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Infectious complications in multiple myeloma patients undergoing autologous peripheral blood stem cell transplantation

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Summary

Multiple myeloma (MM) accounts for approximately 10% of blood malignancies and 1% of all cancers in general. The concept of high-dose chemotherapy followed by transplantation of autologous hematopoietic stem cells (ASCT) remains the standard for treating newly diagnosed multiple myeloma in young and in selected, fit, elderly patients. Infectious complications represent important cause of morbidity and mortality in MM patients. Bloodstream infections remain the most severe bacterial complication in recipients of hematopoietic stem cell transplantation, whereas herpesviruses, especially, cytomegalovirus (CMV), dominate among viral complications. We analyzed data on 38 patients with MM who underwent ASCT from January 2018 to February 2020. Reactivation of cytomegalovirus (CMV) was revealed in 5 cases (13.2%), and Epstein-Barr virus (EBV), in 3 patients (7.9%). Pneumonia was diagnosed in one case (2.6%). Bacterial bloodstream infections were detected in 3 patients (7.9%). The bloodstream infections were stratified in accordance with the Sepsis-3 criteria, thus enabling us to identify patients with unfavorable prognosis who developed sepsis and/or septic shock. Infectious complications were observed over the period of 60 days after ASCT. Meanwhile, CMV and EBV reactivation and bloodstream bacterial infections did not affect overall survival rate.

Conclusion

Our results demonstrate that bacterial complications and viral (CMV and EBV) reactivation aggravate the course of primary disease in MM patients over the post-transplant period. The methods of infection control in clinical practice (genotyping of multidrug-resistant strains, and antimicrobial control protocols) should improve the treatment strategies in patients with MM following ASCT.

Keywords

Autologous hematopoietic stem cells transplantation, bacterial and viral infectious complications, sepsis, septic shock.

Introduction

Over recent decades, significant advances were made in treatment of hematological malignancies, which were primarily associated with intensive antitumor therapy and hematopoietic stem cell transplantation (HSCT). Probability of 10-year survival among hematological cancer patients subjected to HSCT is 85%, as shown by the large study performed by Wingard et al. [1].

Multiple myeloma accounts for approximately 10% of oncohematological disorders, and 1% of total cancer incidence. The concept of high-dose chemotherapy followed by autologous HSCT was dated back to early 980s and remains the 'golden standard' for treating newly diagnosed MM in young and some older patients. The advent of novel agents, such as immunomodulatory drugs, proteasome inhibitors and monoclonal antibodies does not compete with ASCT. Instead, the novel approaches supported its central role as the standard of care [2].

However, implementation of modern therapy programs in MM may increase the risk of infectious complications that require urgent treatment [3]. In turn, early administration of antibiotic therapy requires rapid identification of infectious agents, in particular, over recent years, due to widespread prevalence of nosocomial multidrug-resistant (MDR) microorganisms [4]. Septic complications in patients with hemoblastoses after HSCT develop, mostly, due to bacterial translocation from intestines to the bloodstream, though other ways of pathogen penetration are possible [5]. Suppression of immune system during chemotherapy of oncohematological diseases is an additional prerequisite for severe infectious complications, thus leading to impairment of complex anti-infectious defense systems.

Hence, the aim of our study was to determine the frequency of infectious complications in patients with multiple myeloma in the post-transplant period and their influence on the results of autologous hematopoietic stem cell transplantation.

Patients and methods

The study included 38 adult patients with MM who were treated at the Russian Research Institute of Hematology and Transfusiology, from January 2018 to February 2020. All the patients received a conditioning regimen with melphalan: monotherapy at a dose of 200 mg/m^2 (29 patients), and 140 mg/m^2 (4 cases), or combined therapy with melphalan and carfilzomib (5 patients).

Infectious complications were diagnosed, as based on routine clinical examination and laboratory tests, including bacterial cultures and tests for antibiotic resistance. Herpesviruses in peripheral blood were detected by means of PCR techniques.

Antibacterial therapy was started immediately upon diagnosis of infection. First-line anti-infectious therapy was usually performed at empirical basis, in accordance with conventional regimens, at average doses of antibiotic drugs [3]. The antimicrobial therapy could be modified upon changing data on antibiotics resistance, carbapenems were added in the most severe cases. When detecting CMV or EBV, the therapy was accomplished by antiviral drugs, i.e., Acyclovir, Ganciclovir.

The *Sepsis-3* Criteria were used to characterize bacterial infections. In accordance with the definition adopted by the International Consensus Commission on Sepsis and Septic Shock [6], sepsis was defined as a condition characterized by the presence of an infectious locus and multiple organ failure. For the diagnosis of sepsis (SEPSIS 3), the Quick SOFA scale (rapid scale for assessing the severity of organ dysfunction) was used, which included only 3 criteria: (1) respiratory rate of >22/min or higher; (2) changing mental status, and (3) systolic blood pressure of <100 mm Hg. The patients with proven or suspected bacterial infection, organ dysfunction and more than 2 points on the Quick SOFA scale were defined as patients with sepsis. Clinical verification of septic shock was based on the need for vasopressor support to the mean arterial pressure values of >65 mm Hg, along with serum lactate over 2 mmol/l (18 mg/dl), in the absence of hypovolemia [6].

Before starting antibacterial therapy, and later, during febrile episodes, 8 mL of peripheral blood were taken regularly, both from peripheral vein and central venous catheter, with standard aseptic precautions, and incubated in aerobic/anaerobic bioMerieux BacT/ALERT culture media using BacT/ALERT 3D automated microbial detection system until positive results, or till day 7. Bacteriological analyses and identification of micromycetes were performed by routine technique over the entire study period, according to current guidelines [7]. We have also used a molecular biology method for rapid identification of microorganisms in blood cultures by means of real-time multiplex PCR technique [8]. Upon the RT-PCR-based detection of Gram-negative microorganisms in the cultures, we tested them for acquired carbapenemase genes, i.e., metallo-β-lactamases (VIM, IMP, NDM groups), KPC, and OXA-48-like groups were. To this purpose, we used PCR kits manufactured by InterLabService (AmpliSens®, Moscow, Russia).

RT-PCR was also used to detect respiratory viruses in nucleic acids extracted from the throat swabs. The diagnostic panel included PCR kits from InterLabService (AmpliSens®, Moscow, Russia) for the following pathogens: respiratory syncytial virus (RSV), 4 types of parainfluenza virus (PIV), rhinoviruses, coronaviruses (OS43, 229E, NL63, HKU1), metapneumovirus, adenovirus and human bocavirus, as well as *Clamydophila pneumoniae* and *Mycoplasma pneumoniae*. To detect the genomes of herpesviruses in blood, we used RT-PCR. The herpesvirus panel included herpes simplex viruses type 1 and 2 (HSV 1,2); cytomegalovirus (CMV); Epstein-Barr virus (EBV), and human herpesvirus type 6 (HHV6). PCR techniques were performed according to the manufacturer instructions (AmpliSens®, Moscow, Russia). The declared analytical sensitivity for the test systems was 500…1000 copies/mL for HSV1/2, and 5×10^5 *per* 10^5 leukocytes for EBV, CMV, and HHV type 6.

Statistical evaluation

The analysis of the data obtained was performed with IBM SPSS Statistics 22 software. To evaluate the results, mean values, medians, and ratios were presented as percentage values. The life expectancy curves according to Kaplan-Meier were calculated from the day of ASCT (D0) to the time of death, or date of last contact with the patient. Competing conditions (death from progression, or alternative reasons) have not been revealed in this group. Statistically the difference was considered significant at $p < 0.05$. ROC-analysis was used, in order to analyze probability of CMV and EBV reactivation and development of bacterial complications in the patients at different ages.

Results

Clinical response and survival

We studied 38 patients (18 women and 20 men) aged 39-70 years treated at the Russian Research Institute of Hematology and Transfusiology, during the period of January 2018 to February 2020. All the patients were diagnosed with multiple myeloma. Baseline demographic and clinical characteristics of the patients included into the study are shown in Table 1.

Table 1. Demographic and clinical baseline characteristics of patients, included in the study

Baseline characteristics	No (%)
Age (years, median, interquartile range)	57 (39-70)
65 years	33 (87%)
≥ 65 years	5 (13%)
Sex	
M	20 (52.6%)
F	18 (47.4%)
Type of ASCT	
single	29 (76.3%)
tandem	9 (23.7%)
ISS Durie-Salmon staging	
II	8 (21.0%)
III	30 (79.0%)
Renal injury	
Yes	6 (15.8%)
No	32 (84.2%)
Type of monoclonal protein	
Ig A	10
Ig G	24
Bence Jones myeloma	4
Chemotherapy regiments	CVD

The median age of patients at the time of ASCT was 57 years. Most patients were at the III, Durie-Salmon stage of MM. Renal impairment was found in 15.8% of the cases. The patients were treated with bortezomib-based combination (CVD), followed by ASCT (29 single and 9 tandem). Clinical response rates to CVD therapy are shown in Table 2.

Table 2. Antitumor response to CVD therapy of MM achieved before ASCT (n=38)

Age group	ISS Durie-Salmon staging	Response to CVD therapy		
		CR	VGPR	PR
<65 n=33	IIA n=8		1	7
	IIB n=1		1	
	IIIA n=20	8	3	9
	IIIB n=4	2	2	
>65 n=5	II n=0			
	IIIA n=4	1		3
	IIIB n=1	1		

In 28.9% of the patients, complete response (CR) to therapy was shown, very good partial response (VGPR) was observed in 21.1%, and partial response (PR), in 50.0%. The median follow-up was 370 days (range, 9 to 826 days). During first 60 days after ASCT, one patient (2.6%) died due to acute heart failure. Among the remaining 37 patients, there were no deaths during the follow-up period (Fig. 1)

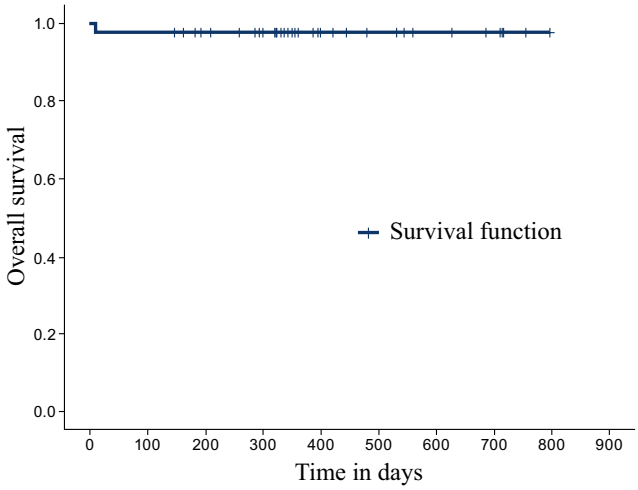

Figure 1. Overall survival rate after ASCT during the 826-day follow-up (Kaplan-Meier method)

Infectious complications after ASCT

During the first 60 days after the ASCT, 12 episodes of infectious complications were recorded: CMV reactivation occurred in 5 cases, EBV was detected in 3 patients. In one case, a mixed-pathogen pneumonia was diagnosed, as based on conventional symptoms of chest infection and radiographic findings. In this patient, respiratory syncytial virus (RSV) genome was detected in throat swab, along with *S.aureus* in sputum. EBV was detected in blood at the same terms. Bacterial infections of the bloodstream were diagnosed in 3 patients (7.1%).

We have also asked a question of chances to develop infections for the patients of different ages. ROC-analysis was used to assess the probability of reactivation of CMV and EBV herpes viruses in patients after ASCT (Fig. 2).

The threshold value of the "age" index at the cut-off point of 57 years was determined by the ROC-analysis, i.e., if the value of the index "age" is higher or equal to 57 years, the probability of reactivation of CMV and EBV infections is predictable. The resulting model was statistically significant (p= 0.036). The sensitivity and specificity of the method were 69% and 66.7%, respectively.

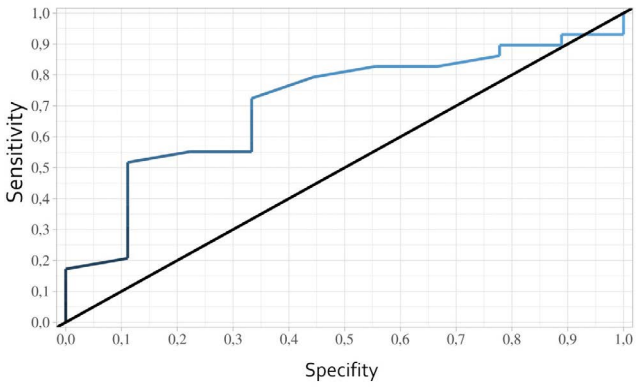

Figure 2. ROC curve that shows dependence of the probability between the "CMV and EBV reactivation" index and the "Age" index

Bacterial bloodstream infections

According to the *Sepsis-3* criteria [6], bacterial infections of different severity were diagnosed in three patients, as follows: bloodstream infection, sepsis, and septic shock. In the first patient, the infection occurred on the 6th day after transplantation in presence of agranulocytosis and grade 4 thrombocytopenia, with fever up to 38.3°C, and a decrease in blood pressure to 80/40 mm Hg, heart rate – 114/min, and respiratory rate 20/min. The condition was regarded as septic shock. The second patient had an episode of *E. coli* infection found in peripheral blood by the day +40 after ASCT, regarded as septic state (2 points on the Quick SOFA scale). In both cases, the infection was caused by multidrug-resistant *E. coli*. In the third patient, on the 6th day after ASCT, in presence of fever (up to 38°C), a Gram-negative microorganism of the *Enterobacteriaceae* family was detected. No symptoms compliant with *Sepsis-3* criteria were registered, and this infectious episode was considered as a bloodstream infection. Despite severity of clinical manifestations, these infectious complications did not have a negative prognostic effect on the 100-day overall survival.

ROC-analysis was used to assess the probability of developing bloodstream infections in patients from different age groups in the period after ASCT (Fig. 3).

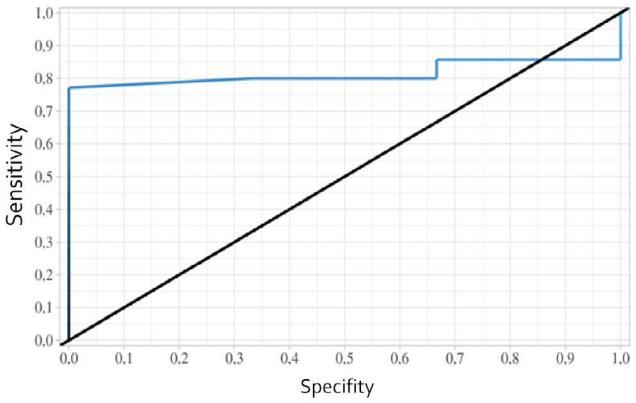

Figure 3. ROC curve that shows dependence of the probability between the "Bloodstream infection" index and the "Age" index

The threshold value of the "age" index was established at the cutoff point of 53. If the value of the age index is higher or equal to 53 years, the probability of developing bloodstream infections is well predicted. The resulting model was statistically significant ($p<0.001$). The sensitivity and specificity of the method were 80% and 66.7%, respectively.

Discussion

Multiple myeloma, a bone marrow-resident plasma cell malignancy, still remains largely incurable, despite dramatic improvements in the patient outcomes with advent of myeloma-targeted and immunomodulatory agents. ASCT remains an important consolidation treatment in the patients with MM. It has recently become clear that T cells from the MM patients are able to recognize and eliminate myeloma [9]. These data provide new insights into mechanisms of action of ASCT and provide rational approaches to improving clinical outcomes.

Infectious complications in MM, especially in elderly patients, remain an important issue. They restrict further development and improvement of therapies in hemato-oncology, in particular, after HSCT. The difficulty of treating and preventing infections in HSCT is associated with a variety of potential infectious pathogens, a need for their rapid detection, and early causal treatment.

The role of CMV infection in patients with hemoblastoses is well known [10]. CMV reactivation is often diagnosed in allogeneic HSCT recipients and therefore could lead to CMV-related disease, involving many organs in these immunocompromised patients. We have also previously found mixed bacterial/viral infections [11]. In contrast, few studies concerned CMV reactivation in ASCT since these patients are considered at low risk for both CMV reactivation and disease [12]. Our study demonstrated that CMV activation is quite often observed in the patients during early post-transplant period, e.g., after ASCT.

As to the EBV, in most cases its reactivation proceeds subclinically, and does not require special therapy. However, in some HSCT patients, EBV may cause life-threatening complications: post-transplant lymphoproliferative disorder (PTLD), or end-organ diseases such as encephalitis/myelitis, pneumonia, or hepatitis. EBV might be transmitted with the graft, since EBV-PTLD after HSCT is usually of donor origin. The risk of EBV-PTLD is higher, when the donor is seropositive [12]. However, there is a report on PTLD cases in MM patients after ASCT [13].

In the present work, we revealed that, at the age of more than 57 years, reactivation of CMV and EBV infection is highly probable. On the other hand, no clinical manifestations of CMV or EBM infection were documented. We can speculate that this can be explained by the increased probability of developing systemic bacterial infections, due to immunosuppression under the influence of CMV and EBV activation, especially in elderly patients. Previously, we performed a comparative study of herpesvirus frequency in cases of proven bacterial infections in bloodstream. We have revealed a statistically significant ($p<0.05$) increase of CMV and EBV incidence in blood of the patients who developed bacteremia, as compared with bacteremia-free cases [11].

In one case, pneumonia was diagnosed on day +16 after ASCT. Pneumonia diagnosis was based on traditional signs and symptoms of chest infection and chest radiography, as well as RSV and EBV positivity. We have previously shown the importance of respiratory viruses and, especially, RSV and their associations with CMV in the development of bacterial complications in MM following allogeneic bone marrow transplantation [14]. The present results suggest that respiratory viral infections should be carefully controlled also in ASCT patients.

Development of bacterial infections of the bloodstream and sepsis is a serious issue in HSCT setting. Among the causative agents of sepsis in hematological cancer patients, Gram-negative microbes are more common and dangerous, the mortality rate with these infections can reach 57% [11].

In our study, bloodstream infections were revealed in three patients. In all cases, they were caused by gram-negative

microorganisms. In addition, multidrug-resistant (MDR) bacteria were identified by detecting carbapenemase genes, and faster diagnostic methods by PCR-RT were applied, thus reducing analysis time by 24-48 hours [8].

Despite severe clinical manifestations of bloodstream infections caused by gram-negative microbes, their presence did not adversely affect the overall survival rate. In our opinion, this is to a certain extent related to the use of infection control methods in clinical practice: detection of MDR strains, the use of accelerated methods for identifying bacteria and timely determination of antimicrobial therapy strategy, taking into account the results obtained.

Conclusion

Over decades, ASCT remains the standard of care for young patients with newly diagnosed multiple myeloma. Autologous stem cell transplant is increasingly used also in older patients with MM. Meanwhile, such care causes negative effects, associated with significant risks of infectious complications, such as bacterial sepsis and activation of viruses, especially herpes viruses (CMV and EBV).

Cytomegalovirus reactivation is often diagnosed in allogeneic hematopoietic cell transplant recipients and, therefore, could lead to CMV disease in immunocompromised patients. In contrast, few studies investigated CMV reactivation in the patients undergoing ASCT, since they are considered at low risk for both reactivation and disease. In present work we revealed a significant role of CMV also in ASCT setting.

The present work has supported our previous results on the role of respiratory viruses and especially RSV and their associations with CMV in development of bacterial infectious complications, i.e., pneumonia in MM following allogeneic bone marrow transplantation [12]. Hence, the respiratory viral infections should be thoroughly controlled also in ASCT patients.

Development of bloodstream bacterial infections and sepsis remain a serious issue. The Sepsis 3 Criteria can be successfully used in patients with ASCT to discern the groups with dismal prognosis (progression to severe sepsis and septic shock).

In our study, bloodstream infections were diagnosed in three patients. In all cases, they were caused by Gram-negative microorganisms. In addition, the multidrug-resistant bacteria were monitored, and the methods of rapid identification of bacteria by RT-PCR were applied, thus sufficiently shortening the terms of analysis. More fast and precise methods of revealing the infectious pathogens in clinical practice (identification of multidrug-resistant strains and usage of antimicrobial therapy control strategies) will improve efficiency of treatment in MM patients following ASCT.

Conflict of interest

None declared.

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Инфекционные осложнения у пациентов с множественной миеломой, перенесших аутологичную трансплантацию стволовых клеток периферической крови

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Резюме

Множественная миелома (ММ) составляет примерно 10% гемобластозов и 1% всех онкологических заболеваний в целом. Концепция высокодозной химиотерапии с последующей трансплантацией аутологичных гемопоэтических стволовых клеток (АТСК) была разработана еще в 1980-х годах и остается стандартом лечения впервые выявленной множественной миеломы у молодых и избранных пожилых пациентов. Появление новых агентов, таких как иммуномодулирующие препараты, ингибиторы протеасом и моноклональные антитела, не заменили АТСК, а лишь укрепили его центральную роль в качестве стандарта лечения. Таким образом, в эпоху появления новых агентов трансплантация подвергается дальнейшему изучению. Важной причиной заболеваемости и смертности больных ММ являются инфекционные осложнения. Инфекции кровотока остаются наиболее серьезным бактериальным осложнением у реципиентов трансплантации гемопоэтических стволовых клеток, тогда как вирусы герпеса, особенно цитомегаловирус (ЦМВ), преобладают среди вирусных осложнений. Мы проанализировали данные 38 пациентов с ММ, которым была проведена АТСК в период с января 2018 г. по февраль 2020 г. Частота реактивации цитомегаловируса (ЦМВ) выявлена у 5 (13,2%), и вируса Эпштейна-Барра (ВЭБ) у 3-х (7,9%) пациентов. Пневмония диагностирована в 1 (2,6%) случае. Бактериальные инфекции кровотока выявлены у 3 (7,9%) пациентов. Инфекции кровотока были стратифицированы в соответствии с критериями сепсиса-3. Это позволило выявить пациентов с неблагоприятным прогнозом (развитие сепсиса и септического шока). Инфекционные осложнения наблюдались в период до 60 дней после АТСК.

Однако влияния реактивации ЦМВ и ВЭБ и инфекций кровотока на общую выживаемость (ОВ) не отмечено. Результат показывает, что бактериальные и вирусные (реактивация ЦМВ и ВЭБ) инфекционные осложнения усугубляют течение заболевания у гематологических больных. Критерии «Сепсис-3» позволяют своевременно выделить группы пациентов с неблагоприятным прогнозом (возможность развития сепсиса и септического шока). Использование методов инфекционного контроля в клинической практике (выявление штаммов с множественной лекарственной устойчивостью и использование стратегий контроля антимикробной терапии) улучшает тактику лечения пациентов с ММ в период после АТСК.

Ключевые слова

Трансплантация аутологичных гемопоэтических стволовых клеток, бактериальные и вирусные инфекционные осложнения, сепсис, септический шок.