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Results of Autologous Hematopoietic Stem Cell Transplantation in Patients with Multiple Myeloma (MM) and Renal Impairment: A Retrospective Single-Center Study

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ABSTRACT

Background: To assess the efficacy of autologous hematopoietic stem cell transplantation (auto-HSCT) in multiple myeloma (MM) patients with acute renal failure.

Materials and Methods: A retrospective single-center study included 64 patients (30 men, 34 women) with MM and kidney damage at the onset of the disease, aged 19 to 65 years (median 54), who underwent auto-HSCT from 2013 to 2019. 23 patients (36%) were dialysis-dependent at the time of diagnosis. The analysis was carried out in two groups: the "HD-" group (patients who were independent of hemodialysis during auto-HSCT, n = 54), and the "HD +" group (patients who underwent auto-HSCT while treated with programmed hemodialysis, n = 10). Research results were statistically processed using the Statistica software (version 10.0); the data obtained were presented graphically. Statistical analysis was performed using survival analysis (using the Kaplan-Meier method, with a Log-Rank Test) and frequency analysis (using contingency tables and Fisher's test).

Results: The patients dependent on hemodialysis were significantly more likely to require red blood cell transfusions compared to the dialysis-independent patients (100% versus 35%, p = 0.0001). Reactivation of a herpes viral infection and reversible toxic encephalopathy developed significantly more often in the patients from the "HD +" group compared with the patients from the "HD-" group (30% versus 6%, p = 0.04 and 20% versus 0%, p = 0.02, respectively). As a result of the treatment (induction + auto-HSCT), 14 patients (61%) became hemodialysis-independent. There was no transplant-related mortality. With a median follow-up of 48 months, the 5-year overall survival (OS) and progression-free survival (PFS) were 70% and 42%, respectively.

Conclusion: Auto-HSCT is a safe and effective treatment for patients with MM complicated by acute kidney injury. Fourteen of 23 (61%) patients became dialysis-independent.

Keywords: Multiple myeloma; Autologous Hematopoietic Stem Cell Transplantation (Auto-HSCT); Hemodialysis; Acute kidney injury; Cast nephropathy; Renal response

INTRODUCTION

One of the most important manifestations of symptomatic MM is specific kidney damage, which occurs in 20-50% of cases according to different authors[1,2]. Severe kidney damage with loss of function and the need for renal replacement therapy is observed in 5-9% of patients [3,4]. According to the Russian registry, at the time of diagnosis of MM, 22% of patients showed a decrease in GFR of less than 40 ml/min/m^2, and 23% of patients required renal

replacement therapy[5]. The main cause of renal damage in MM is the toxic effect of monoclonal immunoglobulin light chains on the basement membrane of the renal tubules. Acute kidney damage in more than 50% of cases is due to myeloma cast nephropathy. Myeloma cast nephropathy develops when the production of light chains (LC) exceeds the capability of tubular cells for endocytosis and catabolism. Cast nephropathy is a potentially reversible condition. One of the clinical predictors of the reversibility of renal damage is the achievement of an antitumor response. The severity of morphological changes in the kidney is also the most important prognostic factor for the restoration of its function. In their work, Russian researchers have shown that with severe fibrosis of the tubular interstitium, even if an antitumor response is achieved, the probability of reversibility of renal damage is extremely low[6].

Previously, patients with severe kidney damage were not considered as candidates for high-dose chemotherapy followed by auto-HSCT. However, in later studies, it was shown that high-dose chemotherapy followed by auto-HSCT in some cases helps to restore renal function. In 2016, the International Myeloma Working Group (IMWG) developed recommendations for the diagnosis and treatment of patients with MM complicated by kidney damage[1]. The medical community is still wary of high-dose chemotherapy with subsequent auto-transplantation in MM patients with severe kidney damage. We have previously reported on the safety and efficacy of auto-HSCT in patients on hemodialysis[7]. This article presented our 7-year experience in performing auto-HSCT in MM patients with varying degrees of renal damage. The aim of this work was to study the clinical efficacy and safety of high-dose chemotherapy with subsequent auto-HSCT in MM patients with acute kidney injury, including those who require hemodialysis.

MTERIALS AND METHODS

The retrospective single-center study included 64 patients (30 men, 34 women) with MM, occurring with kidney damage at the onset of the disease, aged 19 to 65 years (median - 54), who underwent auto-HSCT from 2013 to 2019. Diagnosis was made in accordance with the criteria of IMWG 2014[8]. Table 1 presented the clinical characteristics of the patients.

Overall characteristics of the patients

All patients excreted Bence-Jones protein, while half of the patients (53%) secreted only free light chains (FLC) of immunoglobulin in the serum, 28% of patients also had paraprotein G secretion, 14% of patients had paraprotein A secretion, in isolated cases, the secretion of paraprotein D and M was observed. Approximately an equal number of patients had both κ-FLC and λ-FLC of immunoglobulin. Most patients were stage III according to the generally accepted classifications (Durie-Salmon, ISS and R-ISS). One of the main criteria for inclusion in the study was an increase in the serum creatinine above 177 μmol/L at the onset of MM. The median of creatinine level at the time of diagnosis was 462 μmol/L. Glomerular filtration rate (GFR) was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula. At the onset of MM, the GFR values varied from 1 to 37 ml/min (the median - 10). Renal replacement therapy was required in 36% of patients (n = 23). Median time from the start of HD to the start of induction therapy was 23 days.

The therapy and response to treatment

All patients underwent induction therapy with bortezomib-containing regimens. Due to insufficient antitumor response, the 2nd line of therapy with the use of immunomodulators was performed in 20% of cases, the 3rd line of therapy was required for 3% of patients.

Antitumor and renal responses were assessed according to the IMWG criteria [9,10]. Before the auto-HSCT, complete response (CR) was achieved in 45% of patients, very good partial response (VGPR) - in 36% of patients, partial response (PR) - in 10% of patients, stabilization was noted in 6% of cases, progression - in 3% of patients. Renal response to auto-HSCT was achieved in 80% of patients, with complete renal response (CR) in 28% of patients, partial renal response (PR) in 18% of patients, minor renal response (MR) in 34% of patients. In 20% of patients, no renal response was observed upon completion of induction therapy. As a result of

induction therapy, 13 of 23 patients (57%) managed to stop HD. Auto-transplantation in patients with renal replacement therapy was performed in 10 cases. In most patients, hematopoietic stem cells (HSC) mobilization was performed once (94% of patients); in 6% of cases, a repeated cell mobilization procedure was required. In 77% of patients, HSC mobilization was carried out according to the scheme: cyclophosphamide + G-CSF; in 17% of cases, G-CSF was performed in monotherapy. In the case of first ineffective mobilization, the repeated procedure was carried out with the use of plerixaphor. The number of harvested HSCs varied from 1.94 to 33.5 × 10^9 CD34+ cells/kg (median - 7.15 × 10^9 / kg CD34). Pre-transplant conditioning with melphalan at a dose of 200 mg / m^2 was carried out in 80% of patients. A decrease in the dose of melphalan to 140 mg / m^2 was required in 20% of cases due to severe kidney damage. Single transplantation was performed in 73% of patients (n = 47), tandem auto-HSCT was performed in 27% of patients (n = 17).

Assessment of antitumor and renal responses was carried out at control periods (+ 100 days and + 1 year of auto-HSCT).

Table 1: Clinical characteristics of the MM patients with renal impairment

Parameters	Patients with MM n=64
Age	54 (19-65)
Sex (m/f)	30/34
Type of secretion	
A	9 (14%)
G	18 (28%)
D	2 (3%)
M	1 (2%)
Only FLC	34 (53%)
Bence-Jones excretion	64
Type of FLC	
κ	35
λ	29
D-S stage	
II	10 (16%)
III	54 (84%)
ISS stage	
I	1 (2%)
II	5 (8%)
III	47 (73%)
Not available	11 (17%)
R-ISS stage	
II	5 (8%)
III	34 (53%)
Not available	25 (39%)
Hemoglobin (g/l), median (references)	85 (50-118)
LDH (U/l), median (references)	423 (96-1800)
Not available	20
β 2- microglobulin	
<5,5 mg/l	4
>5,5 mg/l	51
Not available	9
Cytogenetic testing	
Done	23 (36%)
Creatinine (μmol/L), median (references)	462 (178-2435)
GFR, ml/min/1,73m^2 (CKD-EPI)	10 (1-37)
% plasma cells in bone marrow aspiration, median (references)	36% (1-92)
Median time from the start of hemodialysis (HD) to the start of induction therapy, median (references) (days)	23 (0-72)
Hemodialysis	23 (36%)

Statistical analysis

Analysis was carried out in two groups: the "HD –" group (patients who were independent of programmed hemodialysis during auto-HSCT, n = 54), and the “HD +” group (patients who underwent auto-HSCT while treated with programmed hemodialysis, n = 10).

Research results were statistically processed using the Statistica software (version 10.0); the data obtained were presented graphically. Statistical analysis was performed using survival analysis (using the Kaplan-Meier method, with a Log-Rank Test) and frequency analysis (using contingency tables and Fisher's test).

RESULTS

The characteristics of patients

Table 2 shows the clinical and laboratory characteristics of the patients depending on the need for dialysis during auto-HSCT. Two or more lines of therapy were more often required by patients from the “HD-” group compared with patients from the “HD +” group. Despite the achievement of a rapid antitumor response in the majority of dialysis-dependent patients, a renal response has not been obtained. Patients from the “HD +” group more often required repeated HSC mobilization compared to patients from the “HD-” group (20% versus 4%). The median number of harvested HSCs was two times lower in dialysis-dependent patients compared with patients without the need for dialysis (3.83 versus 7.4 × 106 / kg CD34 + cells). Due to severe kidney damage in most patients from the "HD +" group, the dose of melphalan was reduced to 140 mg/m^2. In the “HD-” group, the dose reduction of melphalan was performed in 8% of patients for a similar reason. Tandem auto-HSCT was performed in one third of patients from the “HD-” group and only one patient from the “HD +” group due to the limited number of harvested cells.

The complications after auto-HSCT

We have analyzed the frequency and spectrum of complications in the early post-transplant period in patients from the “HD +” and “HD-” groups (Table 3). As can be seen from the Table, the reactivation of the herpes-viral infection developed significantly more often in patients from the “HD +” group compared to patients from the “HD-” group (30% versus 6%, p = 0.04). Patients of both subgroups had severe mucositis (III-IV grade) with the same frequency. There was a tendency for the frequent development of such infectious complications as pneumonia and septicemia in patients dependent on dialysis during auto-HSCT. Most patients were treated with antibiotics in the early post-transplant period. The need to escalate antimicrobial therapy was noted somewhat more often in the group of patients receiving HD than in patients without HD (70% versus 52%, although the differences are unreliable).

Table 2. The clinical and laboratory characteristics of patients depending on the need for renal replacement therapy during auto-HSCT

Characteristics	Patients who were independent of HD during auto-HSCT (n=54)	Patients who underwent auto-HSCT while treated with HD (n=10)
Age, years	52,7 (19-65)	57 (39-65)
Sex, m/f	28/26	2/8
Type of FLC		
κ	30 (56%)	5 (50%)
λ	24 (44%)	5 (50%)
Creatinine (μmol/L), median (references)	133 (33-450)	740 (475-1029)
GFR, ml/min/1,73m^2 (CKD-EPI), median (references)	47 (9-116)	5 (3-9)
Induction therapy		
1st line of therapy	40 (74%)	9 (90%)
≥2nd line of therapy	14 (26%)	1 (10%)
Median time from the start of induction therapy to auto-HSCT, median (references) (days)	350 (151-751)	314 (164-830)
Response before auto-HSCT		
CR	46%	40%
VGPR	35%	60%
PR	10%	-
Stabilization	6%	-
Progression	3%	-
Number of HSC mobilization		
1	52 (96%)	8 (80%)
2	2 (4%)	2 (20%)
Number of harvested HSCs	7,4 (2,5-33,5)	3,83 (1,94-6,83)
Dose of melphalan		
140 mg/m^2	4 (8%)	9 (90%)
200 mg/m^2	50 (92%)	1 (10%)
Tandem auto-HSCT	16 (30%)	1 (10%)
Maintenance therapy	30 (56%)	4 (40%)

Table 3: Characteristic of complications in the early post-transplant period in patients from the "HD +" and "HD-" groups

Characteristics		Patients who were independent of HD during auto-HSCT (n=54)	Patients who underwent auto-HSCT while treated with HD (n=10)	p
Complications in the early post-transplant period	Mucositis 3-4 deg.	19 (35%)	3 (30%)	1
	Pneumonia	8 (15%)	4 (40%)	0,08
	Septicemia	9 (17%)	4 (40%)	0,19
	Herpes viral infection	3 (6%)	3 (30%)	0,04
	Antibiotics were not used	3 (6%)	0	1
	≥2 lines of antibacterial therapy	28 (52%)	7 (70%)	0,3
	Encephalopathy	0	2 (20%)	0,02
	Heart attack	0	1 (10%)	0,16
	Cardiac arrhythmias	3 (6%)	1 (10%)	0,5
Timing of recovery of blood cell counts	Recovery of white blood cells >1 × 10^9 / L, day after auto-HSCT, median (references)	14 (10-52)	13 (10-21)	
	Recovery of platelets >50×10^9/л, day after auto-HSCT, median (references)	15 (9-73)	13,5 (11-21)	
	Duration of myelotoxic agranulocytosis, days, median (references)	9 (6-18)	8,5 (7-11)	
Transfusion replacement therapy	Red blood cell transfusions	19 (35%)	10 (100%)	0,0001
	Therapeutic doses of red cell concentrate, median (references)	1 (1-5)	3 (1-5,2)	
	Thromboconcentrate transfusions	54 (100%)	10 (100%)	1
	Therapeutic doses of thromboconcentrate, median (references)	3,6 (1,2-20,9)	4,2 (2,5-14,1)	

Attention was drawn to the emergence of reversible encephalopathy in the early post-transplant period in dialysis-dependent patients. Clinically, toxic encephalopathy manifested itself in confusion, disorientation, impaired critical judgment, and developed significantly more often in patients from the "HD +" group in comparison with patients from the "HD –" group (20% versus 0%, p = 0.02).

Cardiovascular system complications were most often expressed in the development of various cardiac arrhythmias and occurred in patients of both subgroups in 6-10% of cases. The trigger mechanism for the development of arrhythmias was electrolyte disturbances that developed during the early post-transplant period.

Timely diagnosis, adequately selected treatment, careful monitoring of the main parameters of vital activity made it possible to prevent complications in all patients in the department; transfer to the intensive care unit was not required.

We drew attention to the fact that patients dependent on hemodialysis significantly more often require transfusion of red blood cells compared to dialysis-independent patients (100% of cases versus 35%, p = 0.0001). The median of the applied doses of red cell concentrate in the "HD +" group was 3 versus 1 in the "HD-" group. There was no such dependence in relation to thromboconcentrate transfusions - all patients of both subgroups required replacement transfusion therapy with apheresis platelets in similar amounts (median 3.6 and 4.2 therapeutic doses).

Recovery of blood cell counts was noted at a similar time in patients of both groups. Thus, the median time to increase the white blood cells >1 × 10^9 / L was 14 days for patients from the "HD –" group and 13 days for patients from the "HD +" group. The median time to increase the platelets >50 × 10^9/l was from 15 to 13.5 days, respectively.

The response to treatment

At the control time of the examination, 100 days after auto-HSCT, antitumor and renal responses were assessed. As shown in Figure 1, auto-HSCT enhanced the antitumor response. Thus, the achievement of a general antitumor response (CR + VGPR + PR) increased from 91 to 96%, the percentage of CR increased from 45% to 64%.

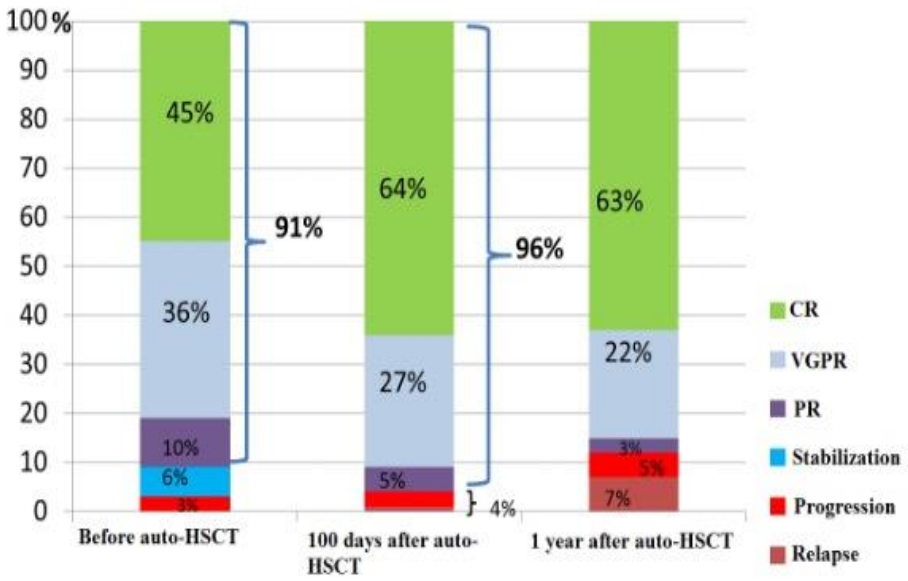

Figure 1. Antitumor response in MM patients before and after auto-HSCT

Additionally, the number of patients with VGPR and PR decreased - patients with this category of antitumor response moved to the group of complete remissions. In the case of performing auto-HSCT in the progression of the disease, no improvement in the antitumor response was observed. During the first year after auto-HSCT, four patients died. Two patients died due to progression of MM, one dialysis-dependent patient died at home with progressive cardiovascular failure, and in another case, death occurred from a different tumor. One year after transplantation, treatment results were assessed in 60 patients. CR was preserved in 63% of patients. Figure 2 shows the parameters of the renal response during treatment.

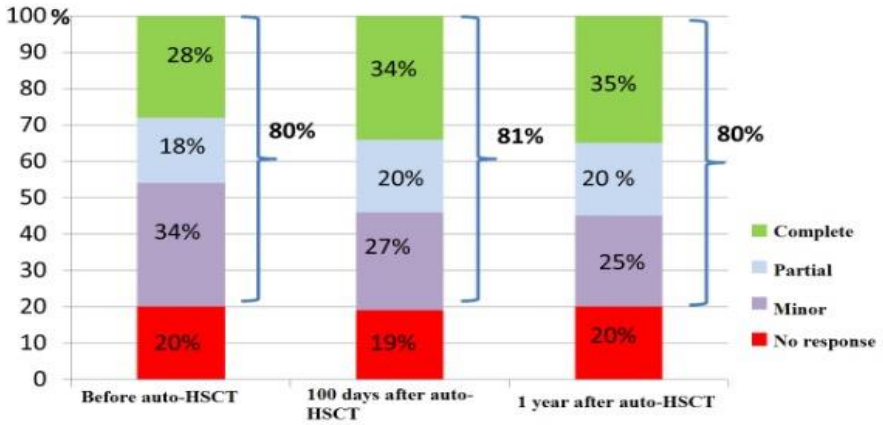

Figure 2. Renal response in MM patients before and after auto-HSCT

Thus, because of induction therapy, the achievement of complete renal response (CR), partial renal response (PR), minor renal response (MR) was recorded in 28%, 18%, 34% of patients, respectively. After auto-HSCT, there is an increase in the frequency of achieving complete renal responses - from 28% to 34%; however, the frequency of the general renal response (CR + PR + MR) did not change significantly and remained at 80%. In the early stages after transplantation, in one observation, achievement of a minor renal response made it possible to stop programmed hemodialysis. Therefore, at the onset of MM, 23 patients were dependent on renal replacement therapy. As a result of treatment (induction therapy followed by auto-HSCT), 14 of the patients (61%) became hemodialysis-independent. Observation of these patients lasted from 1.5 to 7 years, they did not resume HD. An interesting fact is that the parameters of the renal response achieved after auto-HSCT did not practically change when evaluated one year after transplantation. In patients who had not achieved a renal response after transplantation, there was no further improvement in renal function.

The dynamics of the changes in the functional state of the kidneys at different stages of treatment in patients with MM are presented in Figure 3. It is clearly shown that the most significant decrease is in creatinine and, accordingly, an increase in GFR occurs at the induction stage of treatment. High-dose melphalan also brings some positive changes, but they are no longer so significant.

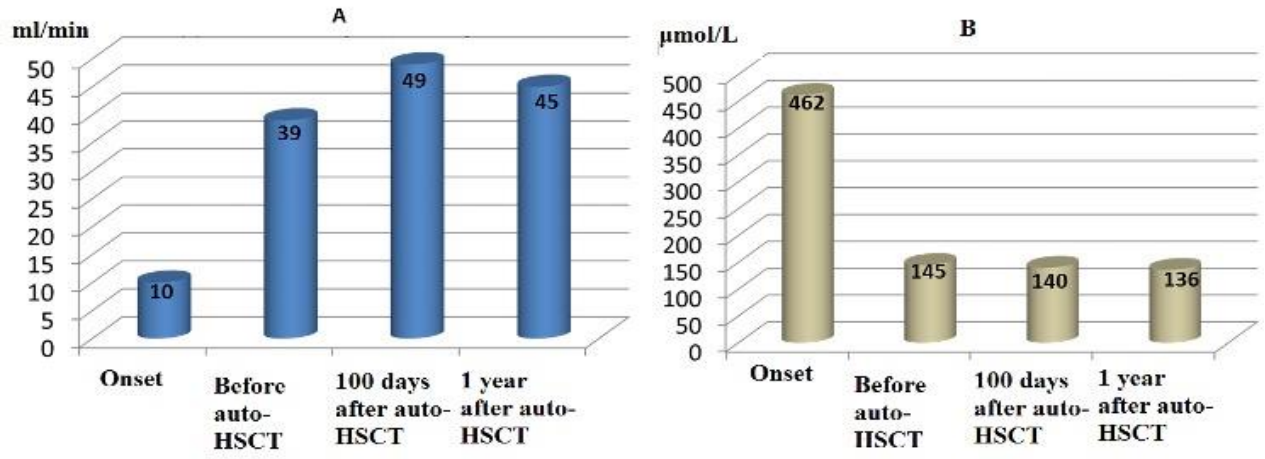

Figure 3. Dynamics of changes in the median of GFR (A) and creatinine level (B) at the different stages of therapy

In the studied patients, there was no transplant-related mortality. With a median follow-up of 48 months, the 5-year overall survival (OS) of the patients was 70% (median was not reached). The 5-year relapse-free survival (RFS) of the patients was 42% (the median was 48 months). OS and RFS were analyzed depending on the dose of melphalan (140 mg / m^2 versus 200 mg / m^2), no statistically significant difference was obtained.

DISCUSSION

With the development of acute kidney injury at the onset of MM, an immediate initiation of specific anticancer therapy is required for a rapid reduction of FLC.

According to a study from Poland, the median time between the start of dialysis and the start of a specific anticancer therapy was 14 days[11]. In the work presented by us, this indicator is 23 days. Long-term differential diagnosis and late initiation of chemotherapy reduce the likelihood of achieving a renal response. However, even with timely diagnosis

and adequate reduction of FLC, improvement in renal function is not observed in everybody. In the case of acute kidney injury requiring dialysis, an adequate rapid reduction of FLC leads to improved renal function in about 61–65% of patients as seen in published studies[12,13]. The results of this study are consistent with the literature data - after the end of the induction therapy, 57% of patients (13 of 23 patients) managed to stop hemodialysis.

Thus, out of 23 dialysis-dependent patients at the beginning of treatment, the need for dialysis at the stage of auto-HSCT remained in 10 patients. For all patients with severe kidney damage, the dose of melphalan was reduced to 140 mg/m^2 according to the recommendations of the IMWG-2016. Without doubt, dependence on hemodialysis aggravates the patient's condition. Attention is drawn to a significant difference in the reactivation of a herpes virus infection in dialysis-dependent patients compared with patients who do not need renal replacement therapy. In general, the entire group of patients with kidney damage demonstrates a wide range of various infectious complications. A third of patients had grade 3-4 mucositis. Septicemia and pneumonia developed more often in dialysis-dependent patients. Infectious complications were stopped by the timely administration of broad-spectrum antibacterial drugs. The escalation of antibiotic therapy was required somewhat more often in dialysis-dependent patients.

The emergence of temporary neurologic complications after auto-HSCT in MM patients with kidney damage has been described in the literature. Thus, C-K Lee et al. reported manifestations of metabolic encephalopathy in 13% of dialysis-dependent patients[14]. Researchers from Canada published a study in 2015 in which 30% of dialysis-dependent patients developed delirium early after transplantation. Symptoms included confusion, hallucinations, paranoid reactions, and aggressive behavior. The authors associated such a high frequency of neurological deficits with the prescription of narcotic analgesic drugs in the early post-transplant period[15]. A Polish group of authors compared the incidence of complications after auto-transplantation in dialysis-dependent patients and patients with normal renal function. The emergence of neurologic complications was noted in 13% of dialysis-dependent patients and in 2% of patients without kidney damage[11]. According to this study, dialysis-dependent patients significantly more often develop reversible encephalopathy compared with patients who did not undergo hemodialysis (20% versus 0, p = 0.02).

According to the results of our study, it can be concluded that dialysis-dependent patients reliably more often require red blood cell transfusions compared to patients who do not undergo hemodialysis during auto-HSCT. Similar results are described in the work of Polish colleagues[11].

The parameters of hematopoiesis recovery after transplantation were similar in the "HD +" and "HD-" groups. The terms of recovery of leukocytes and platelets are comparable with data presented in the literature[11,16]. The duration of agranulocytosis also did not differ in the "HD +" and "HD-" groups.

Carrying out auto-HSCT allowed to deepen the antitumor response, in the first control period (+100 days) an increase in the percentage of complete responses was noted. This parameter remains stable one year after auto-HSCT. Transplantation performed in the progression of the disease, generally, does not bring additional antitumor effect. The effectiveness of therapy in MM patients with severe kidney damage is expressed not only in the frequency and duration of a deep antitumor response. An extremely important outcome of the treatment of this category of patients is the achievement of a renal response and the frequency of discontinuation of HD. According to Waszczuk-Gajda et al. renal replacement therapy after auto-HSCT was discontinued in 13% of cases[11]. Researchers from Canada published a study according to which 25% of MM patients stopped hemodialysis after auto-HSCT [16] In other studies, this parameter ranges from 0 to 28%[14,17-19]. According to the data of our work, 10% of patients managed to terminate programmed HD after transplantation. After induction therapy and auto-HSCT 61% of patients achieved independence from HD.

The question of the incidence of mortality associated with transplantation in dialysis-dependent patients remains open. In the era of key randomized trials,

severe renal injury was the exclusion criterion. Therefore, the literature on this issue is based on retrospective studies, and usually works with small sample sizes. Transplant-related mortality rates in this category of patients vary from 4% to 29% [18,20,21]. In our study, there was no mortality associated with transplantation.

Overall and relapse-free survival rates of MM patients with kidney damage are also a topic of discussion in expert circles. The presence of dialysis-dependent renal failure is still a risk factor for early death today [22] in the structure of the causes of death predominates cardiovascular and infectious complications. According to the European Association for Dialysis and Transplantation, after the start of dialysis, half of the patients die within 5 years [23]. According to the data presented by us, the 5-year OS and RFS were 70% and 42%, respectively.

CONCLUSION

Thus, the results of this single-center study indicate that auto-HSCT is an effective treatment method in MM patients with severe kidney damage. 61% of patients became dialysis-independent. Careful selection of patients is extremely important, given the high risk of complications in the early post-transplant period. A wide choice of modern concomitant therapy and careful monitoring ensured the absence of mortality associated with transplantation. With a median follow-up of 48 months, the 5-year OS and RFS were 70% and 42%, respectively.

CONFLICT OF INTEREST

The authors declare no conflicts of interest in this work.

Ethical approval and consent to participate

This study was approved by the Ethics Committee of FSFI «National Research Center for Hematology» of the Ministry of Healthcare of the Russian Federation.

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