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Clinical Impact of Colonization with Multidrug-Resistant Organisms on Outcome after Autologous Stem Cell Transplantation: A Retrospective Single-Center Study

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A significant increase in infections caused by multidrug-resistant organisms (MDRO) has been observed in recent years, resulting in an increase of mortality in all fields of health care. Hematological patients are particularly affected by MDRO infections because of disease- and therapy-related immunosuppression. To determine the impact of colonization with MDRO on overall survival, we retrospectively analyzed data from patients undergoing autologous hematopoietic stem cell transplantation at our institution. In total, 184 patients were identified, mainly patients with lymphomas (n = 98, 53.3%), multiple myelomas (n = 80, 43.5%), germ cell cancers (n = 5, 2.7%), or acute myeloid leukemia (n = 1, .5%). Forty patients (21.7%) tested positive for MDRO colonization. At a median follow-up time of 21.5 months, the main causes of death were infection in colonized and disease progression in noncolonized patients. Nonrelapse mortality (NRM) was higher in patients who tested positive for MDRO than in the noncolonized group (25.4% versus 3%, $P < .001$). Interestingly, NRM in neutropenia after autologous transplantation did not differ between colonized and noncolonized patients. Colonized patients, however, had inferior overall survival after autologous transplantation in univariate (61.7% versus 73.3%, $P = .005$) as well as in multivariate analysis (hazard ratio, 2.463; 95% confidence interval, 1.311 to 4.626; $P = .005$). We conclude that the period after discharge from hospital after autologous transplantation seems critical and patients with MDRO colonization should be observed closely for infections in the post-transplantation period in outpatient care.

INTRODUCTION

In recent years, an increase of infections with multidrug-resistant organisms (MDRO), namely multidrug-resistant gram-negative bacteria (MDRGN), vancomycin-resistant *Enterococcus faecium/faecalis* (VRE), and methicillin-resistant *Staphylococcus aureus* (MRSA), has been observed in all fields of health care, probably caused by widespread use of antibiotics [1]. The mortality due to infections with MDRO is considerably higher than those with non-MDRO [2,3] and 1 of the major risk factors for developing an MDRO infection is prior MDRO colonization [4,5].

In patients with hematological malignancies, bacterial infections represent a common complication because of immunosuppression related to disease or therapy, which often causes neutropenia and mucositis. MDRO infections represent an emerging problem in this patient cohort, with up to 45% mortality [6].

High-dose (HD) chemotherapy followed by autologous (auto) hematopoietic stem cell transplantation (HSCT) is an important treatment option for patients with multiple myeloma and with relapsed or refractory lymphomas and germ cell cancers. After HD chemotherapy, patients undergo a period of severe neutropenia lasting up to 2 weeks. During this time, nearly 80% of the patients develop fever [7]. Bloodstream infections (BSI) occur in nearly 20% of the patients

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during neutropenia [8] and are associated with higher mortality [9].

However, data concerning the outcome after auto-HSCT in patients who are colonized with MDRO are widely lacking. Therefore, we conducted a retrospective analysis at our institution to assess patient outcomes after auto-HSCT in relation to colonization with MDRGN and/or VRE and/or MRSA. We hypothesized that colonization and subsequent infection of patients with MDRO result in a higher mortality after auto-HSCT.

MATERIALS AND METHODS

Study Design and Microbiological Definitions

This retrospective single-center study evaluated clinical data of 184 patients admitted to the Department of Hematology and Medical Oncology at the University Hospital Frankfurt for auto-HSCT between January 2012 and October 2015. For patients receiving more than 1 auto-HSCT during the study period, only the first auto-HSCT was included. All patients were routinely screened for MDRO by rectal, pharyngeal, and nasal swabs on the day of admittance. Patients were classified as *colonized* if any MDRO were detected in any swab during the stay for auto-HSCT. In our setting, *MDRO* is a collective term for VRE, MRSA, and MDRGN. MDRGN has been previously defined as *Enterobacteriaceae* with extended-spectrum beta lactamase (ESBL)–like phenotype and *Enterobacteriaceae, Acinetobacter baumannii*, and *Pseudomonas aeruginosa* resistant against piperacillin, any third/fourth-generation cephalosporin, and fluoroquinolones ± carbapenems [10,11]. In accordance with the local infection control guidelines, all patients admitted to the hematology-oncology department are screened for MDRO on day of admittance as well as weekly during their entire stay.

Detection of MDRO and Molecular Resistance Analysis

To identify MDRGN, rectal swabs were collected using culture swabs with Amies collection and transport medium (Hain Lifescience, Nehren, Germany) and streaked onto selective CHROMagar ESBL plates (Mast Diagnostica, Paris, France). Species identification was done by matrix-assisted laser desorption ionization-time of flight analysis (VITEK MS, bioMérieux, Nürtingen, Germany). Antibiotic susceptibility testing was performed according to Clinical and Laboratory Standards Institute guidelines using VITEK 2 and/or antibiotic gradient tests (bioMérieux). In case of gram-negative carbapenem-resistant isolates, detection of genes encoding carbapenemases are routinely performed via PCR analysis and subsequent sequencing from carbapenem-resistant *Enterobacteriaceae* including the *bla* genes for carbapenemases NDM, VIM, IMP, OXA-48, OXA-48 like, and KPC as well as OXA-23, OXA-24, OXA-51, and OXA-58 for *Acinetobacter baumannii* [12,13].

For the detection of VRE, swabs were inoculated on ChromID VRE agar (bioMérieux). Identification of presumptive VRE was done by matrix-assisted laser desorption ionization-time of flight analysis and antibiotic susceptibility testing according to Clinical and Laboratory Standards Institute guidelines using VITEK 2 and antibiotic gradient tests.

Clinical Characteristics and Definitions

All patients were housed in air-filtered rooms on a dedicated transplantation unit. Auto-HSCTs were performed according to local procedure with routinely inserted central venous catheters and anti-infective prophylaxis with levofloxacin (n = 3 with cefotaxime) and fluconazole until neutrophil engraftment. *Neutropenia* was defined as an absolute neutrophil count <500/μL (neutropenia grade 4). Cotrimoxazole/trimethoprim was administered to prevent *Pneumocystis jirovecii* pneumonia for at least 6 months after transplantation, and acyclovir was administered from the day of HSCT until day +90.

Fever was defined as body temperature exceeding 38.3°C. If fever or any clinical suspicion of infection occurred, the prophylactic antibiotic regimen was changed in noncolonized patients to piperacillin/tazobactam and escalated if infection persisted. Colonized patients received antibiotics covering the resistance profile of their colonizing MDRO. Blood cultures were taken with every fever episode and inoculated into culture bottles (BD BACTEC Lytic/10 Anaerobic/F and BD BACTEC Plus Aerobic/F, Becton Dickinson, Heidelberg, Germany). According to the Centers for Disease Control, *BSI* was defined as at least 1 positive blood culture, except of coagulase-negative bacteria, where 2 consecutive positive blood cultures were required [14].

Endpoints of the Study

The primary endpoint was overall survival (OS); surviving patients were censored at last follow-up. Death other than from relapse/progression was defined as *nonrelapse mortality* (NRM). NRM was divided into NRM in neutropenia after auto-HSCT and NRM in non-neutropenic patients. Secondary endpoints were the rate of intensive care unit (ICU) treatment, fever, and *disease progression*, which was defined as progression requiring therapy after auto-HSCT. All patients provided written consent to the use of medical records for research. The study was approved by the local ethics committee (ethical approval number SHN 13-2016).

Statistical Analysis

SPSS (version 20.0; IBM Corp., SPSS Institute Inc. Chicago, IL) and R version 3.3.2 (packages "cmprsk" and "survival") were used for statistical analysis. For comparisons of continuous variables, we used the Student's *t*-test and the Mann-Whitney U test; for categorical variables, the Fisher's exact test and the chi-square test were used. For survival curves, the Kaplan-Meier method was used and curves were compared by log-rank test. For NRM and progression, cumulative incidence curves were drawn and compared using Gray's test. To test an association between death and different variables, multivariate analysis with Cox's proportional hazards was used.

RESULTS

Patient Characteristics

The clinical baseline patient characteristics are displayed in Table 1. One hundred eighty-four (184) patients were included into the study, of whom 107 (58.2%) were male. The most common diagnosis was lymphoma with 98 patients (53.3%), followed by 80 patients (43.5%) with multiple

Table 1
Baseline Patient Characteristics

Characteristic	All Patients (n = 184)	Noncolonized (n = 144)	Colonized (n = 40)	*P* Value*
Year of auto-HSCT, median (range)	2014 (2012-2015)	2014 (2012-2015)	2014 (2012-2015)	.227
Male sex	107 (58.2)	83 (57.6)	24 (60)	.789
Age at auto-HSCT, median (range), yr	55 (19-75)	55 (19-75)	52 (29-74)	.763
Diagnosis				.022
Lymphoma	98 (53.3)	69 (47.9)	29 (72.5)	
Multiple myeloma	80 (43.5)	70 (48.6)	10 (25.5)	
Other	6 (3.3)	5 (3.5)	1 (2.5)	
Prior therapies > 2	31 (16.8)	23 (16)	8 (20)	.547
Months from diagnosis to auto-HSCT, median (range)	9.7 (2.5-243.9)	9.9 (2.5-243.9)	8.7 (3.5-216)	.720
ECOG performance score <2	178 (96.7)	140 (97.2)	38 (95)	.484
Diabetes	14 (7.6)	11 (7.6)	3 (7.5)	.977
HIV	7 (3.8)	5 (3.5)	2 (5)	.655
Lung disease	7 (3.8)	5 (3.5)	2 (5)	.655
Liver disease	7 (3.8)	6 (4.2)	1 (2.8)	.626
Heart disease	17 (9.2)	9 (6.3)	8 (20)	.008
Renal dysfunction	13 (7.1)	9 (6.3)	4 (10)	.484

Data presented are n (%) unless otherwise indicated.
HIV indicates human immunodeficiency virus.
* *P* value reveals differences between noncolonized and MDRO-colonized patients