

# Analysis Of Efficiency Of Multiple Myeloma Therapy By The Method Of Translation Of Autologic Hemopoetic Stem Cells In Uzbekistan

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**Abstract- Purpose of the research.** Implementation of the method of collecting CD34 + cells by apheresis, their storage and analysis of the effectiveness of transplantation of autologous hematopoietic stem cells (autoHPSC) in patients with multiple myeloma. **Materials and methods.** The study included 107 patients (median age -  $55.3 \pm 2.3$  years; men - n = 52, women - n = 55) with a diagnosis of multiple myeloma who were registered in the dispensary and treated in the period from 2013 to 2019 years at the Scientific-research institute of Hematology and blood transfusion of the Ministry of Health of the Republic of Uzbekistan (Uzbekistan, Tashkent). **Results.** According to results the effectiveness of the apheresis of peripheral blood cells as a component of the treatment of multiple myeloma with autologous hematopoietic cells. The success of mobilization in the treatment of multiple myeloma plays an important role, since tandem transplantations significantly increase the likelihood of achieving remission of the disease and the quality of life of patients with multiple myeloma. Proof of this is the increase in the number of patients with multiple myeloma with relapse-free survival and overall survival who received polychemotherapy in combination with autologous hematopoietic cell transplantation (autoHPCT) in comparison with patients who received only polychemotherapy (PCT).

**Index Terms-** multiple myeloma, apheresis, mobilization, polychemotherapy, autologous hematopoietic stem cell transplantation, relapse-free survival, overall survival.

## I. INTRODUCTION

Multiple myeloma is a malignant lymphoproliferative disease characterized by bone marrow infiltration by plasma cells, pathological protein synthesis, and bone and kidney damage [1]. The annual increase in new cases of multiple myeloma indicates a steady increase in the disease [2], which until now is incurable. Along with this, relapses of the disease and various complications (infectious complications, bone fractures, renal failure) lead to the aggravation of its course, further exacerbating the quality of life of patients with multiple myeloma [3].

Despite the long study period and the large number of multicenter studies conducted, the mechanisms of the formation and prediction of multiple myeloma are still poorly understood [4]. Multiple myeloma, like many other diseases, is by its nature

pathology with an unclear etiology; a variety of exogenous and endogenous mutually contributing factors are involved in its pathogenesis [5, 6].

The introduction of modern research methods has increased the level of diagnosis of multiple myeloma, by identifying immunochemical variants of the disease, which differ in the features of the clinical course and outcome of the pathological process.

In recent years, progress has been achieved in the treatment of multiple myeloma due to the use of high-dose polychemotherapy, which improves the quality of life of patients by increasing the non-relapse survival and overall survival of patients with multiple myeloma [7, 8, 9, 10]. However, aggressive and prolonged cytostatic therapy increases the risk of complications (toxic damage to the cardiovascular system, liver, kidneys), and even when the maximum effectiveness of PCT is achieved, the tumor clone remains in the patient's body, which again leads to the return of the disease [11, 12, 13]. In this regard, the search for new, most effective treatment methods has led to the introduction of bone marrow transplantation into the practice of treating patients with multiple myeloma in particular, autologous hematopoietic stem cell transplantation. Hematopoietic stem cells obtained from peripheral blood after mobilization and hardware leukocytapheresis are increasingly used as a source of stem cells [14]. However, despite the progress achieved at all stages of mobilization, according to various studies, in 10-30% of patients it is not possible to obtain a sufficient number of cells for transplantation.

In addition, in a significant group of patients, the transplant optimal in cellularity can be obtained only by using various mobilization modes and multiple apheresis sessions [15]. One of the important components of corticosteroids therapy is their collection and isolation from the patient's peripheral blood through apheresis of cells carrying CD34 + receptors on their surface [16].

According to multicenter studies, the use of autoHPCT in the treatment of multiple myeloma increases the number of complete remissions, as well as the indicator without relapse and overall survival of patients [17, 18]. Therefore, to increase the quality of life of patients with multiple myeloma, it is necessary to conduct high-tech modern treatment methods, which is a priority in the whole world.

## II. PURPOSE OF THE RESEARCH

Implementation of the method of collecting CD34 + cells by apheresis, their storage and analysis of the effectiveness of transplantation of autologous hematopoietic stem cells in patients with multiple myeloma.

### III. MATERIALS AND METHODS

The study included 107 patients (average age -  $55.3 \pm 2.3$  years; men -  $n = 52$ , women -  $n = 55$ ) with a diagnosis of multiple myeloma who were registered in the dispensary and treated in the period from 2013 to 2019 years at the Scientific-research institute of Hematology and blood transfusion of the Ministry of Health of the Republic of Uzbekistan (Uzbekistan, Tashkent).

Patients, depending on the treatment method, were divided into two groups: group 1 ( $n = 90$ ) patients with multiple myeloma who received 4 courses of PCT according to the VCD protocol (Bortezomib (PS-341) at  $1.3 \text{ mg} / \text{m}^2$  intravenously in 1, 4, 8 and 11 days; cyclophosphamide  $300 \text{ mg} / \text{m}^2$  intravenously on days 1, 8, 15 and dexamethasone  $20 \text{ mg}$  orally or intravenously on days 1-2, 4-5, 8-9, 11-12) and group 2 ( $n = 20$ , aged 31-55 years) who received 4 courses of PCT according to the VCD + autoHPSCT protocol (autologous hematopoietic stem cells transplantation).

All patients included in the study signed a written consent to use the data for scientific purposes. The diagnosis of multiple myeloma has been verified according to WHO recommendations (2008), including the identification of disease markers. The stage of the disease was established according to the classification of G.M. Durie and S.E. Salmon (1975) [18]. When verifying the diagnosis according to generally accepted international diagnostic criteria, clinical and laboratory parameters and immunological variants of the production of immunoglobulins of types of heavy and light chains were taken into account [19]. An immunochemical study included electrophoresis with immunofixation of blood serum proteins on an analyzer from "Interlab Pretty" (Italy) using reagents from the same firm.

CD34 + fractions from peripheral blood were isolated by leukocytapheresis using Fresenius brand cytoplasmapheresis equipment (Germany). Isolation of hematopoietic stem cells was performed after a preliminary 4-6 day stimulation of the release of hematopoietic stem cells into the vascular bed using granulocyte colony stimulating factor (G-CSF) and the "Neupogen" drug. The isolated cells were frozen in a solution of dimethyl sulfoxide (DMSO) until reaching a 10% concentration at  $-196^\circ\text{C}$ . On the "BD CALIBUR" cytofluorimeter, the total number of HPSC, CD34+ and CD45+ were determined, and the ratio before and after apheresis was also determined. Before transplantation, the number of live HPSC was determined. Digital material processed by the method of variation statistics.

### IV. RESULTS AND DISCUSSION

All patients with a diagnosis of multiple myeloma ( $n = 20$ ) included in the study were successfully treated with hematopoietic cells. Analysis of the level of hematopoietic stem cells in the vascular bed in patients, depending on the time of administration of G-CSF and the Neupogen preparation, showed the highest cell yield on days 4-6. At the same time, the average yield of hematopoietic stem cells was  $5,806 \pm 0,95 \times 10^6$  cells

and  $3,637 \pm 0,77 \times 10^6$  cells, respectively, on the 5<sup>th</sup> and 6<sup>th</sup> days of sampling. It should be noted that in our studies a high variability of indicators was noted. So, if in 16 (80.0%) patients the level of hematopoietic stem cells ranged from  $4.5 \times 10^6$  cells to  $11.62 \times 10^6$  cells, then in 4 (20.0%) it amounted to  $1.4-0.38 \times 10^6$  cells. Apparently, this was due to the effect of a long course of therapy of patients with a diagnosis of multiple myeloma with alkylating agents on the efficiency of hematopoietic stem cell mobilization.

Prior to apheresis, the level of the total CD34 + fraction was  $92.541 \mu\text{m} / \text{L}$ , and after apheresis, this indicator increased to  $206.518 \pm 86.98 \mu / \text{L}$  and  $115.182 \pm 32.04 \mu / \text{L}$ , respectively, for periods of 5 and 6 days of sampling. Confirmation of the separation efficiency was the ratio of CD34+ to CD45+. This coefficient before apheresis averaged  $0.261 \pm 0.09\%$ , after this procedure -  $0.546 \pm 0.08\%$  and  $0.375 \pm 0.08\%$ , respectively. The results of the study indicate the highest output of hematopoietic stem cells on the 5<sup>th</sup> day of sampling.

In order to assess the effectiveness of treatment, dynamic monitoring of patients was carried out with all research methods.

A month after the therapy, clinical examination of patients in both subgroups showed a significant decrease in the percentage and intensity of ossalgia, infectious complications and extramedullary manifestations. No new pathological fractures were observed among patients. However, there was an improvement in renal function in patients with multiple myeloma.

In the 1<sup>st</sup> group, ossalgia was observed in 36.7% of patients (with the IgG $\kappa$  variant in 6.9%; IgG $\lambda$  -10.3%; IgA $\kappa$  - 1.2%; IgA $\lambda$  -9.2% and rare types in 9.2%). Infectious complications in the form of bronchitis and pneumonia were observed in 8.0% of patients with multiple myeloma, severe impaired renal function - chronic renal failure (CRF) - in 21.8% of patients with multiple myeloma. Extramedullary manifestations of multiple myeloma are significantly in almost two times decreased in comparison with the manifestations before treatment and persisted only in 6.9% in the form of damage to the soft tissues of the face, scalp (in patients with multiple myeloma IgG $\kappa$  (2.3%) and IgG (4.6%).

Clinical analysis in 2<sup>nd</sup> group in the early days of the post-transplant period showed the development of angina and exacerbation of chronic bronchitis in 5.0% of the patients, the development of thrombophlebitis in 5.0% of the patients, bronchopneumonia in 10.0% of patients. The described infectious complications 1 month after the autoHPSCT were not observed.

Positive dynamics was also observed in relation to the severity and frequency of anemic syndrome (Table 1).

So, in 1<sup>st</sup> group, a severe degree of anemic syndrome was recorded in 13.7%, an average in 21.8%, and a mild in 42.5% of patients. In 2<sup>nd</sup> group, a severe degree of anemic syndrome was not recorded, an average degree was noted in 25% and a mild in 55%.

Studying the level of platelets with various immunochemical variants of multiple myeloma, allowed us to note the positive dynamics of this indicator after treatment, relative to its level before treatment. A comparative assessment of the platelet content in the blood in 1<sup>st</sup> & 2<sup>nd</sup> groups 1 and 2,

depending on the method of therapy, did not reveal a significant difference after treatment.

On the part of the number of leukocytes, the average values were kept within normal parameters both before treatment and after treatment.

A comparative analysis of the results of the study of the erythrocyte sedimentation rate in patients with multiple myeloma in dynamics, determined a rather positive tendency to decrease its level after treatment, in relation to the initial data recorded before treatment. The decrease in the erythrocyte sedimentation rate level in patients after treatment in both subgroups is primarily associated with a decrease in the tumor clone and a decrease in the production of pathological protein, and these data in turn emphasize the effectiveness of the treatment.

The level of plasmocytes with immunochemical variants of multiple myeloma in the 1<sup>st</sup> group decreased with the IgGκ variant - in 5.8 (6.5 ± 1.2% versus 37.5 ± 3.4%; p <0.001) IgGλ - in 4.6 (7.9 ± 1.6% against 36.2 ± 5.6%; p <0.001), IgAκ in 1.8 (19.9 ± 8.0% against 36.4 ± 9.4%; p <0.01); IgAλ - in 2.0 (26.4 ± 8.0% versus 53.4 ± 7.9%; p <0.05); in rare cases, 3.7 (9.0 ± 2.8% versus 33.3 ± 6.3%; p <0.01).

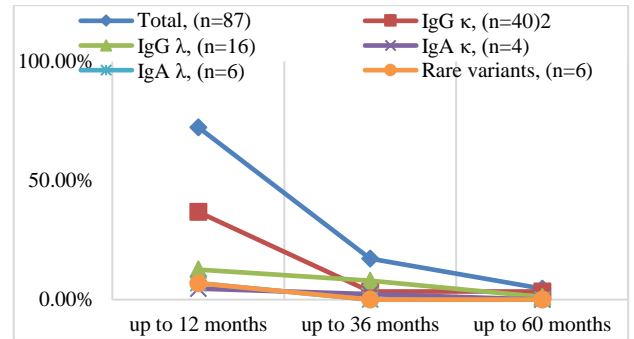
In the 2<sup>nd</sup> group, with the IgGκ variant, the content of plasmocytes was 1.2 ± 0.4%, against 37.5 ± 3.4% (p <0.001) with the IgGλ variant, 2.3 ± 0.6% and against 36.2 ± 5.6% (p <0.001), IgAκ - 0 ± 0% against 36.4 ± 9.4% (p <0.01); IgAλ - 1.0 ± 0.3%, against 53.4 ± 7.9% (p <0.001); in rare cases, 0.05 ± 0.02%, versus 33.3 ± 6.3% (p <0.01).

An important stage of our work was the analysis of the survival of patients with multiple myeloma in the first and second groups, depending on the treatment and in accordance with the immunochemical variant of multiple myeloma.

**Table 1**  
The dynamics of peripheral blood parameters after treatment in patients with multiple myeloma (n = 107) depending on the immunochemical variant (M ± m)

Type of Ig	Hemoglobin, g/l	Red blood cells, x 10 <sup>12</sup> /l	Platelets, X10 <sup>9</sup> /l	White blood cells, X 10 <sup>9</sup> /l	Erythrocyte sedimentation rate, mm/h	
Before treatment, (n=107)						
G	κ	83,3±3,2***	3,0±0,10	157,3±11,1***	7,1±1,3	20,0±2,0***
	λ	73,2±5,1***	2,7±0,17***	134,3±15,0***	5,5±0,53	23,8 ±5,5**
A	κ	80,5±9,4***	3,2±0,31***	143,3±26,6**	7,4±1,9	56,0±12,8
	λ	75,0±6,7***	2,7±0,21***	107,2±18,5***	6,1±1,1	39,1±9,2
Rare variants	105,9±6,6*	82,9±6,9***	3,1±0,25***	171,2±22,9*	5,5±0,65	
1 <sup>st</sup> - group, (n=87)						
G	κ	99,7±3,3**	3,3±0,11*	169,3±13,2	6,1±0,60	20,0±2,0***
	λ	98,9±6,4**	3,5±0,16**	201,3±22,1*	5,5±0,62	23,8 ±5,5**
A	κ	96,6±11,2	3,6±0,25	198,5±7,1*	4,1±0,49	56,0±12,8
	λ	92,7±8,3	3,3±0,25*	193,5±24,4*	6,56±1,2	39,1±9,2
Rare variants	106,5±3,0**	105,9±6,6*	3,5±0,21	164,2±18,8	4,5±0,57	
2 <sup>nd</sup> - group, (n=20)						
G	κ	111,1±4,2***	3,9±0,08***	217,1±16,3*	8,2±2,02	11,7±1,2***
	λ	95,9±3,3**	3,30,11*	164,6±15,5	4,6±0,5	33,0 ±5,8*
A	κ	113,0±3,7**	3,8±0,12	144,0± 12,4	9,5±2,3**	48,0±4,1
	λ	112,5±3,6***	4,1±0,03	187,0±33,8*	2,7±0,09	12,5±0,8***
Rare variants	106,5±3,0**	3,63±0,14	185,5±37,8	7,45±1,2	36,5±3,6	

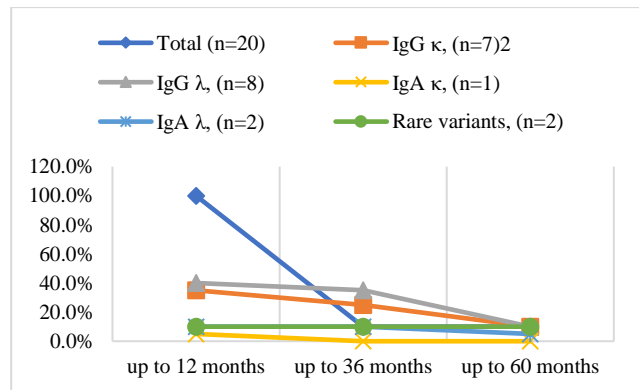
With a median follow-up of 60 months, relapse-free survival and overall survival (OS) of patients with multiple myeloma, depending on the treatment, had significant differences. So, in the 1<sup>st</sup> group of multiple myeloma patients who received only PCT according to the VCD protocol (4 courses) (n = 87), relapse-free survival up to 12 months was registered in 63 patients, which averaged 72.4 ± 4.8% (p > 0.05), up to 36 months - at 15 (17.2 ± 4.1%; p <0.01) and up to 60 months and more - at 4 (4.6 ± 2.3%; p <0.01 and p < 0.05) patients (Figure 1).



**Fig. 1.** Analysis of relapse-free survival among multiple myeloma patients of 1<sup>st</sup> group who received PCT according to the VCD scheme

A comparative assessment of CVD among patients of 1<sup>st</sup> & 2<sup>nd</sup> groups showed that on average, CVD of up to 12 months, up to 36 months and 60 or more months in the 2<sup>nd</sup> group in relation to the 1<sup>st</sup> group exceeded 1.38 (100%, p <0.05); 4.7 (80.0 ± 9.2%; p <0.05) and 7.6 times (35.0 ± 10.9%; p <0.001), respectively (Figure 2).

Depending on the immunochemical variant, relapse-free survival in the 2<sup>nd</sup> group exceeded that in the 1<sup>st</sup> group up to 12 months: with IgGκ detection at 1.25, with IgGλ variant at 1.5, with IgAκ at 1.25, with IgAλ 2.0 times, with rare forms 1.4 times; up to 36 months: with IgGκ of 2.3, with the IgGλ variant of 2.04, with IgAλ of 2, with rare forms 4.7 times; up to 60 months or more: with IgGκ 1.7, with the IgGλ variant 7.0 times.



**Fig. 2.** Analysis of relapse-free survival among patients with multiple myeloma in 2<sup>nd</sup> group who received PCT according to the scheme VCD + autoHPSCT.

A comparative assessment of overall survival among patients of the 1<sup>st</sup> and 2<sup>nd</sup> groups showed that the overall survival of up to 12 months, up to 36 months, and also up to 60 months or

more in the 2<sup>nd</sup> group in relation to the 1<sup>st</sup> group exceeded 1.06; 1.42 and 2.8 times, respectively. In particular, in the 1<sup>st</sup> group of multiple myeloma patients who received only PCT according to the VCD protocol (4 courses), overall survival up to 12 months was registered in 82 patients (94.3 ± 2.5%;  $p > 0.05$ ), up to 36 months - in 49 (56.3 ± 5.3%;  $p < 0.001$ ) and up to 60 months or more in 22 (25.3 ± 4.7%;  $p < 0.001$  and  $p < 0.001$ ) (Figure 3).

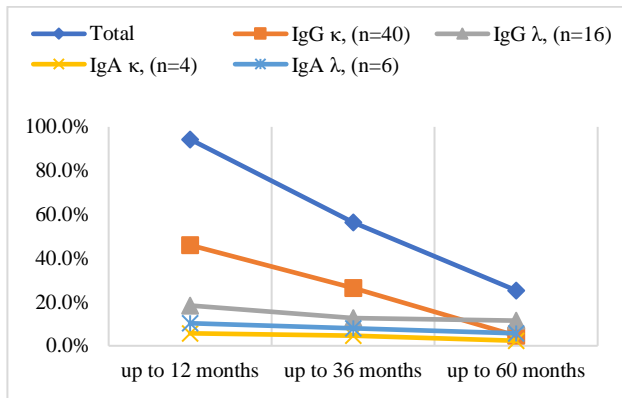


Fig. 3. Analysis of overall survival among patients with multiple myeloma of the 1<sup>st</sup> group receiving PCT according to the VCD scheme

In the 2<sup>nd</sup> group of multiple myeloma patients receiving only PCT according to the VCD protocol (4 courses) + autoHPCT (n = 20), overall survival up to 12 months was registered among all 20 patients, which amounted to 100% ( $p > 0.05$ ), up to 36 months - in 16 (80.0 ± 9.2%;  $p < 0.05$ ) and up to 60 months or more - in 14 (70.0 ± 10.5%;  $p < 0.05$ ) (Figure 4).

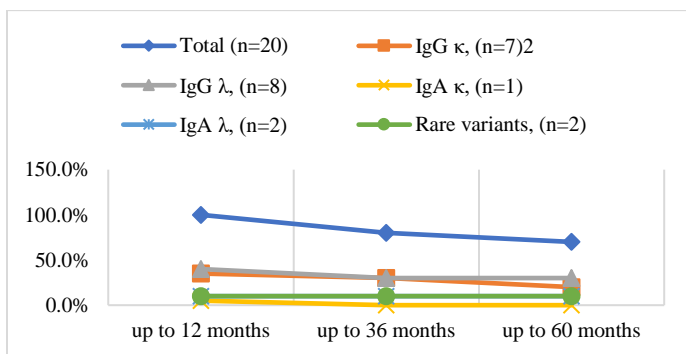


Fig. 4. Analysis of overall survival among patients of multiple myeloma 2<sup>nd</sup> group who received PCT according to the scheme VCD + autoHPCT.

Thus, the results obtained indicate that the percentage of patients with multiple myeloma with CVD and overall survival in the 2<sup>nd</sup> group exceeds those in the 1<sup>st</sup> group. This, in turn, is evidence of a higher efficiency of the use of autoHPCT, which is reflected in an increase in the quality of life and prolongation of both relapse free survival and their overall survival of multiple myeloma patients in the 2<sup>nd</sup> group.

#### V. CONCLUSION

Summarizing the above data, we can conclude that we have successfully mastered multiple myeloma therapy with autoHPCT and in particular, apheresis of hematopoietic cells of peripheral blood, which in the future has great potential for its use in various diseases. The results of the study show the clinical

efficacy of apheresis of peripheral blood cells as a component of autologous therapy of multiple myeloma with hematopoietic cells in a clinic. The treatment in both groups of patients with multiple myeloma indicates an improvement in both clinical and laboratory status. However, the dynamics of the studied clinical and laboratory parameters after treatment in the 2<sup>nd</sup> group was characterized by the highest recovery compared to the 1<sup>st</sup> group, which was clinically expressed in the disappearance of the characteristic symptoms of multiple myeloma in the laboratory - a greater increase in hemoglobin, red blood cells and platelets, and a decrease in the erythrocyte sedimentation rate in the blood, as well as the level of plasma cells in the bone marrow. In addition, the indicated positive dynamics was accompanied by an increase in disease-free survival and overall survival of patients with multiple myeloma after autoHPCT. Thus, all this directly convincingly proves the great effectiveness of using autoHPCT. At the same time, the conducted study is only the first step towards the full-scale introduction of autologous hematopoietic stem cell transplantation in the treatment of hematologic diseases.

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