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Risk Factors and Outcomes of Infections by Multidrug-Resistant Gram-Negative Bacteria in Patients Undergoing Hematopoietic Stem Cell Transplantation

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A B S T R A C T

The objective of this study was to determine risk factors and outcomes of infections by multidrug-resistant gram-negative (MDR GN) bacteria in 241 recipients of hematopoietic stem cell transplantation (HSCT). The cumulative incidence of infections was 10.5% (95% CI, 12.0% to 25.8%), with 57% of infections occurring during the period of severe neutropenia (neutrophil count $< .1 \times 10^6$/L). In multivariate analysis, allogeneic transplant and colonization with MDR GN bacteria at admission to the transplant unit were significantly associated with an increased risk of infection. Although we observed neither transplant-related mortality (TRM) nor deaths due to infections by MDR GN bacteria after autologous transplant, in the allogeneic setting a significant difference was reported in terms of overall survival (OS) and TRM between patients who developed infections and those who did not (1-year OS, 39% versus 68%; 1-year TRM, 42% versus 19%). In multivariate analysis, refractory disease and development of grades III to IV graft-versus-host disease (GVHD) were factors that affected both TRM and OS, whereas occurrence of infections by MDR GN pathogens significantly reduced OS. We conclude that eligibility to allogeneic HSCT in MDR GN bacteria carriers should be carefully evaluated together with all other factors that independently influence outcome (disease status, donor, and GVHD risk).

INTRODUCTION

Bacterial infections are 1 of the most common complications in cancer patients and in recipients of hematopoietic stem cell transplantation (HSCT). Although published epidemiologic data on resistance to antibiotics are scanty and mostly dated, important differences in infection etiology and drug resistance exist among centers and geographic areas. In recent years, a reduction in the incidence of gram-negative (GN) in favor of gram-positive infections and higher rates of multidrug-resistant (MDR) infections in south-eastern versus north-western European regions have been observed [1]. Moreover, MDR GN infections have been recognized as 1 of the leading cause of mortality after solid organ transplantation [2-5], whereas their epidemiology and impact on patients with hematologic diseases and HSCT recipients have been less studied [6-9].

Theoretically, the emergence of antimicrobial resistance represents a challenging problem in patients undergoing HSCT for the following reasons: (1) eligibility to transplant in patients who have acquired the bacteria before the procedure (colonized patients or carriers); (2) risk of infection spread into the transplant center in spite of isolation procedures, leading to epidemic episodes (infection control); and (3) high mortality associated with infectious complications during the aplastic period and after the engraftment in highly immunocompromised patients due to graft-versus-host disease (GVHD) prophylaxis or treatments. We conducted a study to analyze the epidemiologic, microbiologic, and clinical factors associated with the acquisition of infections by MDR GN bacteria in our transplant center, with the objective

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to determine risk factors and outcomes of these infections in recipients of HSCT.

METHODS

Patients

In this observational retrospective study, we collected the data of all 241 consecutive patients who underwent HSCT at the Transplant Center of Udine between January 2013 and June 2015. Two thirds of the candidates to HSCT were treated at the Hematology Department located near the Transplant Center, whereas one third came from centers located in the surrounding towns (Trieste, Treviso, Padua). One hundred twenty-three patients underwent allogeneic HSCT and 118 autologous HSCT.

Patient and transplant characteristics are summarized in Table 1. Median patient age was 56 years (range, 15 to 77). Lymphoma and myeloma were the most common indication for autologous HSCT, accounting for 38% and 57% of cases, respectively, whereas 56% of patients undergoing allogeneic HSCT were affected by acute leukemia. Advanced disease after a heavy pretreatment, defined as at least 2 previous therapy lines, was reported in 37% of patients before autologous HSCT and in 68% of patients before allogeneic HSCT. Stem cell source was peripheral blood for all autologous transplants and for 67% of allogeneic transplants. Reduced-intensity conditioning regimens [10] were administered in 70% of the allogeneic transplants. Allogeneic stem cells came from HLA-matched sibling donors, haploidentical donors, and unrelated donors in 27%, 12%, and 51% of the patients, respectively. For unrelated donors, HLA typing for HLA-A, -B, -C, and -DRB1 loci was required. Forty-five of 75 unrelated transplants (60%) were HLA-mismatched, because at least 1 allelic or antigenic mismatch between donor and recipient was present in class I.

GVHD prophylaxis consisted of cyclosporine plus 3 to 4 methotrexate courses for HLA-matched sibling transplants, with the addition of antithymocyte globulin Thymoglobulin (Genzyme Europe, Naarden, Netherlands) for unrelated transplants. GVHD prophylaxis in haploidentical transplants consisted of cyclosporine, mycophenolate mofetil, and post-transplant cyclophosphamide. Acute GVHD was graded according to the 1994 Consensus Conference on Acute GVHD Grading criteria [11], and chronic GVHD was staged according to criteria developed by the National Institute of Health [12].

Definitions

A bacterial colonization was defined as the isolation of the microorganism from any nonsterile body site (usually rectum, urine, and oral cavity) in the absence of clinical findings of infection. A bacterial infection was defined as the isolation of the microorganism from blood culture or other usually sterile body sites in association with clinical signs of systemic inflammatory response syndrome and after the exclusion of other possible etiologies. MDR was defined as acquired nonsusceptibility to at least 1 agent in 3 or more antimicrobial categories [13]. Invasive fungal disease (IFD) was defined according to the revised definitions by the EORTC/MSG consensus group [14].

Monitoring and Management of MDR GN Infections

At admission to the transplant unit, history of previous infections and/or colonization was collected from all patients. Throat, nasal, and rectal swabs and urine culture were collected at admission and were repeated when necessary, as clinically required. In case of fever > 38°C, patients underwent 3 sets of blood cultures by peripheral veins and central catheters.

All patients were isolated in single rooms and received anti-infective prophylaxis with intravenous levofloxacin, fluconazole, and acyclovir. Patients with history of previous infection or colonization by MDR GN bacteria (independently of the results of swabs at admission) and patients with any positive swabs at admission were considered as MDR GN bacteria carriers. Hospital staff and all people who came in contact with carriers and their body fluids had to use additional contact precautions (such as gloves and disposable coats).

Patients who had previous infections by carbapenem-resistant *Klebsiella pneumoniae* and were still colonized before transplant received 1 or more courses of oral gentamicin at the dose of 80 mg q.i.d. for 7 days to reach negative rectal swabs before admission [15]. If an MDR carrier developed fever > 38°C during the neutropenia period, he or she was treated with an antibacterial combination effective against the MDR GN pathogen until blood cultures results were available.

Two antimicrobial combinations against the most common carbapenem-resistant Enterobacteriacae were administered [16]. Pre-emptive treatment directed to carbapenem-resistant *K. pneumoniae* was meropenem 6 g/24 hours i.v. continuous infusion, tigecycline 200 mg i.v. and then 100 mg × 2/day, and gentamicin 140 mg i.v. once daily. Antibacterial combination against MDR *Pseudomonas aeruginosa* was meropenem 6 g/24 hours i.v. continuous infusion or piperacillin/tazobactam 18 g i.v. continuous infusion, amikacin 20 mg/kg i.v. daily, and/or colistin 9,000,000 UI i.v. and then 4,500,000 b.i.d. i.v. on the basis of pattern of sensitivity to antimicrobial agents of the previous isolations and severity of infection. Once diagnosis of MDR GN bacteria infection was established, treatment followed in vitro antibacterial drugs testing in vitro.

Amikacin, meropenem, gentamicin, and piperacillin/tazobactam dosages were driven by regular therapeutic drug monitoring. Treatment of documented infections by MDR GN bacteria was carried on until the infection was microbiologically eradicated, all clinical signs of infection were resolved, and the patient was afebrile for at least 4 consecutive days.

Surveillance Cultures

Rectal, nasal, and throat swabs and urine were inoculated into a nonselective culture media and incubated for 24 hours. Colonies screening for

Table 1
Characteristics of Patients and Transplants

	Autologous HSCT (n = 118)	Allogeneic HSCT (n = 123)	All (N = 241)
Median age, yr (range)	58 (22-77)	52 (15-69)	56 (15-77)
Sex (male/female)	67/51	69/54	136/105
Diagnosis			
Leukemia	5 (4%)	69 (56%)	74 (31%)
Lymphoma	45 (38%)	19 (15%)	64 (26%)
Multiple myeloma	67 (57%)	9 (7%)	76 (32%)
Other	1 (1%)	26 (22%)	27 (11%)
Disease status at transplant			
Responsive	110 (93%)	84 (68%)	194 (80%)
Resistance/progression	8 (7%)	39 (32%)	47 (20%)
Disease phase*			
Early	75 (63%)	39 (32%)	114 (47%)
Advanced	43 (37%)	84 (68%)	127 (53%)
Donor and HLA matching			
HLA-identical sibling		33 (27%)	
HLA-haploidentical		15 (12%)	
Matched unrelated		30 (24%)	
Mismatched unrelated		45 (37%)	
Stem cell source			
Bone marrow	118 (100%)	41 (33%)	41 (17%)
Peripheral blood		82 (67%)	200 (83%)
Conditioning			
Myeloablative	118 (100%)	37 (30%)	155 (64%)
Reduced intensity		86 (70%)	86 (36%)

* Early phase, a single line of treatment before transplant; advanced phase, at least 2 lines of treatments before transplant.

MDR GN bacteria were identified by conventional phenotypic microbiologic techniques (culture characteristics, Gram stain, biochemical reactions, and susceptibility to antimicrobial agents). Antibiotic susceptibility confirmation was performed using both a microdilution method and standardized criteria defined by the Clinical Laboratory Standards Institute and the European Committee on Antimicrobial Susceptibility Testing. A phenotypic resistance was determined by an increase in the minimum concentration of antimicrobial agent required to inhibit the growth of a microbe. Standard operating procedures and robust quality control guaranteed accuracy and reproducibility of the results.

Statistical Analyses

Data were collected in an XLS database (Microsoft Office 2010; Microsoft Corporation, Redmond, WA) from patient medical records and reviewed by a senior hematologist and an infective diseases consultant, and data were imported into Stata/SE 9.0 for Windows (StataCorp, College Station, TX) for statistical analysis. The close-out date for analysis was December 31, 2015.

Transplant-related mortality (TRM) was defined as death due to all causes not related to the underlying disease. Overall survival (OS) was defined as the time (months) from transplantation to either death or last observation. OS was described according to the Kaplan-Meier approach. Comparison between groups was performed using the log-rank test.

The cumulative incidence method was used to estimate TRM and MDR infection incidence accounting for the presence of competing risks. For TRM, relapse was the competing event; for MDR GN infection incidence, death was the competing event. We collected patient-related and transplant-related variables and explored which patient-related and transplant-related factors were associated with incidence of MDR GN infections, TRM, and OS. We examined the potential association between variables and incidence of MDR GN infections in the overall sample of 241 patients. We limited the analysis of the potential association between variables and TRM and OS to the population of allogeneic transplant recipients, because no TRM event occurred in the group of autologous transplants.

Patient-related variables included age (as continuous variable), sex (males versus females), underlying disease (acute leukemias, lymphoma, or myeloma or other diagnoses), disease status at HSCT (responsive versus resistance/progression), and phase of transplant (early versus advanced). Transplant-related variables included donor type (HLA-identical sibling versus unrelated or partially matched), stem cell source (bone marrow versus peripheral blood), conditioning regimen (myeloablative versus reduced intensity), duration of severe neutropenia (number of days with neutrophil count $< .1 \times 10^6$/L, as continuous variable), duration of severe thrombocytopenia (number of days with platelets count $< 20 \times 10^9$/L, as continuous variable), GVHD prophylaxis (antithymocyte globulin or not), and acute GVHD (grades 0 to II versus III to IV). Other factors that were correlated with incidence of MDR infections, TRM, and OS were previous history of infection or colonization with MDR GN bacteria before transplant (yes or no), colonization with MDR GN bacteria at transplant (yes or no), infections by gram-positive bacteria (yes or no), infections by GN bacteria sensitive to antibacterial agents (yes or no), and proven or probable IFD (yes or no).

Univariate and multivariate Cox regression were used to estimate which patient-related and transplant-related factors were associated with OS. Based on the method of Fine and Gray [17], univariate and multivariable backward stepwise competing-risk regression were used to explore which patient-related and transplant-related factors were associated with incidence of infections by MDR GN bacteria and TRM. This model is based on the hazard of the subdistribution and provides a simple relationship between covariates and cumulative incidence [17].

Multivariate analyses included all variables significant at $P \leq .10$ in univariate analysis. Retention in the stepwise model required the variable to be significant at $P \leq .05$ in a multivariate analysis.

RESULTS

Monitoring of Colonization and/or Infection by MDR GN Bacteria

Eighteen of 241 patients (7%) had a previous history of colonization (5 patients) or infection (13 patients) by MDR GN bacteria occurring at a median time of 135 days (range, 28 to 352) before admission. At the time of admission to the transplant unit, 13 patients (5%) were MDR GN bacteria carriers: 8 patients had positive rectal swabs, 4 patients had positive urine cultures, and 1 patient had both positive rectal swab and urine culture. Nine of 13 patients (69%) were colonized by *K. pneumoniae* (Table 2). Only 1 of 4 patients infected and colonized with carbapenem-resistant *K. pneumoniae* had obtained a negative rectal swab after a course of oral gentamicin before entering the Transplant Center. One hundred forty-three of 241 patients (59%) developed at least 1 infective episode due to a documented bacterial or fungal etiology: 54 patients had infections by gram-positive bacteria, 64 patients showed infections by GN bacteria, 15 patients developed IFDs, and 10 patients presented both bacterial infections and IFDs.

Table 2
Characteristics of Colonizations at Admission to the Transplant Center and Infections after Transplant by MDR GN Bacteria

	K. pneumoniae	*P. aeruginosa*	*E. coli*	Total
GN MDR colonization at transplant				
Rectal swabs	7	2	0	9
Urine cultures	3	2	0	5
Throat swabs	0	0	0	0
Total sites (total patients)	10 (9*)	4 (4)	0	14 (13*)
Site of GN MDR infections				
Blood	6	7	0	13
Lung	1	4	0	5
Gut	1	3	0	4
Urogenital	4	6	1	11
Total sites (total patients)	12 (9*)	20 (15*)	1	33 (25*)

* The number includes patients with more than 1 site of colonization or infection.

Twenty-five of 241 patients (10%) developed at least 1 infective episode by MDR GN bacteria at a median of 9 days (range, 0 to 75) after HSCT, with 57% of infections occurring during the period of severe neutropenia (neutrophil count $< .1 \times 10^6$/L). With a median follow-up of 11 months (range, 1 to 30) after transplant, the cumulative incidence of infections by MDR GN pathogens was 10.5% (95% confidence interval [CI], 12.0% to 25.8%) overall and 2.5% (95% CI, .7% to 6.7%) and 18.4% (95% CI, 12.0% to 25.8%) after autologous and allogeneic HSCT, respectively. A documented infection by a MDR GN bacteria with the same pattern of sensitivity to antimicrobial drugs occurred in 6 of 13 colonized patients (46%): Infections developed in none of the 3 recipients of autologous transplant and in 6 of 10 recipients of allogeneic transplant. Twenty-five patients presented 33 infective episodes. MDR GN bacteria were isolated from 13 blood cultures (40%), 11 urine cultures (33%), 4 stool cultures (12%), and 5 broncholavage fluids (15%). The MDR GN microorganism was *P. aeruginosa* in 20 samples (61%), *K. pneumoniae* in 12 (36%), and *Escherichia coli* in the remaining case (3%) (Table 2). The pattern of sensitivity of the MDR GN bacteria to antimicrobial drugs is provided in the Supplementary Table 1.

Factors Associated with Development of MDR GN Infections

Among factors related to patient and disease characteristics, an advanced disease phase and resistant disease at transplant significantly increased the incidence of MDR infections, whereas younger age and lymphoma or myeloma as indications for transplant were associated with a significant reduction of MDR infection incidence (Table 3). The factors related to transplant procedure that were significantly ($P \leq .10$) associated with the development of infections by MDR GN bacteria were type of transplant, intensity of conditioning, stem cell source, duration of severe neutropenia, and thrombocytopenia. We did not observe any significant correlation between donor type or GVHD occurrence and MDR infections. Moreover, a history of previous MDR infections or

Table 3
Univariate Analysis of Risk Factors for Incidence of Infections by MDR GN Bacteria

Risk Factor	SHR	95% CI	*P*
Sex			
Male	1	.916-4.516	.081
Female	2.034		
Median age at transplant (yr) modeled as continuous variable	.971	.943-.999	.048
Diagnosis			
Leukemia	1		
Other diagnosis	.184	.079-.424	.000
Disease status			
Responsive	1	1.125-5.790	.025
Resistant	2.552		
Disease phase*			
Early	1	1.003-5.687	.049
Advanced	2.390		
Procedure			
Autologous transplant	1	2.301-26.015	.001
Allogeneic transplant	7.737		
Preparative regimen			
Myeloablative	1	1.340-6.573	.007
Reduced intensity	2.966		
Stem cell source			
Bone marrow	1	.182-.958	.039
Peripheral blood	.417		
Median days of neutrophils $< .1 \times 10^6$/L modeled as continuous variable	1.174	1.107-1.246	.000
Median days of platelets $< 20 \times 10^9$/L modeled as continuous variable	1.051	1.023-1.080	.000
Donor			
HLA-identical sibling	1	.409-2.725	.911
Unrelated or partially matched	1.056		
GVHD prophylaxis			
No ATG	1	.375-2.132	.802
ATG	.894		
Acute GVHD			
Grades 0-II	1	.449-2.474	.903
Grades III- IV	1.054		
Infections or colonizations with MDR GN bacteria before transplant			
No	1	3.849-20.904	.000
Yes	8.971		
Colonizations with MDR GN bacteria at transplant			
No	1	2.808-17.178	.000
Yes	6.945		
Non-MDR GN infections			
No	1	.587-3.555	.423
Yes	1.444		
GP infections			
No	1	.734-3.664	.227
Yes	1.640		
Proven/probable IFD			
No	1	1.733-9.880	.001
Yes	4.137		

SHR indicates subdistribution hazard ratio; ATG, antithymocyte globulin; GP, gram-positive.
* Early phase, a single line of treatment before transplant; advanced phase, at least 2 lines of treatments before transplant.

colonization before transplant, positive swabs at admission to the transplant unit, and concomitant or subsequent IFDs were significantly associated with increased infection incidence. In multivariate analysis, allogeneic transplant and colonization with MDR GN bacteria were significantly associated with a higher risk of infections (subdistribution hazard ratio, 18.822; 95% CI, 2.477 to 143.008; $P = .005$; subdistribution hazard ratio, 8.256; 95% CI, 3.374 to 20.203; $P = .000$, respectively).

Outcome

With a median follow-up of 11 months (range, 1 to 30) after transplant, 184 of 241 patients (76%) were alive with a 1-year OS of 79% (95% CI, 73% to 84%). In total, 57 patients died: 30 of disease progression and 27 of transplant-related complications. All TRM events occurred after allogeneic transplant. Among 122 assessable patients after allogeneic transplant, 51 (42%) developed acute GVHD (grades I to II in 42 patients and grades III to IV in 9 patients). We did not observe a significant association between colonization or infection by MDR GN bacteria and incidence of acute GVHD, which occurred in 4 of 10 carriers (40%) compared with 47 of 112 noncolonized patients (42%) ($P = .590$) and in 9 of 21 MDR infected patients (43%) in comparison with 42 of 101 patients without MDR infection (41%) ($P = .550$). Moreover, there were no significant differences in rates of grades III to IV acute GVHD and visceral organ involvement (MDR positive patients: grades III to IV acute GVHD 2/9 [22%], gut involvement 2/9 [22%], liver involvement 1/9 [11%]; MDR negative patients: grades III to IV acute GVHD 7/42 [17%], gut involvement 11/42 [26%], liver involvement 8/42 [19%]; $P = .504$, $P = .586$, $P = .496$, respectively].

Cumulative incidence of 1-year TRM was 0% after autologous transplant and 23% (95% CI, 16% to 32%) after allogeneic transplant. Among the 27 patients dying of TRM, infection by MDR GN bacteria was considered the primary cause of death in 9 patients (33%), followed by GVHD in 6 patients, organ toxicities in 5 patients, central nervous system hemorrhage in 3 patients, and other infections in 4 patients. Nine of the 25 patients infected by MDR GN microorganisms died because of the infection, with an overall infection-related mortality rate of 36%. Deaths were due to septic shock in 4 patients and respiratory failure secondary to pneumonia in 5 patients. *P. aeruginosa* and *K. pneumoniae* equally contributed to mortality (5 and 4 deaths, respectively).

Because neither TRM events nor deaths due to MDR infections occurred after autologous transplant, we focused our analysis on factors affecting the outcome only in the setting of allogeneic transplant. There was a statistically significant difference in terms of OS and TRM between patients who developed MDR GN infections after allogeneic HSCT and those who did not (1-year OS, 39% versus 68%; 1-year TRM, 42% versus 19%; log-rank test $P = .014$; Gray test $P = .003$) (Figures 1 and 2). In univariate analysis, factors significantly associated with TRM were resistant disease at transplant ($P = .002$), duration of severe neutropenia ($P = .005$), development of

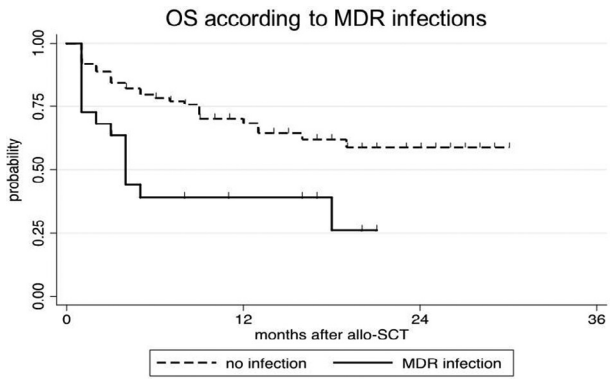

Figure 1. OS according to infections by MDR GN bacteria after allogeneic stem cell transplantation (allo-SCT) ($P = .014$).

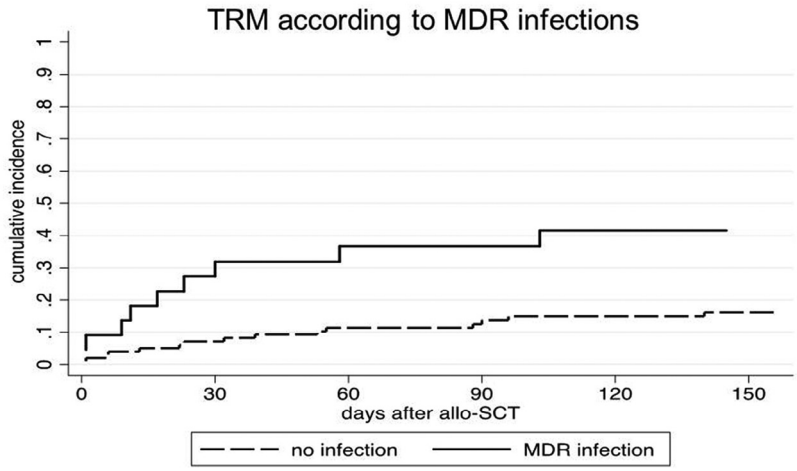

Figure 2. Cumulative incidence of TRM according to infections by MDR GN bacteria after allo-SCT ($P = .003$).

Table 4
Multivariate Analysis of Risk Factors for TRM and OS

	TRM			OS		
Factor	HR	*P*	95% CI	HR	*P*	95% CI
Disease status at transplant:						
Responsive	1	.006	1.386-6.938	1	.001	1.649-6.011
Refractory/progressive	3.101			3.148		
Acute GVHD						
Grades 0-II	1	.000	2.187-10.108	1	.033	1.085-6.640
Grades III-IV	4.702			2.685		
Infections by MDR GN bacteria after transplant						
No				1	.006	1.344-5.657
Yes				2.757		

HR indicates hazard ratio.

grades III to IV acute GVHD ($P = .012$), need for secondary treatment for acute GVHD ($P = .014$), development of infections by MDR GN bacteria ($P = .000$), and diagnosis of IFD ($P = .057$). The variables that showed a significant association with OS in the univariate analysis were leukemia as underlying hematologic disease ($P = .055$), resistant disease at transplant ($P = .000$), duration of severe neutropenia ($P = .001$), development of grades III to IV acute GVHD ($P = .033$), need for secondary treatment of acute GVHD ($P = .001$), history of previous infections or colonization by MDR GN bacteria before transplant ($P = .012$), positive swabs at admission ($P = .035$), and MDR infections after transplant ($P = .014$). In multivariate analysis, a refractory disease at transplant and development of grades III to IV acute GVHD were factors that independently affected both TRM and OS after allogeneic transplant, whereas occurrence of MDR infections significantly reduced OS (Table 4).

DISCUSSION

Antimicrobial resistance among GN bacteria isolated in hospitalized patients is a growing problem, with a heterogeneous distribution around the world. This phenomenon has reached Northern Italy only in recent years [18], with a few cases identified recently in our hospital. The emergence of MDR GN bacteria among some HSCT candidates and the risk of spread in the transplant unit have led us to develop a strict program for infection control. The protocol was based on (1) identification of all MDR GN bacteria carriers before admission to the transplant unit, (2) increased contact precautions in colonized and/or infected patients, and (3) prompt treatment with antimicrobial associations of all febrile episodes in MDR GN bacteria carriers, stopping the treatment in case of negative microbiologic cultures.

At the time of admission, colonization was identified in 5% of patients. Rectal swabs were more informative than urine cultures and identified *K. pneumoniae* more often than *P. aeruginosa*. We tried to decolonize patients with swabs positive for carbapenem-resistant *K. pneumoniae*, but only 1 of 4 patients reached negativity, confirming that this treatment cannot represent a standard practice and needs to be investigated further. The incidence of infections by MDR GN bacteria was 10% after transplant, with most infections occurring before engraftment. Forty six percent of patients with positive swabs at transplant developed an overt infection, confirming the infection rate observed by a recent Italian survey in patients colonized with carbapenem-resistant *K. pneumoniae* undergoing HSCT [19]. Factors predictive for risk of infection by MDR GN bacteria in multivariate analysis were allogeneic transplant and colonization at transplant. The association with allogeneic transplant probably reflects the clinical characteristics of recipients of this procedure, who were more likely affected by acute leukemias and were more often heavily pretreated compared with patients receiving autologous transplant. Moreover, these patients were more likely exposed to antimicrobial drugs before transplant and had more severe immunosuppression and alteration of the endogenous flora, which increased the susceptibility to different pathogens.

Development of infections by MDR GN bacteria had no impact on the outcome of autologous HSCT recipients, because the few episodes resolved without clinical consequences. In contrast, MDR infections significantly increased TRM and reduced OS of allogeneic HSCT recipients, being an independent predictor for poor OS. We found that development of infections by MDR GN microorganisms was an independent risk factor for mortality, along with other well-known predictors for negative transplant outcome, such as active disease and severe acute GVHD. Moreover, in our study the rates and severity of acute GVHD were similar in patients with and without colonization or infection by MDR GN bacteria, differently from what reported by Bilinski et al. [20], who found that gut colonization with antibiotic-resistant bacteria predisposed to more frequent and severe GVHD, especially of the gastrointestinal tract.

Our results may support the position of some transplant experts, who do not consider MDR GN bacteria colonization "per se" a contraindication to allogeneic transplant [21]. In fact, eligibility to transplant in patients who have acquired the pathogen before the procedure should be evaluated in the context of all other factors known to influence the outcome, such as disease status, HLA-matching of donor, and risk for acute GVHD, to weigh the overall risk-to-benefit ratio of performing HSCT. Because deaths secondary to MDR infections were more common before engraftment, in clinical practice if we plan a transplant in MDR GN bacteria carriers, we should adopt all measures to speed up neutrophil engraftment, such as use of peripheral blood stem cells, infusions of a large amount of cells, and reduced-intensity conditioning, even if these measures have not yet been proven to reduce mortality .

A comparison of our infection-related mortality rate with previously reported data is hard, because of differences in study designs, patient populations, and MDR microorganisms involved. Most published studies are on infections by carbapenem-resistant *K. pneumoniae* and were collected in intensive care units, in solid organ transplants, and in patients with hematologic malignancies [22-25]. Recently, an Italian survey by Girmenia et al. [19] reported the outcome of colonizations and infections by carbapenem-resistant *K. pneumoniae* in recipients of HSCT. Comparing the mortality rate reported in that survey with our study, we note a reduction after both autologous and allogeneic transplants (from 16% to 0% and from 64% to 36%, respectively). It can be hypothesized that our infection control strategy, based on screening of MDR carriers and administration of first-line MDR bacteria-targeted therapy, contributed to lower the mortality rate after transplant in comparison with patients enrolled in a multicenter survey and treated with empirical antimicrobial regimens.

We acknowledge that our study has several limitations. First, the data were collected in a single center of southern Europe, where incidence of infections by MDR GN pathogens has been increasing; therefore, the results cannot be generalized to other centers with different epidemiologic data. Second, we studied both autologous and allogeneic transplant recipients, who had different risks of infection and mortality. However, this study suggests a positive impact of a strict infection control strategy that every transplant center should adopt on the basis of its own epidemiologic data.

In conclusion, in a 3-year surveillance program of MDR infections in the HSCT setting, all eligible patients could proceed to autologous transplant with a negligible risk of toxicity. In case of allogeneic transplantation, patients who developed MDR infections had a poorer outcome than patients without infection, suggesting that eligibility to allogeneic transplant in colonized patients should require a careful evaluation of the risk-to-benefit ratio.

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SUPPLEMENTARY DATA

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