is evidence that transplantation of more than 15 HSCs/kg of body weight does not affect the recovery time of hematopoiesis [10], at the same time, prolonged operation leads to the increase of anticoagulant load on the patient. Consequently, treatment of excessive blood volume during leukocytapheresis operation is also inexpedient.

It should be noted that in the treatment of oncohematological patients the successful collection of the transplantation dose from the patient or donor is very important for the outcome of the disease. The course of the disease often does not leave time for a second attempt to obtain transplantation material and can determine an unfavorable outcome. In addition, it should be taken into account that G-CSF is not only an effective mobilizing drug, but also can stimulate HSCs differentiation in vivo, which inevitably reduces the pluripotency and proliferative potential of these cells [29]. Therefore, it is advisable to perform a single leukocytapheresis and, if possible, at the earliest possible time, in order to collect earlier precursors of hematopoiesis. In turn, reducing the duration of G-CSF administration even by one day is preferable, since the drugs

of this group can cause clinically significant side effects.

Thus, it is optimal to procure a sufficient dose of HSCs using a single timely leukocytapheresis operation with a minimal but sufficient volume of treated blood. The development of an algorithm for such an approach appears to be an urgent task for the implementation of successful transplantation in oncohematological practice.

CONCLUSION

Today it is known that the use of autologous HSCT in the treatment of MM increases the number of complete remissions, as well as the index of relapse-free and overall survival of patients [16]. Consequently, in order to increase the quality life expectancy of patients it is necessary to carry out high-tech modern methods of treatment, which is a priority all over the world. In this regard, development of clear methodological approaches to obtaining, transportation and preparation for storage of HSCs intended for autotransplantation in MM is important and necessary.

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