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STUDYING THE INFLUENCE OF MULTIPLE MYELOMA, TREATMENT AND CO-MORBİD DISEASES ON THE COLLECTION OF PERIPHERAL STEM CELLS

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Applicant: **Valeh Tariverdi Huseynov**

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of the submitted dissertation

ABSTRACT

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The dissertation work was carried out in 2015-2020 in the Hematology Department of the Educational-Therapeutic Clinic of the Azerbaijan Medical University and the Hematology Department of the Medical Faculty of Ankara University (MFAU).

Scientific adviser: doctor of medical sciences, professor **Nasrullayeva Gulnara.**

Official opponents: doctor of medical sciences, professor **Aliheydar Agaalakbar Rahimov**

doctor of medical sciences, professor **Tulin Tuğlu Fıratlılar**

doctor of medical sciences **Eldor Jasur Isxakov**

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Tibb elmləri doktoru, professor
Nəsirov Adil oğlu Pənahi
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GENERAL CHARACTERISTICS OF WORK

Relevance of the work. Multiple myeloma (MM) is a malignant disease of plasma cells that leads to the synthesis of monoclonal light and heavy chain proteins and is one of the most important problems in modern medicine. Thus, despite being a relatively rare malignancy, myeloma is one of the leading cancers in the world in terms of the number of cases[1]. According to the literature, this disease accounts for 10-15% of malignant hematological diseases and 1% of all cancers. Every year, about 86,000 new cases are diagnosed worldwide, of which about 47,000 are men and 39,000 are women, and this number is growing every year. At the same time, every year more than 63,000 people die from this disease, which is 0.9-2% of cancer deaths[1]. At present, autologous peripheral stem cell transplantation (APSC) continues to occupy one of the most important places in the treatment of myeloma[2] In recent years, scientific research has been carried out on a more detailed study of other factors affecting the collection of stem cells[3]. The Gimema working group has developed a new risk scale for myeloma patients to prevent CD34 + hematopoietic stem cell accumulation failure . This scale included cytopenia, age, treatment, and their toxic effects at the time of diagnosis. Studies carried out in AMU clinic and in the hematology department of the Medical Faculty of Ankara University investigated the effect of renal failure, peripheral

[1] Dickran K. Multiple myeloma epidemiology and survival, a unique malignancy // Semin Oncol. 2016 Dec; 43(6): 676–681.

[2] Anderson K.C., Alsina M., Atanackovic D. et al. NCCN Guidelines insights: Multiple myeloma // J. Natl. Compr. Canc. Netw., 2016, v.14, (4), p.389–400.

[3] I M Ghobrial [1], A Dispenzieri, K L Bundy, D A Gastineau, S V Rajkumar at all, Effect of thalidomide on stem cell collection and engraftment in patients with multiple myeloma**,** Bone Marrow Transplant2003 Sep;32(6):587-92.

neuropathy and other factors on the mobilization and accumulation of autologous PSC during MM.[4] However, the effects of other concomitant diseases (diabetes, arterial hypertension) and new drugs on the mobilization and accumulation of APSC along with these factors have not yet been studied in detail. Thus, it can be concluded that the application of newly discovered drugs in the treatment of MM each year, improvement of techniques for the collection of peripheral stem cells and the study of factors affecting their mobilization, as well as standard treatment APSC transplantation application after after high-dose chemotherapy remains a very urgent problem in our country, as well as around the world.

The purpose of the work. To study the factors influencing the mobilization and accumulation of autologous peripheral stem cells after radiation and primary chemotherapy, as well as the optimize the mobilization regimen of peripheral stem cells and treatment tactics in multiple myeloma.

Research objectives. 1. To study the influence of the types of immunoglobulins of multiple myeloma, protein chains, genetic mutations on the course of the disease and the collection of peripheral stem cells in our country;

2. To determine the effect of different types of primary chemotherapy on the course of multiple myeloma and the collection of peripheral stem cells;

3. To study the effect of comorbidities such as diabetes and hypertension on the course of multiple myeloma and collection of autologous stem cells;

4. To study the effect of new drugs (Velcade, Thalidomide, Lenalidomide) on the collection of peripheral stem cells used in the treatment of multiple myeloma;

[4] M. Beksaç, O. İlhan, G. Gurman ve ark. Multiple Myeloma olgularında, çevre kanından hematopoietik kök hücre toplanmasında olumsuz rol oynayan iki etken: tanıdakı sitopeni ve eşlik eden diyabetes mellitus varlığı. Turkish J of Hematology, 2014; abst/ 0696; SS-059; p51-52.

5. Develop an algorithm for more effective treatment tactics based on the obtained results.

Scientific novelty. The incidence of MM in Azerbaijan has been studied taking into account the types of immunoglobulins and protein chains, clinical and immunological characteristics, genetic mutations and their influence on the course of the disease.

The influence of genetic translocations on the collection of stem cells and the effectiveness of treatment has been determined.

The effect of concomitant diseases such as diabetes mellitus (DM) and arterial hypertension (AH) on the clinical course of MM and the collection of APSCs was studied.

An algorithm has been developed for the most effective treatment tactics for MM, taking into account various options for primary chemotherapy (CT), as well as concomitant diseases.

Scientific and practical value. The results of the study established the undoubted influence of concomitant diseases and other factors affecting the accumulation of a sufficient number of stem cells for high-dose chemotherapy.

• The development of effective individual treatment protocols, taking into account the comorbidities of multiple myeloma cases, is of critical practical importance in the development of optimal treatment tactics.

• The results of the study have of great scientific and practical importance for the introduction into practice of hematological and oncological examinations of patients with MM, as well as for the development of appropriate teaching aids.

Publications on the dissertation. On the topic of the dissertation, 10 publications were published, recommended by the Supreme Attestation Commission of the Republic of Azerbaijan for the defense of dissertation research.

Lenght and structure of the dissertation. The dissertation consists of 135 pages, introduction, literature review, research materials and methods, the author's own research, chapters on

discussion of results, results, practical recommendations and bibliography. The dissertation is described in 7 figures and 22 tables using 206 sources.

MATERIALS AND METHODS OF RESEARCH

The research work was carried out in 2012-2018 in the Hematology department of the Educational-Therapeutic Clinic of the Azerbaijan Medical University, the Central Clinic and the Hematology department of the Medical Faculty (MFAU) of Ankara University. On the eve of the study, 101 patients were examined in Azerbaijan, and 138 patients were treated in the Hematology and bone marrow transplantation departments of MFAU.

Biochemical analyzes were performed in the examined patients to diagnose the disease, assess the activity of one or another organ, etc., as well as to detect changes characteristic of myeloma.

Clinical and laboratory methods of examination. General and biochemical blood test. Clinical parameters for HDC and subsequent APSCT: patient's age, gender, time since the initial diagnosis according to Salmon-Dury criteria, stage of the disease, type of monoclonal protein, previous (inductive and mobilizing) treatment, results of TAPSC, patient's condition before APSC transplantation, number of transplants CD34 + cells, indicators of hematological changes, concomitant conditions and toxic effects of treatment.

Myelogram (trephine- biopsy) - is the examination of the structural features of bone marrow cells.

Immunophenotyping - flow cytometry (FCM). Multiparametric immunophenotyping was performed with monoclonal antibodies against CD56, CD19, CD138 (CD38) and CD45. Each monoclonal antibody with a specific fluorochrome - anti-CD56 with isothiocyanate (FITC); anti-CD19 with phycoectrin (PE); anti-CD138 with peridine chlorophyll protein (PerCP); PerCP was combined with conjugated anti-CD38, and allophycocyanin (APC) with anti-CD45 (BD Pharmingen ™, BD Horizon ™ San Jose, USA).

. The collected 50,000 events (number of nucleated cells) were analyzed on a FACS Canto II cytometer (BD Bioscience, San Jose, CA, USA). Plasma cells were isolated in the skatergram window for lateral light distribution with the CD138 marker, and then CD56, CD19, and CD45 were identified in the CD138 + (positive) cell population.

If both neoplastic and reactive plasma cells are detected at the same time, CD138 (+) / CD56 (-) or (+) / CD19 (-) / CD45 (-) are assigned to the tumor cells. Reactive plasma cells are CD138 (+) / CD56 (-) or (+) / CD19 (+) / CD45 (-).

The optimal number of stem cells (CD34 +) for a single transplant is 4-55x10^6 cells / kg, and the minimum number for bone marrow retention is 2.5x106 cells / kg.[5]

Stem cell apheresis (collection). The apheresis procedure is performed on Therumo BCT (Japan) devices after proper preparation of the patient. The patient is injected with GSF (neupogen) 5mg \ kg 5 days sub-cutaneous in combination with chemotherapy or alone as a preparation regimen for stem cell mobilization. On days 3-5, the number of stem cells (CD34 +) in the peripheral blood is examined. When appropriate, the patient is connected to the apheresis device.[6] The apheresis procedure lasts 2-3 hours. If the patient collects stem cells for 2 autotransplants at a time, it is good, 2-3 times is enough, 2-3 procedures are collected for 1 time for transplantation is less, if 1 time is collected, it is considered a failed collection.

Abbott with the Vysis-Abbott protocol, fluorescence in-situ hybridization (FISH). Vysis Abbott ready-made commercial test kits: 13q34, CCND1 / CEP, IGH / CCND1, IGH / CCND1, IGH / FGFR3, IGH / MAF, 13 (13q14), 13 (13q14), 13q34, CCND1 (11q13), D13. 3), D13S319 (13q14.3), IGH Break Apart, IGH / BCL2 Dual Fusion Translocation, IGH / CCND1 Dual Fusion Translocation, IGH / FGFR3 Dual Fusion, IGH / MAF Dual Fusion, MDM2, TP53 (17p13.1) (Abbott molecular, USA).

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[5] Demirer T, Buckner CD, Gooley T, Appelbaum FR, Rowley S, Chauncey T, Lilleby K, Storb R, Bensinger WI. Factors influencing collection of peripheral blood stem cells in patients with multiple myeloma. Bone Marrow Transplant 1996;17(6):937-941.

[6] Kristina Hölig ,Michael Kramer ,Frank Kroschinsky at all , Safety and efficacy of hematopoietic stem cell collection from mobilized peripheral blood in unrelated volunteers: 12 years of single-center experience in 3928 donors, Blood *(2009)* 114 (18): 3757–3763.

.The analytical phase and evaluation are performed under a fluorescent microscope (Nikon, with epi-fluorescence illuminator, Japan).

Instrumental examination methods. X-ray examination allows to detect signs of focal or diffuse osteoporosis. It should be noted that contrast agents should not be used during radiography. Thus, iodine in contrast agents forms insoluble complexes with proteins synthesized by myeloma cells, which severely damage the kidneys and lead to acute renal failure.

With the help of spiral CT, foci of fractures in the bones, tumors of soft tissues, deformations of the bones and vertebrae were identified. In general, computed tomography can identify foci of bone damage and assess the prevalence of myeloma.

Methods of statistical processing of material. All results obtained during the study were statistically analyzed taking into account modern recommendations. The indicators in the groups are arranged in a series of variations, and the average value (M), standard error (m), minimum and maximum errors of these indicators are calculated for each variation series. The results obtained are shown in the tables in the form of $M \pm m$.

In addition, a correlation analysis was performed in the examination groups to determine the purity between the various indicators. For this purpose, the correlation coefficient was calculated and the Z-Fisher transformation was used to determine the accuracy of the obtained result. To evaluate the quantity Z, the coefficient t_z was determined.

The obtained t_z coefficient was evaluated in the Student's t-criteria table by comparing the corresponding boundary values of the n-2 degree of causality with the statistical validity of the dependence.

All calculations were performed in EXCEL spreadsheet, the results are summarized in tables and diagrams.

239 patients with multiple myeloma were treated in Azerbaijan and Turkey. According to the purpose of the study, patients were divided into the following groups according to the types of immunoglobulins and the type of light chains:

• Immunoglobulin A
• Immunoglobulin G
• Immunoglobulin D
• Mild chain disease
• Non-secretory

According to comorbidities, patients were divided into the following groups:

• Patients with diabetes
• Patients with arterial hypertension

Main evaluation criteria: Primary responses to CT of IgA and IgG patients will be assessed based on treatment response and relapse criteria by the International Myeloma Working Group.[7] The effect of different gene mutations (de1 13q, t (11; 16), t (4; 14), P53) on primary response to CT and stem cell accumulation during MM will be analyzed separately and comparatively.[8] Stem cell counting is planned by flow cytometry (FCM) and cytogenetic mutations by fluorescence in situ hybridization (FISH).[9]

Characteristics of patients included in the study

239 of the patients involved in clinical examination and treatment, 101 were examined in Azerbaijan and 138 in Turkey (Table 1).

The average age of 101 patients involved in clinical examination and treatment in Azerbaijan was 58.8 (min. 28 - max. 78). 57 of them are men and 44 are women. According to the purpose of the study, patients were divided according to the types of immunoglobulins and the type of light chains (Table 5).

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[7] Durie B.G., Harousseau JL., Miguel J.S. et al. International Myeloma Working Group. International uniform response criteria for multiple myeloma // Leukemia, 2006, vol. 20 p.1467-1473.

[8] Magrangeas F., Lode L., Wuilleme S., Genetic heterogeneity in multiple myeloma. Leukemia 2005;19(2):191-4

[9] Sezer O., Heider U., Zavrski I,. Possinger K. Differentiation of monoclonal gammopaty of undetermined significance and multiple myeloma using flow sytometric characteristics of plasma cells. //Hematologica 2001:86:837-843.

Table 1

Patients examined in Azerbaijan and Turkey

	Number	Percentage
Azerbaijan	101	42,3
Turkey	138	57,7
Total	239	100,0

The distribution of patients according to different criteria is given in the following tables (Table 2; 3; 4;).

Table 2

Gender distribution of patients

	Number	Percentage
Male	134	56,1
Female	105	43,9
Total	239	100,0

Table 3

Classification of patients with multiple myeloma according to types of immunoglobulins

Types of multiple myeloma	Number	Percentage
Immunoglobulin A	46	19,2
Immunoglobulin G	137	57,3
Light chain disease	52	21,8
Immunoglobulin D	1	0,4
Non-secretory	3	1,3
Total	239	100,0

Table 4

Distribution of patients with MM according to subtypes of immunoglobulins

		Number	Percentage
	Kappa	138	57,7
	Lamda	71	29,7
	Total	209	87,4
	Other	30	12,6
Total		239	100,0

Table 5

Distribution of myeloma patients by immunoglobulin types in Azerbaijan

Types of multiple myeloma	Number of patients	
Immunoglobulin A	19 (19%)	12 (63%) male
		7 (37%) female
Immunoglobulin G	61 (61%)	36 (58%) male
		25 (42%) female
Immunoglobulin D	1 (1%)	1 (100%) male
Light chain disease	16 (16%)	7 (44%) male
		9 (56%) female
No-secretory	3 (3%)	1 (26%) male
		2 (74%) female

As can be seen from Table 5, 61 out of 101 patients (61%) had immunoglobulin type G, 19 (19%) had immunoglobulin type A, 16 had light chain type (16%) and 3 (3%) had non-secretory type myeloma. Of the 61 IgG myeloma patients, 36 (58%) were male and 25 (42%) were female. In contrast to IgG-type myeloma, the number of men and women in 19 patients with IgA type myeloma was 12 (63%) and 7 (37%), respectively, and in mild chain disease the ratio

of men to women was 1: 1.3. In non-secretory myeloma, 1 of the 3 patients was male and 2 were female. In our study, only 1 person was diagnosed with IgD type myeloma.

RESULTS OF THE WORK

As can be seen from Table 6, approximately 80% of patients with both type A and G myeloma responded positively to treatment. In 26.3% of the IgA patients we treated and in 17.8% of the IgG patients, no change was observed or resistance to chemotherapy was noted. The results suggest that similar results were obtained regardless of the immunoglobulin variant when comparing the clinical course of IgA and IgG myeloma patients ($p<0.05$).

Table 6

Response to treatment of CM A and G immunoglobulin types

Conclusion	Immunoglobulin A	Immunoglobulin G
Perfect complete answer	2 (10,5%)	12 (19,3%)
Full answer	3 (15,8%)	10 (16,2%)
Very good partial answer	9 (47,4%)	29(46,7%)
Stable disease	3 (15,8%)	5 (8,1%)
Progressive disease	2 (10,5%)	6 (9,7%)

Given the importance of different genetic factors in the development of multiple myeloma, the response of patients with each gene mutation to treatment after initial chemotherapy in patients with the most common different gene mutations was analyzed separately and comparatively.

Of the 75 MM patients tested for Del 13g, 48 were negative and 27 were positive. There was no difference in response to treatment in these patients, regardless of whether the genetic test was negative or

positive. Thus, complete remission was diagnosed in 21.3% of patients, very good partial remission in 40%, partial remission in 34.7%, and stable disease or progressive disease in only 4%.

Table 7

Responses of patients with Del 13q to primary chemotherapy

Response to treatment		Del 13q		Total
		negative	Positive	
Complete remission	Number	10	6	16
	Percentage	20,8%	22,2%	21,3%
Very good partial remission	Number	20	10	30
	Percentage	41,7%	37,0%	40,0%
Partial remission	Number	17	9	26
	Percentage	35,4%	33,3%	34,7%
Stable disease	Number	1	1	2
	Percentage	2,1%	3,7%	2,7%
Progressive disease	Number	0	1	1
	Percentage	0,0%	3,7%	1,3%
Total	Number	48	27	75
	Percentage	100,0%	100,0%	100,0%

21 of the patients tested for t (11; 14) translocation, 20 had a negative result and 1 had a positive result. In these patients, there was no difference in response to treatment, regardless of whether the genetic test was negative or positive (p=0.055) Thus, complete remission was detected in 19% of patients, very good partial remission in 33.3%, partial remission in 42.9% and stable disease in only 4.8% (Table 8).

Table 8

The effect of t (11; 14) translocation on the course of treatment

Response to treatment		t(11;14)		Total
		negative	positive	
Complete remission	Number	4	0	4
	Percentge	20,0%	0,0%	19,0%
Very good partial remission	Number	6	1	7
	Percentge	30,0%	100,0%	33,3%
Partial remission	Number	9	0	9
	Percentge	45,0%	0,0%	42,9%
Stable disease	Number	1	0	1
	Percentge	5,0%	0,0%	4,8%
Total	Number	20	1	21
	Percentge	100,0%	100,0%	100,0%

33 people were tested for t (4; 14) translocation, and the results were negative in 26 of them and positive in 7 of them. The response to treatment in these patients was as follows: complete remission - 27.3%; very good partial remission - 30.3%; partial remission - 36.4%; stable disease - 6.1% (Table 9).

Table 9

Effect of t (4; 14) translocation in the course of treatment

Response to treatment		t(4;14)		Total
		negative	positive	
Complete remission	Number	8	1	9
	Percentage	30,8%	14,3%	27,3%
Very good partial remission	Number	8	2	10
	Percentage	30,8%	28,6%	30,3%
Partial remission	Number	10	2	12
	Percentage	38,5%	28,6%	36,4%
Stable disease	Number	0	2	2
	Percentage	0,0%	28,6%	6,1%

Total	Number	26	7	33
	Percentage	100,0%	100,0%	100,0%

P53 = 1 gene mutation were examined in 71 patients, of whom 55 had negative and 16 had positive results. In this group of patients complete remission was observed in 23.9%, very good partial remission in 32.4%, partial remission in 39.4% and stable disease in 4.2% of cases (Table 10).

Table 10

The effect of P53 = 1 gene mutation on the course of treatment

Response to treatment		P53=1 mutation		Total
		negative	Positive	
Complete remission	Number	13	4	17
	Percentage	23,6%	25,0%	23,9%
Very good partial remission	Number	17	6	23
	Percentage	30,9%	37,5%	32,4%
Partial remission	Number	23	5	28
	Percentage	41,8%	31,2%	39,4%
Stable disease	Number	2	1	3
	Percentage	3,6%	6,2%	4,2%
Total	Number	55	16	71
	Percentage	100,0%	100,0%	100,0%

A comparative analysis of the results of the response of patients divided according to the results of genetic testing showed that genetic mutations do not lead to different outcomes in the course of the disease. Thus, in all groups, regardless of genetic changes, there was no significant change in the percentage of patients who achieved complete remission, very good partial remission, partial remission and stable disease outcomes after initial chemotherapy. The slight differences seem to be due to the small number of patients in each subgroup. More research would shed light on our point.

Thus, changes in genotype in multiple myeloma do not play a role not only in their occurrence and prognosis, but also in the response to treatment of the disease.

In the next step, we examined the effect of each genetic factor on APSC accumulation, given that the response to treatment was the same after initial chemotherapy, regardless of the immunoglobulin type of the disease. For this purpose, the number of APSC collected by apheresis in patients with each genetic mutation was determined and the differences between them were compared. Depending on the number of APSC collected by apheresis, the results were divided into 3 subgroups and compared, with a less, sufficient and good.

In 25 patients with mutations in the Del 13q gene, APSC was collected by apheresis after HDC. At one time, 8 patients had low, 8 had adequate, and 9 had well-assessed APSC, which accounted for 32%, 32%, and 36%, respectively (Table 11).

Table 11

Effect of Del 13q on autologous peripheral stem cell accumulation

Number of APSC		Del 13q		Total
		negative	positive	
Less	Number	5	3	8
	Percentage	33,3%	30,0%	32,0%
Sufficient	Number	5	3	8
	Percentage	33,3%	30,0%	32,0%
Good	Number	5	4	9
	Percentage	33,3%	40,0%	36,0%
Total	Number	15	10	25
	Percentage	100,0%	100,0%	100,0%

The number of stem cells collected after high-dose chemotherapy in 12 patients with t (11; 14) translocation was estimated as follows (Table 12): less - in 4 people (33.3%); sufficient - in 4 people (33.3%); good - in 4 people (33.3%) (p=0.336).

Table 12

Effect of t (11; 14) translocation on autologous peripheral stem cell collection

Number of APSC		t(11;14)		Total
		negative	positive	
Less	Number	4	0	4
	Percentage	36,4%	0,0%	33,3%
Sufficient	Number	4	0	4
	Percentage	36,4%	0,0%	33,3%
Good	Number	3	1	4
	Percentage	27,3%	100,0%	33,3%
Total	Number	11	1	12
	Percentage	100,0%	100,0%	100,0%

The results of autologous stem cells collected by apheresis after high-dose chemotherapy in 18 patients with t (4; 14) translocation are shown in Table 13 (p=0.424).

Table 13

Effect of t (4; 14) translocation on autologous peripheral stem cell collection

Number of APSC		t(4;14)		Total
		negative	positive	
Less	Number	5	1	6
	Percentage	33,3%	33,3%	33,3%
Sufficient	Number	5	2	7
	Percentage	33,3%	66,7%	38,9%
Good	Number	5	0	5
	Percentage	33,3%	0,0%	27,8%
Total	Number	15	3	18
	Percentage	100,0%	100,0%	100,0%

As can be seen from the table, autologous peripheral stem cells collected by apheresis were identified low in 6 patients (33.3%) , sufficient in 7 patients (38.9%) and good in 5 patients (27.8%)($p<0.05$). Finally, in 37 patients with P53 = 1 gene mutation, the collection of autologous stem cells collected by apheresis after high-dose chemotherapy was as follows (Table 14): less - 40.5% (15 patients), sufficient - 27.0% (10 patients), good - 32.5% (12 patients).

Table 14

The effect of P53 = 1 gene mutation on the accumulation of autologous peripheral stem cells

Number of APSC		P53=1 mutation		Total
		negative	positive	
Less	Number	11	4	15
	Percentage	37,9%	50,0%	40,5%
Sufficient	Number	8	2	10
	Percentage	27,6%	25,0%	27,0%
Good	Number	10	2	12
	Percentage	34,5%	25,0%	32,4%
Total	Number	29	8	37
	Percentage	100,0%	100,0%	100,0%

Thus, in a large number of MM patients with individual genetic mutations, the number of autologous peripheral stem cells collected by apheresis after high-dose chemotherapy did not differ significantly.

Summarizing all the above, it can be concluded that changes in the genotype of patients during MM do not significantly affect the response of the disease to treatment after initial chemotherapy, as well as the accumulation of autologous peripheral stem cells collected by apheresis after high-dose chemotherapy.

Features of the clinical course of MM in diabetes

At present, it is estimated that approximately 8-18% of cancer patients are diagnosed with diabetes mellitus. [15]. In addition, there are

studies in the literature devoted to the fact that diabetes itself increases the risk of developing and worsening of cancer of many organs, including MM.[10] However, there are very few scientific studies in the literature on the occurrence of MM and diabetes in the same patient and their effect on each other's course, and the results are contradictory. Thus, Khan A.E. et al.[11] while claiming that these diseases are not interrelated, according to Chiu B.C.H. et al[12], high blood glucose levels increase the risk of death in patients with MM.

Thus, the fact that both pathological processes occur in the same patient remains an urgent problem in choosing the right treatment regimen with a detailed analysis of the factors influencing the course and prognosis of diabetes mellitus.

In mind with this, when researchers first diagnosed MM in the last 10 years, various new ideas began to emerge about how to begin treatment, taking into account the comorbidities. Thus, recently, extensive information has been collected on the choice of treatment regimens for new drugs used in the treatment of MM[13]. As a result of these studies, many decisive factors influencing the choice of the initial treatment scheme of MM were identified: [14]

- Age of the patient,
- Possibility of stem cell transplantation,
- Complications of multiple myeloma,

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[10] Wu W., Merriman K, Nabaah A. et al. The association of diabetes and anti-diabetic medications with clinical outcomes in multiple myeloma // Br J Cancer. 2014, 111(3), p.628–636.

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[13] Richardson PG, Mitsiades C, Schlossman R. et al. New drugs for myeloma // Oncologist. 2007, 12(6), p.664–689.

[14] Takemori N., Goro Imai G., Hoshino K. A novel combination of bortezomib, lenalidomide, and clarithromycin produced stringent complete response in refractory multiple myeloma complicated with diabetes mellitus – clinical significance and possible mechanisms: a case report J Med Case Rep. 2018; 12: 40.

• Comorbidities and their progression

• Proper control of blood sugar levels, especially in patients with diabetes, has a positive effect on the course and prognosis of the disease.

The above indicates that the mechanisms of action of drugs in the mobilization, accumulation and transplantation of APSC used in the treatment of diabetes mellitus and primary chemotherapy in MM patients with DM have not yet been studied in detail. The aim of this study was to investigate the effects of drugs used in the treatment of diabetes and primary chemotherapy on the course of the disease, as well as the accumulation of APSC in MM associated with diabetes, and to select the optimal treatment regimen. For this purpose, 16 patients with diabetes mellitus were examined at the hematology department of the Educational- Therapeutic Clinic of the Azerbaijan Medical University. The patients involved in the examination were divided into two groups. The first group included 16 MM patients with diabetes mellitus, and the second group included 84 patients with only MM.

Patients in the first group continued treatment of diabetes mellitus with insulin and other groups of anti-diabetic drugs beside chemotherpy. To confirm the diagnosis of the disease, blood tests showed the following results: calcium levels in the blood 8.92 ± 0.33 mg/dl, creatinine 2 ± 0.6 mg/dl, albumin 3.44 ± 0.2 U/ml, ß2-microglobulin 5.78 ± 1.41 qr/dl and lactate dehydrogenase 259 U/l , Was 4 ± 30.7 U/l. In the second group of patients, the biochemical parameters characteristic of MM were as follows: calcium level 7.65 ± 0.4 mg/dl, creatinine 1.6 ± 0.2 mg/dl, albumin 4.58 ± 0.29 U/ml, ß2-microglobulin 5 , 46 ± 0.51 qr/dl, lactate dehydrogenase 262.6 ± 20.7 U/l. Comparing the results obtained in both groups, it was found that there were no significant differences between them. The results of the general examination of the blood did not differ significantly from each other, and were characterized by cytopenia and increased erythrocyte sedimentation rate.

All patients received initial chemotherapy, taking into account the absence of contraindications by the cardiovascular system and

kidneys. The response to chemotherapy was as follows according to international criteria (Figure 1).

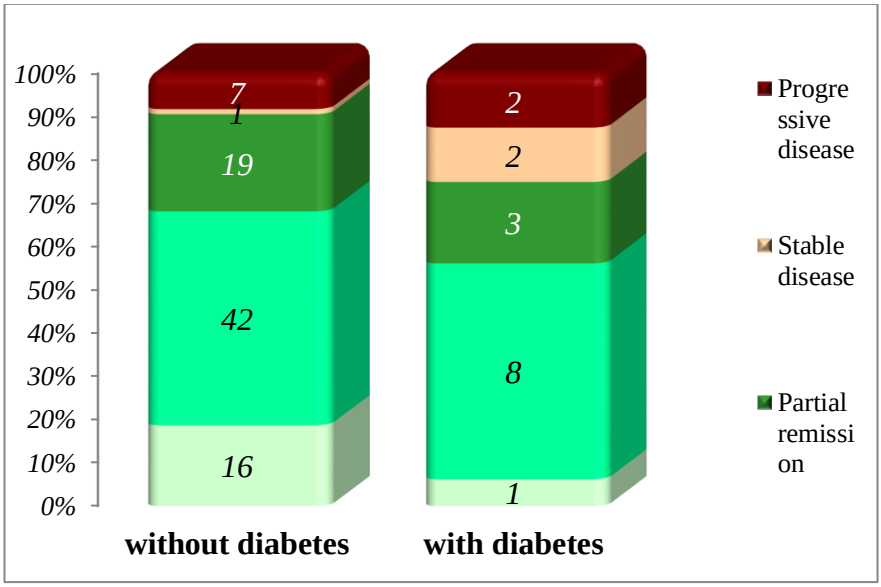

Figure 1. The effect of diabetes on the clinical course of multiple myeloma

An analysis of the results in both groups showed that in patients with long-term diabetes and insulin treatment, failure was observed in 2 patients with progressive disease and 2 patients with stable disease, which accounted for 25% of multiple myeloma patients with diabetes mellitus. Thus, taking into account the fact that 4 patients in this group had unsuccessful results after the initial chemotherapy, after several courses of chemotherapy, the patients received the status "plateau" and continued treatment with alkylating agents. These patients did not receive high-dose chemotherapy, so mobilization and collection for APSC did not been performed for them.

In 8 patients with MM without diabetes mellitus in the second group, progressive and stable disease results were obtained after initial chemotherapy, which is 9% of the total number of patients ($p<0.05$).

From the patients in this group, 16 had complete remission, 42 had very good partial remission, and 19 patients had partial remission, which is 91% of the total number of patients.

In patients with good results, APSC can be performed by apheresis after high-dose chemotherapy (Table 15).

Table 15

APSC in patients without AH or DM

Number of APSC		Gender		Total
		male	female	
Less	Number	12	10	22
	Percentage	34,3%	40,0%	36,7%
Sufficient	Number	10	3	13
	Percentage	28,6%	12,0%	21,7%
Good	Number	13	12	25
	Percentage	37,1%	48,0%	41,7%
Total	Number	35	25	60
	Percentage	100,0%	100,0%	100,0%

After initial chemotherapy, only 4 out of 12 diabetic patients with MM who had autologous peripheral stem cell collection by apheresis were able to collect enough stem cells for a single transplantation. In 7 of these patients, apheresis was required 2 times to collect enough APSC for one transplant, and in 1 person 3 times apheresis. It should be noted that none of these patients was able to accumulate enough stem cells twice.

Thus, in multiple myeloma associated with diabetes, both the response to treatment after initial chemotherapy and the number of APSC collected by apheresis are unsatisfactory compared to MM patients without diabetes.

In the treatment of diabetes, 12 out of 14 patients treated with other oral anti-diabetic drugs instead of insulin received a positive reaction after initial chemotherapy. In 10 of these patients, it was possible to collect enough ($2x10^6$ / kg) stem cells at a time for PSC transplantation after HDC.

Features of the clinical course of multiple myeloma in arterial hypertension

About 1/3 of patients admitted to the hospital with a diagnosis of MM have high blood pressure, which is twice as common in women as in men.[15]

In addition to the characteristic changes in the blood as a result of the disease in multiple myeloma, high blood pressure also leads to disruption of bleeding and coagulation processes. As a result, the structure and function of the heart are more deeply impaired, significantly affecting the clinical picture, course and prognosis of the underlying disease. If we take into account that the structural and functional disorders of the heart during MM are observed even in the absence of any concomitant disease, then the urgency of this problem becomes even clearer.[16]

101 patients with MM were involved in the examination and they were divided into 2 groups. The first group included 88 patients diagnosed with MM based on the criteria of M. Durie, S.E.Salmon, and the second group included 13 patients with arterial hypertension along with MM. Patients in the examined groups were matched according to age and gender.

The diagnosis of arterial hypertension was made on the basis of criteria developed on the basis of the recommendations of the Russian Society of Cardiologists.[17]

Echocardiographic examination in M- and B-mode was performed in all patients selected for initial chemotherapy to detect structural and functional changes in the heart after the diagnosis of MM.

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The echocardiographic parameters of the observed patients are shown in Table 16.

Table 16

Echocardiographic parameters of patients in the examined groups

Indicators	I group (MM) n = 88	II group (MM+AH) n = 13
LVDmm	54,4 ± 0,06	57,0 ± 0,06
LVS mm	36,3 ± 0,05	37,9 ± 0,06
TPLVmm	10,9 ± 0,02	11,2 ± 0,03
IVS	13 ± 0,02	14,2 ± 0,03
SMMK, q	281,2 ± 4,5	302,5 ± 6,5
LDV, ml	144,6 ± 3,8	151,1 ± 5,2
LSV, ml	55,7 ± 2,9	59,3 ± 3,7
SV	80,3 ± 2,5	77,6 ± 3,4
AF, %	58,9 ± 1,2	57,9 ± 1,5
%ΔS, %	31,8 ± 0,9	30,7 ± 0,8

As can be seen from the table, there was no significant difference in parameters studied between the groups. This can be explained, on the one hand, by the presence of such structural and functional changes in the cardiovascular system of MM patients even without arterial pressure, and, on the other hand, to the fact that patients receive certain chemotherapy before examination. At the same time, it should be noted that the number of patients involved in the examination is small, and patients with a progressive course were not included in these groups.

Thus, the dynamic observation of MM patients with arterial hypertension with a comprehensive examination, including echocardiography, allows detection of left ventricular dysfunction in these patients. Both groups were compared to investigate the effect of arterial hypertension on primary chemotherapy during MM in these patients (Table 17).

Table 17

Treatment response of multiple myeloma associated with arterial hypertension

Response to treatment		Arterial hypertension		Total
		no	yes	
Complete remission	Number	16	1	17
	Percentage	18,2%	7,7%	16,8%
Very good partial remission	Number	42	8	50
	Percentage	47,7%	61,5%	49,5%
Partial remission	Number	20	2	22
	Percentage	22,7%	15,4%	21,8%
Stable disease	Number	2	1	3
	Percentage	2,3%	7,7%	3,0%
Progressive disease	Number	8	1	9
	Percentage	9,1%	7,7%	8,9%
Total	Number	88	13	101
	Percentage	100,0%	100,0%	100,0%

As can be seen from the table, complete remission was achieved only in 1 (7.7%) MM patient with arterial hypertension, while complete remission was achieved in 16 (18.2%) patients with MM. In other responses, there was no significant difference in percentage. Progressive diseases were the same in both groups. 1 (7.7%) of patients with MM accompanied by AH and 8 (9.1%) of non-AH patients did not receive high-dose chemotherapy due to progressive disease as a result of primary chemotherapy (Figure 2) and APSC collection was not performed ($p<0.05$).

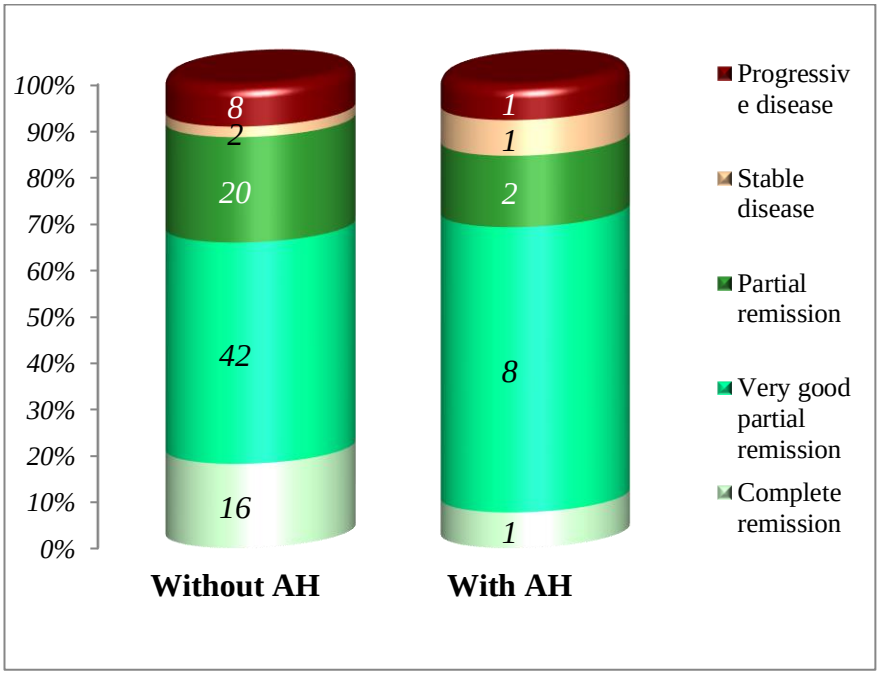

Figure 2. Comparison of response to treatment in MM patients with and without arterial hypertension

After the initial chemotherapy, among 12 MM patients with AH who had successful results it was possible to collect a sufficient number of stem cells for a single transplant by apheresis in 6 patients. In 4 of the remaining patients, it was possible to collect a sufficient number of stem cells once by applying apheresis 2 times, in 2 patient 3 times. It was not possible to collect enough stem cells for 2 time use from any of these patients as from diabetics.

Thus, although responses to treatment after primary chemotherapy in MM patients with AH differed little from those in patients with MM only, there was a significant difference in the number of autologous peripheral stem cells collected by apheresis after initial chemotherapy.

Summarizing the above, it can be concluded that although the arterial hypertension itself and the drugs used in its treatment did not

significantly affect the response to the initial chemotherapy of the underlying disease, the number of APSC accumulated after high-dose chemotherapy significantly reduces.

When we analyzed the results, it was found that MM in a patient with hypertension may develop as a separate nosological form with age, or as a complication of the underlying disease. In addition, according to Kistler and co-authors, primary chemotherapy and other drugs used in the treatment of MM also cause hypertension.According to another group of authors, hypertension during MM can develop both unrelated to the disease and as a complication of the treatment of the disease. It should be noted that renal failure is an unsatisfactory prognostic factor in such cases, because renal dysfunction occurs in both cases as a result of the complication of MM and due to the hypertension.

At the same time, in patients with arterial hypertension accompanied by CM, in the absence of complications in other organs, as in other patients, primary chemotherapy is performed and autologous peripheral stem cell transplantation is possible.

Taking into account all the above, an algorithm for the treatment of myeloma has been developed in accordance with international protocols. According to the algorithm, patients with MM are divided into two groups after diagnosis: candidates for ASCT and patients who are not undergoing ASCT. Patients who are candidates for the ASCT are divided into two subgroups: those with co-morbidities and those without. Our attention is attracted by those who have co-morbidities, in the treatment of which it is necessary to take into account the points mentioned above and in the practical recommendations.

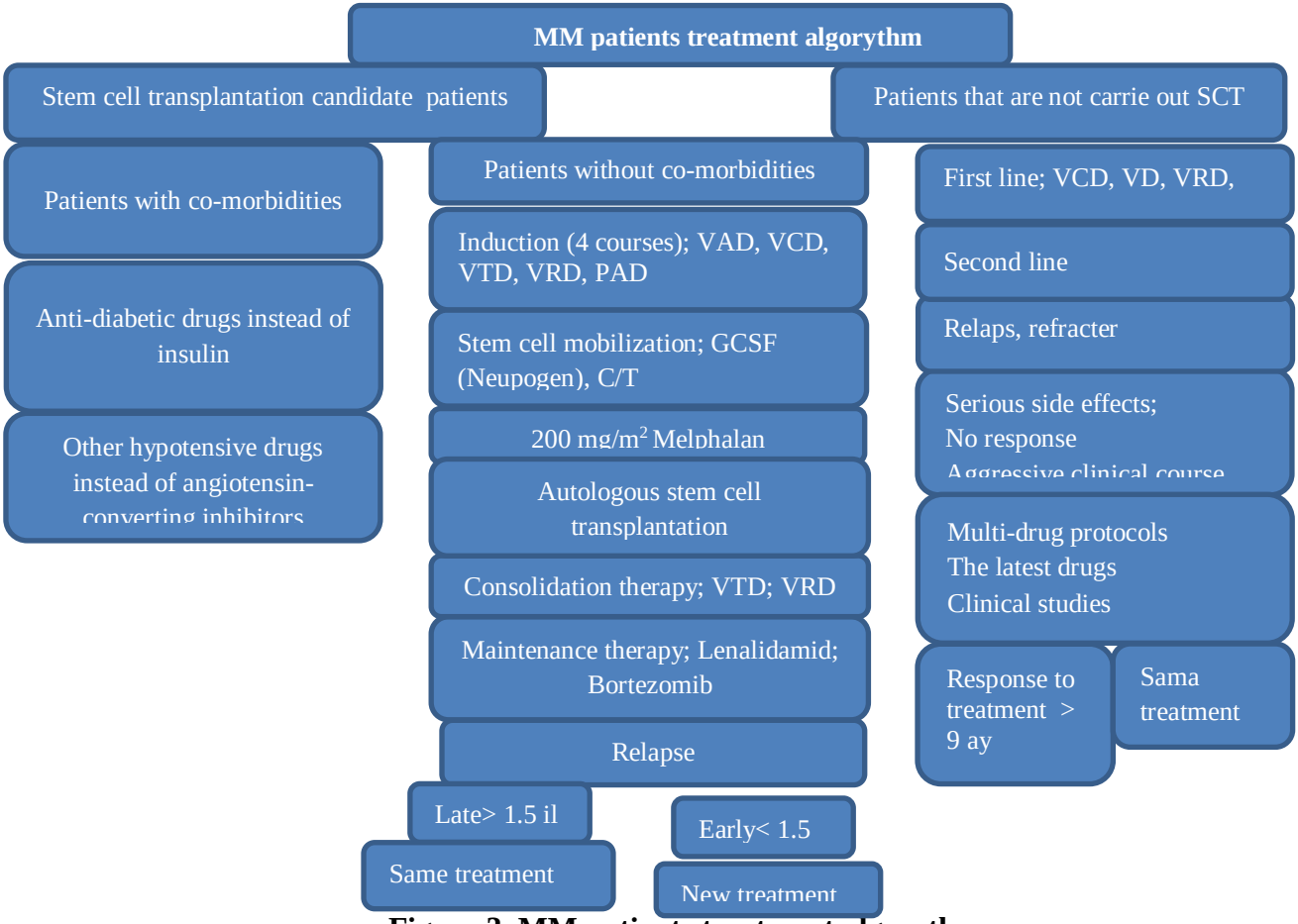

Figure 3. MM patients treatment algorythm

CONCLUSION

1. 61% of myelomas in Azerbaijan are IgG and 17% are IgA myeloma, and the number of men is relatively high (1.3:1). In contrast, the number of men with light chain disease (16%) was half that of women. IgD and non-secretory myeloma are rare and together account for only 4% of the total number of patients. IgE type of myeloma was not detected in any of the examined patients.
2. It was found that the immunochemical types and subtypes of multiple myeloma do not significantly affect the clinical course of the disease and the collection of autologous peripheral stem cells, while the high ratio of heavy and light chains of pathological immunoglobulins after primary chemotherapy can be considered as an indicator of more frequent relapses of the disease.
3. Although genetic mutations - del 13q, t (11; 16), t (4; 14), P53- in multiple myeloma affect the course and prognosis of disease, they do not affect the accumulation of autologous peripheral stem cells.
4. In diabetes mellitus with multiple myeloma, both the response to treatment after initial chemotherapy and the number of autologous stem cells collected by apheresis are unsatisfactory compared to MM patients without diabetes.
5. Although the response to treatment after primary chemotherapy in MM patients with arterial hypertension is slightly different from MM patients without arterial hypertension, there is a significant decrease in the number of autologous peripheral stem cells collected by apheresis after initial chemotherapy.
6. Based on the results obtained, an algorithm for the treatment of myeloma was developed in accordance with international standards.

PRACTICAL RECOMMENDATIONS

1. Patients with multiple myeloma and diabetes mellitus are advised to use oral antidiabetic drugs rather than insulin to regulate blood sugar levels before initial chemotherapy and autologous peripheral stem cell accumulation.
2. Patients with multiple myeloma and arterial hypertension without functional insufficiency of the cardiovascular system have no contraindications to primary chemotherapy. In this case, it is recommended to stop taking angiotensin-converting enzyme inhibitors to control blood pressure before chemotherapy and to use other antihypertensive drugs.

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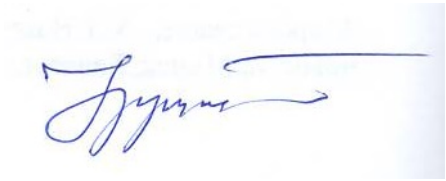
LIST OF ABBREVIATIONS

APKH- autologous peripheral stem cells
AH-arterial hypertension
ACF - enzymes that convert angiotensin
BCR-B cell receptor
Ig- immunoglobulin
OS- lifespan
RFS - life expectancy without relapse
MGUS-monoclonal gammopathy of unknown nature
MBWQ - International Working Group on Myeloma
MGD (MRD) - minimal residual disease
CM - multiple myeloma
SMM-smoldering (incandescent) multiple myeloma
SD - diabetes mellitus
QKSEF - granulocyte colony stimulating factor
PCLI - plasma cell marking index
PH- plasma cell
PKH - peripheral stem cells
PET-positron emission tomography
PKHT - peripheral stem cell transplantation
YDKT- high-dose chemotherapy
CT - computed tomography



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