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INFECTION EVENTS IN MULTIPLE MYELOMA DURING THE EARLY PERIOD OF AUTOLOGOUS STEM CELL TRANSPLANTATION

MULTİPL MİYELOMDA OTOLOG KÖK HÜCRE TRANSPLANTASYONUNUN ERKEN DÖNEMİNDE ENFEKSİYON OLAYLARI

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ABSTRACT

Objective: Multiple myeloma (MM) patients have a high risk of developing infections. In this study, we documented the infection events in patients with MM who underwent autologous haematopoietic stem cell transplantation (AHSCT).

Material and Method: Patients who received an induction regimen and underwent AHSCT were enrolled in the study. Routine antimicrobial prophylaxis was not given. Infection treatment was performed in accordance with the febrile neutropenia guidelines.

Result: Between May 2007 and November 2016, 150 patients with MM underwent AHSCT. The median age was 51.7±7.2 years, and the male-to-female ratio was 84/66. Nearly all patients developed fever. The median time from the HSCT day to the first fever episode was 7.4±2.8 days. Pneumonia and oropharyngeal candidiasis were frequently associated with fever. Blood and urine culture positivity was 18.6% and 20%, respectively. The neutropenia duration was not associated with culture positivity but proved to be longer in patients who had received two types of induction regimen (8.4±3.7 vs. 7.4±2.3 days, p=0.056). The mortality rate in the first 100 days was 0.6%, which was similar to the results of other experienced centers.

Conclusion: Our study encompassed the period when the induction regimen included combinations of chemotherapy, and novel agents were used after chemotherapy refractoriness or for improvement in response quality. In relation to this, most

ÖZET

Amaç: Multipl miyelom (MM) hastalarında enfeksiyon gelişme riski yüksektir. Bu çalışmada, otolog hematopoetik kök hücre nakli (OHKHN) yapılan MM hastalarında enfeksiyon olayları derlenmiştir.

Gereç ve Yöntem: İndüksiyon rejimi ardından OHKHN uygulanan MM hastaları çalışmaya dahil edilmiştir. Rutin antimikrobiyal profilaksi uygulanmamıştır. Enfeksiyon tedavileri febril nötropeni kılavuzlarına paralel yapılmıştır.

Bulgular: Mayıs 2007 ve Kasım 2016 tarihleri arasında toplam 150 MM hastasına OHKHN uygulandı. Ortanca yaş 51,7±7,2 yıl ve erkek/kadın oranı 84/66 idi. Hastaların neredeyse tamamında ateş gelişti. HKHN gününden ilk ateş atağına kadar geçen süre ortanca 7,4±2,8 gündü. Ateşle en sık ilişkili enfeksiyonlar pnömoni ve orofarengeal kandidiyazis idi. Kan ve idrar kültürü pozitifliği sırasıyla %18,6 ve %20 olarak bulundu. Nötropeni süresi kültür pozitifliği ile ilişkili değildi, ancak iki tip indüksiyon rejimi alan hastalarda nötropeninin daha uzun sürdüğü görüldü (8,4±3,7 vs, 7,4±2,3 gün, p=0,056). İlk 100 günde mortalite oranı %0,6 olup diğer deneyimli merkezlerin sonuçlarına benzerdi.

Sonuç: Çalışmamız, indüksiyon rejiminin kemoterapi kombinasyonları ile yapıldığı ve yeni ajanların kemoterapi refrakterliğinden sonra veya yanıt kalitesinde iyileşme için kullanıldığı dönemi kapsamaktadır. Bununla bağlantılı olarak, hastaların çoğu ikinci

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patients received second-line induction therapy. The infection events were manageable, and patients showed acceptable outcomes and a very low early mortality rate.

Keywords: Multiple myeloma, autologous haematopoietic stem cell transplantation, infection, febrile neutropenia

basamak indüksiyon almıştır. Enfeksiyon olayları yönetilebilir nitelikteydi; hastalar kabul edilebilir sonuçlar ve çok düşük erken ölüm oranı gösterdi.

Anahtar Kelimeler: Multipl miyelom, otolog hematopoietik kök hücre nakli, enfeksiyon, febril nötropeni

INTRODUCTION

Multiple myeloma (MM) patients are at increased risk of infection. MM itself, its disease pathophysiology, and treatment contribute to significant cellular and humoral immunity dysfunction. Along with the patient's comorbidities including physical and social compromise, infection in MM was associated with an individual variable rate (1-7).

In the last two decades, MM treatment has evolved from chemotherapy to pathology-targeted therapies. First, drugs that intervene in the microenvironment interaction, increase cellular immunity, and contributing to tumour cell apoptosis are released in the medical area. Thalidomide and its analogues with proteasome inhibitors were the first novel players in MM treatment. The treatment evolution schedules the MM treatment in fragments as induction, consolidation, and maintenance. All these innovations contributed to significantly improved survival, but relapse was inevitable. The second wave of MM treatment came with immunotherapy, first with monoclonal antibody followed by bispecific antibodies, and last with chimeric antigen receptor (CAR)-T cell application, which took MM treatment to the top (8, 9). MM's treatment story created an area where to mention minimal residual disease negative life and cure. Unfortunately, access to this treatment evolution in some low-income countries was a little behind.

We aimed to document the infection rates in patients with MM by reflecting on the MM treatment story in our country, which may assume a role as historical data. Across the AHSCT, the induction, mobilisation regimens, and conditioning were assessed. The duration of neutropenia and the relationship between neutropenia duration and other parameters were evaluated.

MATERIALS and METHODS

We retrospectively assessed 150 patients diagnosed with MM who underwent AHSCT. An institutional electronic database and the European Society of Blood and Marrow Transplantation (EBMT) data collection forms were used for data collection. All of the patients' treatment costs were covered by social insurance, and the treatment protocol was based on the health authority indications and national reimbursement criteria. Transplant eligibility was assessed by the HSCT team of the institution following the EBMT guidelines (10).

The patient's induction regimen is based on drugs licenced by the Ministry of Health and is covered by the Social Security and General Health Insurance. Induction regimens mainly comprised combined chemotherapy (VAD regimen, vincristine (V), doxorubicin (A), and high-dose dexamethasone (D)). Proteasome inhibitors with or without an immunomodulatory drug (IMID) were added to the induction therapy when the disease response was insufficient before AHSCT. Treatment was continued until the completion of AHSCT.

The mobilisation regimen was based on the patient's MM response depth, either with chemotherapy-based regimens, such as cyclophosphamide plus granulocyte colony-stimulating factor (G-CSF), cyclophosphamide+etoposide plus G-CSF, or G-CSF alone. The target CD34-positive cell number was $\geq 2x10^6$/kg.

The conditioning regimen was melphalan administered at a single dose of 200 mg/m^2 (140 mg/m^2 in patients with kidney failure). Reverse isolation rules were applied. Antimicrobial prophylaxis was not routine and was used only as secondary therapy according to the patient's medical history. All patients with HBsAg and/or anti-HBc IgG positivity received antiviral prophylaxis.

Routine antimicrobial prophylaxis was not given. For patients with a history of previous invasive aspergillosis, expected prolonged neutropenia of >2 weeks, or prolonged neutropenia before transplantation, antifungal prophylaxis was applied.

CMV monitoring was not routinely performed. In cases with clinical suspicions such as unexplained and/or unresponsive fever, CMV assessment was performed using CMV PCR. CMV reactivation was defined as the detection of plasma CMV DNA ≥ 500 IU/mL in plasma.

The post-transplant management protocol was based on supportive therapy, mainly febrile neutropenia treatment and transfusion. All patients received G-CSF to accelerate haematopoietic recovery from the 5th HSCT day until engraftment.

Neutropenic fever was defined as a temperature of ≥38.3°C orally or ≥38.0°C over 1 h with an absolute neutrophil count (ANC) of ≤500/ µL, or ≤1000/ µL and expected to fall ≤500/ µL over the next 48 h. This management

was in accordance with the recommendations of the National Comprehensive Cancer Network (NCCN) guideline 2023 (11).

Microbiological evaluation of neutropenic fever included obtaining at least two sets of blood cultures from the catheter lumen and peripheral vein, urine cultures, and other secretions or body fluids in case of clinical suspicion. High-resolution chest computed tomography was performed in patients with fever persisting for >72 hours according to the European Society for Medical Oncology (ESMO) Practise guidelines for the management of febrile neutropenia (12). Thorax CT was skipped when the patient's clinical performance was not suitable for imaging.

All patients with neutropenic fever received empirical intravenous broad-spectrum antipseudomonal antibiotics; in case of pneumonia, diarrhoea, and/or central venous catheter infection, vancomycin was added to the treatment. When an infection agent was documented in culture, the antimicrobials were changed according to the clinical course and antibiotic susceptibility test results. All patients were re-evaluated 48–72 hours after the initiation of antibiotics. In patients with refractory fever, the antipseudomonal antibiotic was changed to carbapenem, and/or vancomycin was added, if not started at the beginning of the fever. Although no clear distinction has yet been made, they were categorised to classify information on the causative agents and resistance patterns produced and to guide antibiotic use strategies at intermediate stages. According to this categorisation, multidrug-resistant (MDR) was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories, extensively drug-resistant (XDR) was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories), and pandrug resistant (PDR) was defined as non-susceptibility to all agents in all antimicrobial categories (13). At the 96th hour after refractory fever, invasive fungal infection (IFI) was evaluated using blood galactomannan analysis and thorax computed tomography (CT). In general, empiric antifungals with caspofungin or liposomal amphotericin B were added to the antibacterial treatment. In cases of proven or probable aspergillosis, voriconazole was added to anti-microbial therapy according to the clinical protocol. Ganciclovir was used to treat CMV-DNA viremia.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 11.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were defined as numbers and percentages for categorical variables and mean, standard deviation, minimum, and maximum values for numeric variables. Student's t-test was used to compare normally distributed parameters, and the Mann–Whitney U test was used for other tests. The qualitative variables were compared using Pearson's Chi-square test. The statistical significance level was defined as $p<0.05$.

The study was approved by İstanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 21/07/2023, No: 15).

RESULTS

The study included patients with MM who underwent AHSCT between May 2007 and November 2016.

The median age of the patients was 51.7±7.2 years (range between 30 and 69 years). The male-to-female ratio was 84 (56%) to 66 (44%). In addition to MM, hypertension (22.6%), diabetes mellitus (15.3%), chronic hepatitis B (6%), coronary artery disease (3.3%), tuberculosis history (1.3%), and chronic obstructive pulmonary disease (0.7%) were noted in the medical records.

VAD was the most frequently used induction regimen related to the social insurance system financial support limitation for other regimens. Table 1 lists the induction regimens used. The total number of induction courses was 8.2±3.4 (between 2-23). The time interval to AHSCT proved to be 179.7±158.7 days from diagnosis.

Table 1: Induction regimen types as first- and second-line regimens

Chemotherapy	n	%
First-line		
VAD	109	73.2
High-dose dexamethasone	15	10.1
VD	16	10.7
CyBORD	5	3.3
TD	4	2.7
Second-line		
VD	68	45.6
CyBORD	25	16.8
Cyclophosphamide, dexamethasone	10	6.7
TD	14	9.4
DCEP	5	3.4
Rd	6	4.0
CEP	1	0.7

VAD: vincristine, adriamycin, dexamethasone, VD: bortezomib, dexamethasone, CyBORD: bortezomib, dexamethasone, cyclophosphamide, TD: thalidomide, dexamethasone, DCEP: dexamethasone, cyclophosphamide, etoposide, cisplatin, Rd: lenalidomide, dexamethasone, CEP: cyclophosphamide, etoposide, cisplatin

G-CSF alone was the most used (59.3%) mobilisation regimen. Chemotherapy-based regimens were equally distributed. G-CSF plus cyclophosphamide was administered to 32 patients (21.3%) and cyclophosphamide plus etoposide to 29 (19.3%). The mean infused CD34-positive cell dose was $6.2x10^6$/kg (range 1.35-$27.2x10^6$). Neutrophil engraftment occurred on 13±3.7 days (between 6-33 days) and platelet engraftment on 14±4.7 days (6-31 days). The duration of neutropenia was longer in patients who received two two-line induction regimens compared with only one line (8.4±3.7 vs. 7.4±2.3 days, p=0.056).

All patients experienced mucositis at different degrees. Diarrhoea developed in 50 (33.3%) patients in the early post-transplant period.

All patients developed fever except 21 (14.0%). The median time from AHSCT day to fever development was 7.4±2.8 days. There was no significant difference between infused CD34-positive cell count and febrile neutropenia (p=0.34) episode. The relationship between neutropenia duration and neutropenic fever was not statistically significant (p=0.74).

The infection source could not be identified in 72 (48%) patients. The most frequently occurring infection was pneumonia (12.0%). Oropharyngeal candidiasis is the second most frequent (10.6%) infection-related clinical diagnosis. Rare infections included skin and soft-tissue infections (5.3%), herpetic stomatitis (4%), and neutropenic enterocolitis (2.6%). One patient (0.66%) with diarrhoea was diagnosed with CMV colitis based on histological examination of tissues biopsied on colonoscopy. Nineteen (12.6%) patients received antifungal therapy due to clinical diagnosis of possible IFI.

Imaging studies were performed on 30 patients. Fourteen (46.6%) patients presented with pulmonary infiltrates with pleural effusion on thorax CT. One patient with severe abdominal pain had intestinal wall thickening on abdominal CT suspecting inflammation and broad-spectrum antimicrobial agents were initiated with a preliminary diagnosis of neutropenic enterocolitis (typhlitis).

A total of 28 patients (21.7%) of 129 who developed neutropenic fever had blood culture positivity (Table 2). When the Gram-negative bacilli isolated from the patients were analysed, ESBL positivity was detected in 75% of the isolates, XDR positivity in 9.5%, and resistance to all tested antimicrobials, PDR, in only one clinical isolate (4.76%). Urine culture positivity was detected in 30 patients (23%) (Table 3). The most commonly isolated microorganisms were coagulase-negative *staphylococci* in blood culture and *Escherichia coli* in urine culture. Among catheter tip cultures, *Staphylococcus* infections were the most frequently encountered agents in 17 patients, followed by methicillin-sensitive *Staphylococcus aureus* positivity in 2 patients, and *Pseudomonas* positivity in 2 patients. *Candida* spp. were isolated from catheter tip cultures of two patients. In two patients with uncontrollable fever, *despite algorithmic management, surveillance culture revealed* vancomycin-resistant *Enterococcus* (VRE), and linezolid was replaced with vancomycin. There was no relationship between neutropenia duration and culture positivity.

Table 2: Results of blood culture during neutropenic fever

Blood culture	n	%
None	122	81.3
MSCoNS	9	6.0
MRCoNS	8	5.3
MSSA	3	2.0
Escherichia coli	4	2.7
Enterococci sp.	1	7.0
Klebsiella pneumoniae	3	2.0

MSCoNS: Methicillin Susceptible Coagulase-negative staphylococci, MRCoNS: Methicillin Resistant Coagulase-negative staphylococci, MSSA: Methicillin-sensitive *Staphylococcus aureus*

Table 3: Results of urine culture during neutropenic fever

Urine culture	n	%
None	120	79.3
Escherichia coli	10	6.7
Enterococcus spp.	6	4.0
Klebsiella pneumoniae	5	3.3
Candida spp.	3	2.0
MSSA	1	0.7
Stenotrophomonas maltophilia	1	0.7
Proteus sp.	1	0.7
Pseudomonas sp.	1	0.7
Acinetobacter sp.	1	0.7
Morganella sp.	1	0.7

MSSA: Methicillin susceptible *Staphylococcus aureus.*

Within 100 days of AHSCT, only one patient (0.6%) required intensive care unit care and died of sepsis.

There was no statistically significant difference between the number of pre-transplant treatment courses and the timing of AHSCT with antimicrobial lines (p=0.34 and p=0.44, respectively).

DISCUSSION

MM, with its disease evolution and pathophysiology, forms a major research area that contributes to the development of new drugs. Every progress in treatment is associated with some adverse effects. Infection is the main adverse effect of MM treatment, but the disease itself causes an immunosuppressive environment.

Our study included a cross-section of MM treatment history from combination chemotherapy to novel drugs. We documented infection events during the early period of AHSCT in patients with MM, which encompassed 4 weeks after transplantation.

We found that all patients developed fever, except 21 (14.0%). The infection source could not be identified in 72 (48%) patients. A study from Poland reported infectious complications after AHSCT, including lymphoma, acute myeloid leukaemia, and MM patients. The infectious complication rate was 92.3% during neutropenia after AHSCT. The clinically documented infection ratio was 9.3%, and fever of unknown origin was 51.7% (14). Another study from Türkiye reported that febrile neutropenia developed in 92% of autologous stem cell transplant recipients (15). This result is also consistent with the review written by Nesher L and Rolston K in Principles and Practise of Transplant Infectious Disease (16). They reported that approximately 40-50% of febrile neutropenic patients have neither clinical evidence of infection nor positive microbiological documentation of infection, which are episodes of unexplained fever.

In our study, only one patient (0.6%) required intensive care unit care and died of sepsis within 100 days of AHSCT. A study from Taiwan reported that the early mortality rate defined as death within 60 days after diagnosis was 12.6%. They reported that infection was the cause in nearly two-thirds of those early deaths (17). Another study from the USA revealed an overall early mortality rate, defined as death within 6 months after MM diagnosis, of 8.3%. Advanced-stage disease, poor ECOG performance, and older patients (aged ≥ 70 years) were found to be predictors of early mortality (18). The low death rate in our study may be related to the restricted definition of transplant candidates.

We experienced that nearly half of the febrile neutropenic patients had no clinical or laboratory evidence of infection. Nearly half of the febrile patients (48%) did not have any clinical symptoms or signs leading to an obvious infection diagnosis. Pneumonia occurred in 12% of patients. The most frequently isolated pathogen was Gram-positive cocci. Urinary tract infection was also not at a low rate. The rate of urinary system infection by *E. coli* was 20%. CMV infection and IFI were not major complications in our cohort. Consistent with our study, a study from Pakistan documented the incidence and main characteristics of infections in patients with MM treated at their centers over 10 years. They found that the lung was the most common site of infection, followed by the genitourinary system, and *E. coli* was the most common organism (19). They also reported that infection was the main cause of death at a rate of 6.3%. The same experience was reported in Germany, which conducted a large retrospective analysis of 479 patients with MM. The study showed that the rate of infections was stable over time and was mainly associated with high disease burden, relapsed disease, and treatment with high-dose chemotherapy (20). A meta-analysis conducted in China showed that patients with MM treated with IMIDs are at high risk of serious infection (21). A systematic review encompassing the frontline, maintenance, and relapsed/refractory settings of MM treatment within randomised clinical trials reported that the significant risk factors were severe infection, pneumonia, and neutropenia (22).

A retrospective data evaluation from China revealed that newly diagnosed patients with MM were highly susceptible to viruses, including mainly Epstein–Barr virus (EBV) and hepatitis B virus (HBV) (23). Our institution's antiviral prophylaxis protocol against HBV was routine according to the criteria defined in the method part of the study. In our study, only one CMV organ disease had intestinal involvement. Therefore, CMV infection was not a significant problem with historical induction regimens. In the study conducted in Italy, covering 327 AHSCT (n=201 MM, n=126 lymphoma), 11% required specific antiviral treatment for symptomatic CMV reactivation (n=32) or end-organ disease (n=4), which increased transplant-related mortality (24).

For antibacterial prophylaxis, levofloxacin is recommended during the first 3 months, particularly in patients at intermediate and high risk for early infection (25). Our institutional protocol excluded antibacterial prophylaxis.

A multicenter study in Melbourne focusing on IFI in MM patients. Based on the clinical and microbiology records review, the IFI rate was low in patients with MM treated with novel drugs, including monoclonal antibodies (26). Similarly, IFI was not a major complication in our cohort.

Our study is retrospective. The emphasis is that in our study population, the total number of treatment courses given for remission induction was high, and the time from diagnosis to HSCT was long. The explanation for this is institution-related. The institution transplant unit's working intensity resulted in an obligatory waiting list. On the other hand, the infection events were manageable, and patients showed acceptable outcomes and a very low early mortality rate. Radiological imaging was performed on a few patients who developed neutropenic fever. These are the limitations of our study. On the other

hand, our results provide historical data and reflect infection events in Türkiye when immunotherapy, either daratumumab, elotuzumab, or isatuximab, has not yet been reimbursed, and combined chemotherapy was allowed as frontline therapy.

Data availability statement: Data available on request from the authors. The data that support the findings of this study are available from the corresponding author upon reasonable request and all authors have access the all data.

Ethics Committee Approval: The study was approved by İstanbul üniversity, İstanbul Faculty of Medicine Clinical Research local Ethics Committee (Date: 21/07/2023, No: 15).

Informed Consent: Consent was obtained from all participants in the study.

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