Araştırma Makalesi
Research Article

Evaluation of infections developing during autologous hematopoietic stem cell transplantation in AML patients

AML HASTALARINDA OTOLOG HEMATOPOETİK KÖK HÜCRE NAKLİNDE GELİŞEN ENFEKSİYONLARIN DEĞERLENDİRİLMESİ

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ABSTRACT

Infections are the leading treatment-related cause of mortality and morbidity associated with high dose therapy with autologous hematopoietic stem cell support (HSCT). The aim of the study is to evaluate the data of 47 patients with AML who developed infections in association with autologous HSCT in Izmir Medicalpark Hospital between November 2012 and April 2018.

Materials and Methods: This study is a retrospective evaluation of the data from 47 patients with AML who developed infections in association with autologous HSCT. All infection episodes were noted, beginning from the neutropenia period until the development of neutrophil engraftment.

Results: 24 patients were female and 23 patients were male. The median age at the occurrence of the condition was 39 years (range:18-68). Neutrophil engraftment occurred at an average of 11 days after the transplantation, platelet engraftment occurred at an average of 21 days. In 41 (87.2%) patients neutropenic fever occurred during transplantation. The cause of fever remained unknown in 20% of the patients, 70% of the patients had a microbiologically documented infection and 10% of the patients had only clinically documented infection. 19 patients had a catheter related infections, 7 patients had pneumonia, 8 patients had urinary tract infection and 3 patients had possible invasive pulmonary aspergillosis.

Conclusion: In our department, infections do not present a significant risk for mortality in autologous HSCT among patients with AML. Early detection of the causative agent of the infection is of crucial importance for an optimal treatment and prognosis.

Keywords: AML, autologous stem cell transplantation, infection

ÖZ

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Enfeksiyonlar, otolog hematopoietik kök hücre nakli (HSCT) esnasında gelişen tedaviye bağlı mortalite ve morbiditenin önde gelen nedenidir. Çalışmamızın amacı, İzmir Medicalpark Hastanesi'nde Kasım 2012-Nisan 2018 tarihleri arasında otolog HSCT'ye bağlı enfeksiyon gelişen 47 AML hastasının verilerini değerlendirmektir.

Gereç ve Yöntem: Çalışmanın amacı; otolog HSCT ile ilişkili enfeksiyon gelişen 47 AML hastasının verilerinin retrospektif bir değerlendirmesidir. Nötropeni döneminden nötrofil engraftmanı gelişimine kadar tüm enfeksiyon atakları değerlendirildi.

Bulgular: 24 hasta kadın, 23 hasta erkekti. Durumun ortaya çıktığı ortanca yaş 39 idi (aralık: 18-68). Transplantasyondan ortalama 11 gün sonra nötrofil engraftmanı, ortalama 21 gün trombosit engraftmanı meydana geldi. 41 (%87,2) hastada transplantasyon sırasında nötropenik ateş meydana geldi. Hastaların %20'sinde ateşin nedeni bilinmiyordu, hastaların %70'inde mikrobiyolojik kanıtlı ve %10'unda sadece klinik olarak belgelenmiş bir enfeksiyon vardı. 19 hastada kateter ilişkili enfeksiyon, 7 hastada pnömoni, 8 hastada idrar yolu enfeksiyonu ve 3 hastada olası invaziv pulmoner aspergilloz mevcuttu.

Sonuç: Bölümümüzde AML hastalarında otolog HKHT'de enfeksiyonlar önemli bir mortalite riski oluşturmamaktadır. Enfeksiyona neden olan ajanın erken tespiti, optimal tedavinin seçimi ve prognoz için çok önemlidir.

Anahtar Kelimeler: AML, otolog kök hücre nakli, enfeksiyon

Infections are the leading treatment-related cause of mortality and morbidity associated with autologous hematopoietic stem cell transplantation (HSCT)(1). Patients experience severe neutropenia for a time period of two to three weeks during this treatment modality. A number of factors contribute to the development of infections associated with HSCT, including neutrophil engraftment time, severity of the disease at the time of transplantation, conditioning regimens used before the transplantation, immunosuppressive treatments, infections experienced during previous neutropenia periods, interventional procedures, indwelling catheters, hospital hygiene and the use of HEPA filter rooms (2,3). Acute Myeloid Leukemia (AML) is the most prevalent type of acute leukemia in adult age groups. Autologous HSCT is indicated as a consolidation therapy in a group of patients with AML, including those classified as good or intermediate 1 risk group, according to cytogenetic and molecular alterations. Recent advances in supportive therapies have reduced the prevalence of infections in this patient population. A meticulous assessment and a close observation are needed to timely initiate the treatment. The aim of the study is to evaluate the data of 47 patients with AML who developed infections in association with autologous hematopoietic stem-cell transplantation in İzmir Medicalpark Hospital between November 2012 and April 2018.

MATERIALS AND METHODS

This study is a retrospective evaluation of the data from 47 patients with AML who developed infections in association with autologous hematopoietic stem-cell transplantation in İzmir Medicalpark Hospital between November 2012 and April 2018. All patients received a regimen including busulfan and cyclophosphamide at myeloablative doses and later on autologous peripheral hematopoietic cells harvested from peripheral blood, frozen at-80^{0}C were administered via a central venous line after thawing.

As an infection prophylaxis strategy, all patients were interned to isolated HEPA filter rooms with visitor restriction, in the bone marrow transplant unit. All healthcare professionals used masks, galoshes and bonnets.

All study subjects received prophylaxis with levofloxacin 500 mg PO, acyclovir 400 mg PO 3 times daily and fluconazole 400 mg PO, before the onset of fever. All infection episodes were noted, beginning from the neutropenia period until the development of neutrophil engraftment. Blood, urine and sputum cultures were obtained from patients who had a body temperature of 38^0C.

Blood cultures and sputum cultures were plated on blood agar, EMB agar and chocolate agar (RTA,Turkey) and isolated strains were identified by automatized Phoenix system (BD,USA). The antimicrobial susceptibility was also studied by automatized Phoenix system (BD, USA). Urine cultures were plated on blood agar and EMB agar (RTA,Turkey) and isolated strains were identified by automatized Phoenix system (BD,USA). The antimicrobial susceptibility was also studied by automatized Phoenix system (BD, USA).

Definitions

Neutropenia is defined as an absolute neutrophil count of <500/mm^3 in peripheral blood and neutrophil engraftment is defined as the first day of two consecutive days where the absolute neutrophil count is >500/mm^3. Neutropenic fever is defined as a body temperature greater than 38.3^{0}C for once or a body temperature greater than 38^0 C sustained for more than 1 hour (4). All patients with fever have to undergo a physical examination; catheter, peripheral blood, urine and sputum cultures should be obtained and any suspected area have to be sampled. All these procedures have to be repeated every 24 hours if fever persists.

Infections during a neutropenic period are defined as;

1- Microbiologically documented, if any etiological agent grows in a culture medium

2- Clinically documented; if any etiological agent cannot be identified, even though symptoms and signs of an localized infection are present

3- Fever of unknown origin; if fever is not accompanied by any symptoms or signs indicating the cause of fever and any etiological agent cannot be identified in a culture

All patients with fever who had a central venous line were empirically started on meropenem and teicoplanin at the onset of fever. Amikacin and/or colistin, tigecycline were added to the therapy regimen in the occurrence of a septic shock. Initiation of antifungal therapy was taken into the consideration if fever persisted longer than 72 hours.

Treatment was adjusted according to the infectious agent responsible for the fever, if identified. Antibiotics were discontinued 3 to 5 days after the neutrophil engraftment occurred and a fever response was obtained(5,6).

Statistical Analysis

Data are demonstrated as mean±SD for normally distributed continuous variables, median (minimum-maximum) for skew distributed continuous variables, and frequencies for categorical variables. Pearson chi-square test was performed for the comparison of categorical variables. Means of normally distributed continuous variables were compared by ANOVA. Skew distributed continuous variables were compared by Mann Whitney U test. Overall survival (OS) was calculated as the time relapsed from the date of diagnosis to the date of last contact or death. Leukemia-free survival (LFS) was calculated from the diagnosis until last follow-up or leukemic progression. Cox regression analysis was used for the multivariate analysis. Statistical Package for Social Sciences (SPSS) for Windows version 15.0 (SPSS Inc., Chicago) was used for the analysis and two sided p value of <0.05 was considered as significant.

RESULTS

Twenty four patients were female and 23 patients were male. The median age at the occurrence of the condition was 39 years (range: 18 -68 years). 37 patients (78.7%) had a ECOG performance status score of 1.

Thirty five out of 47 patients had a complete response to the first line therapy with 7+3 cytosine arabinoside- daunorubicin. 45 patients received autologous hematopoietic stem cell transplant in the first complete

remission and 2 patients received autologous hematopoietic stem cell transplant in the second complete remission. All patients received a preparation regimen including busulfan and cyclophosphamide. The mean time from diagnosis to transplantation was 7.94 months (range: 2-90 months) while the average CD34 count in the harvest was $10.14x10^6$/kg. A temporary 3-way catheter was placed into the subclavian vein under the guidance of ultrasound by an interventional radiologist. Neutrophil engraftment occurred at an average of 11 days after the transplantation while platelet engraftment occurred at an average of 21 days (Table 1).

Table 1: General characteristics of patients

Patients	47	
Female	24	51.1%
Male	23	48.9%
Age at diagnosis (median) (years), range	39	18-68
Leukocyte count at diagnosis (mm^3), range	367007/mm^3	range: 2000-270000/mm^3
Hemoglobin concentration at diagnosis (mg/dl)	8	range: 3.5-12.3
Lactate dehydrogenase	471	range: 220-1477
Bone marrow blast count at diagnosis	76	range: 23-97
Apheresis, days	2	range: 1-5 days
CD34 cell yield	10.14	range: 5-53.34
Time from diagnosis to transplantation	7.94	range: 2-90
Neutrophil engraftment (days)	11	range: 9-19
Platelet engraftment (days)	21	range: 9-110

Developed febrile neutropenia	41	87.2%
Possible invasive pulmonary aspergillosis	3	6.4%
Transplant-related mortality	1	2.1%
Mortality within 100 days after transplantation	1	2.1%
Overall follow-up, months	26	range:4-116
Progression-free survival (average), months	20	range:3-69
Follow up after transplantation (average) months	18.08	range:25-51
Final survival status	Alive	29
	Died	18

Neutropenic fever developed in 41 (87.2%) of 47 patients during autologous hematopoietic stem cell transplantation. A treatment regimen including meropenem and teicoplanin was initiated empirically at the onset of fever. The treatment regimen was adjusted according the infectious agent when the underlying cause of fever was identified. The cause of fever remained unknown in 20% of the patients while70% of the patients had a microbiologically documented infection and 10% of the patients had only clinically documented infection. 3 patients were considered to have possible invasive pulmoner aspergillosis (IPA) and started on antifungal treatment and they were given to 7 other patients as an empirical treatment (21.27%).

Nineteen patients had a catheter related infections, 7 patients had pneumonia, 8 patients had urinary tract infection and 3 patients had possible invasive pulmonary aspergillosis. The assessments of catheter and peripheral blood cultures of 14 the patients revealed methicillin-resistant coagulase negative staphylococcus aereus (MRCNS) growth while methicillin-resistant staphylococcus epidermidis (MRSE) grew in catheter and peripheral blood cultures of 2 patients, ESBL positive E. coli grew in peripheral blood cultures of 4 patients and carbapenem-resistant Klebsiella pneumoniae grew in catheter and peripheral blood cultures of 1 patient. The assessments of urine cultures revealed E.coli growth in five patients, Enterococcus faecium growth in 1 patient, carbapenem-resistant Klebsiella pneumoniae growth in one patient, vancomycin resistant enterococci growth in one patient. The assessments of sputum cultures revealed carbapenem-resistant Klebsiella pneumoniae growth in one patient and carbapenem-sensitive ESBL positive Klebsiella pneumoniae growth in one patient(Table 2).

Table 2 Positive culture results of patients

Blood cultures	Patients.(Noun)	Urine culture	Patients.(Noun)	Sputum culture	Patients(Noun)
MRCNS	14	E. coli	5	Carbapenem-resistant Klebsiella pneumoniae	1
MRSE	2	Enterococcus faecium	1	ESBL+ Klebsiella pneumoniae	1
MSSE	2	Vancomycin resistance	1		
ESBL+E. Coli	4	Carbapenem-resistance	1		
CRKP	1				

MRCNS: Metisiline resistance coagulase negative Staphylococcus Aureus

MRSE: Metisiline resistance Staphylococcus Epidermidis

MSSE: Metisiline sensitive Staphylococcus Epidermidis

CRKP: Carbapenem resistance Klebsiella Pneumonia

A patient developed diffuse pneumonia before the onset of neutrophil engraftment and died. All Gram positive isolates were susceptible to glycopeptides and all carbapenem resistant K. pneumoniae species were sensitive to colistin. The comparisons between culture-positive patients and culture-negative patients did not reveal any statistically significant difference in sex, peripheral blast counts at diagnosis, leukocyte count, hemoglobin concentrations, LDH levels, ECOG performance scores, the degree of mucositis, cytogenetic risk group, time to platelet engraftment, and CD34+ cell harvest whereas bacterial growth was statically significantly less common in cultures from those under the age of 45 and in patients who had a more rapid neutrophil engraftment.($p<0.005$)

No statistically significant intergroup differences were found in overall survival and progression free survival when the patients were stratified according to whether or not their cultures were positive and/or whether or not febrile neutropenia is present.

DISCUSSION

Infections caused by gram-negative or gram-positive microorganisms have a particular impact on the prognosis of immunocompromised patients. In a study of Reich et al. evaluating NPA during autologous

transplantations in a number of malignancies including multiple myeloma and lymphoma, elevated body temperatures were observed in 63% of study subjects (3). However, in patients who receive more intensive cytotoxic treatments and chemotherapy at myeloablative doses, such as patients with AML, neutrophil engraftment occurs relatively late and elevated body temperatures are observed more commonly. In our study, 87.2% of the patients experienced elevated body temperatures. In a study conducted by Bodey et al., they emphasized that infections became more prevalent with prolonged neutropenia, independently from the underlying disease. (7).In our study only one patient (2.1) died due to gram negative bacteremia.

In a study conducted by Auner et al. in 114 patients with hematological malignancies who underwent autologous bone marrow transplantation, elevated body temperatures were observed in 88% of the patients during neutropenic period; the cause of fever remained unknown in 60% of patients, while clinically documented infections were detected in 29% of the patients and microbiologically documented infections were detected in 11% of the patients who experienced fever (8). In a study conducted in 314 patients with hematological malignancies who underwent autologous bone marrow transplantation, Gil et al. reported elevated body temperatures in 92.3% of the patients during neutropenic period, the cause of fever was unknown in 51.7% of these patients while clinically documented infections were detected in 9.3% and microbiologically documented infections were detected in 38.9% of these patients (9). In our study fever was noted in 87.2% of the patients, the cause of fever remained unknown in 20% of these patients while 10% had only clinically documented infections and 70% had microbiologically documented infections. Gram (+) microorganisms were detected in most of the microbiologically documented infections. This result is closely linked to the use of a central venous line (10) and suggests inadequacy of sterile barriers used in transplantations. Therefore, the use of antimicrobial-coated catheters have been suggested and this type of catheters were found to be associated with a reduced incidence of infections in a study conducted in intensive care patients (11). In our center, central venous lines are placed by the same interventional radiologist and sterile catheter dressings are changed every 48 hours.

Possible invasive pulmonary aspergillosis was detected in three (6.38%) of the patients who developed neutropenic fever and these patients were treated with antifungal therapy whereas 7 (14.9%) patients received empirical antifungal therapy.

Higher rates of microbiologically documented infections in our study might be related to catheter, urine, sputum and 10 cc of peripheral blood sampling for cultures every 24 hours as long as the patient remained febrile, beginning from the onset of febrile neutropenia, along with effective working of the Microbiology Laboratory .

We achieved a higher detection rate for documented infections in this patient population by catheter, urine, sputum and peripheral blood sampling every 24 hours during febrile periods and by using imaging modalities more frequently. In addition to measures to prevent infections in this patient population, early detection of the causative agent of the infection is of crucial importance for an optimal treatment and prognosis.

CONCLUSION

Infections caused by gram-negative or gram-positive microorganisms have a particular impact on the prognosis of immunocompromised patients. In our department, infections do not present a significant risk for mortality in autologous HSCT among patients with AML. In addition to measures to prevent infections in this patient population, early detection of the causative agent of the infection is of crucial importance for an optimal treatment and prognosis. Conflict of interest, The authors declare that they have no conflict of interest.

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