EVALUATION OF COLONIZATION AND INFECTION EPIDEMIOLOGY IN ALLOGENEIC STEM CELL TRANSPLANTATION RECIPIENTS: A PROSPECTIVE, MULTICENTER STUDY

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INTRODUCTION

Infection-related mortality (IRM) remains a major challenge associated with allogeneic hematopoietic stem cell transplantation (alloHSCT). The emergence of multidrug-resistant (MDR) pathogens has become a global threat connected with life-threatening opportunistic infections causing an increased risk of both early and late IRM [1, 2]. Despite the development of modern preventive strategies and a better understanding of the mechanisms of immunosuppression, the problem of post-transplantation infections is still crucial.

AIM

The study aimed to analyze the colonization with pathogenic microorganisms, the incidence of infections up to 100 days after alloHSCT, the effectiveness of the prophylaxis, and evaluation of treatment outcomes in patients undergoing alloHSCT.

METHOD

- A multicenter, prospective study of the Polish Adult Leukemia Group (PALG) assessing 239 patients with a median age of 47yr (range: 19-72yr) who underwent alloHSCT between 01-06.2022 in 7 Hematology Departments in Poland.
- The most common indication for alloHSCT was AML - 45%, followed by ALL - 16%, lymphoma - 13%, and other - 26%.
- Microbiological cultures of urine and the anal area were performed on each patient in the pre-transplant period to determine colonization. Additionally, colonization of the throat, and the nasal cavity was assessed in 44% patients.
- Antibacterial prophylaxis was used in 40% of patients (24% - ciprofloxacin, 16% - rifaximin), antifungal (fluconazole) - 60%, antiviral (acyclovir) - 98%, and CMV prophylaxis (letermovir) in 22%.
- Prophylaxis was administered to patients from the start of chemotherapy until the regeneration of the WBC (ANC>0.5G/l) and then phenoxymethylpenicillin, cotrimoxazole, and acyclovir were given until one year after HSCT or until the end of immunosuppression if was used longer.

REFERENCES

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2. Bolon YT, et al. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR summary slides, 2022. [accessed 1 August 2023].

RESULTS

Evaluation of colonization

- The presence of colonization before alloHSCT was detected in 75% patients.
- The most common location of colonization was the anal region (46%), which was mainly colonized by *Escherichia coli* ESBL (-) (18%).
- MDR pathogens accounted for 29% of all positive colonization cultures before alloHSCT.

Evaluation of infection

- Infections occurred in 81% of patients up to 100 days after alloHSCT.
- Bacteremia was observed in 37% cases (mostly by *Staphylococcus epidermidis* MSCNS). 25% of colonized patients developed a total of 59 infections with the pathogen responsible for their previous colonization (Table 1).
- MDR pathogens accounted for 39% of all pathogens responsible for infections. The most common type of MDR was extended-spectrum beta-lactamase (ESBL) (40%).
- Fungal infections occurred in 20% of patients, mostly in gastrointestinal tract (39%). The most frequently detected fungal pathogen was *Candida albicans* (36%).
- CMV reactivation occurred in 40% of patients, and EBV reactivation in 9%.

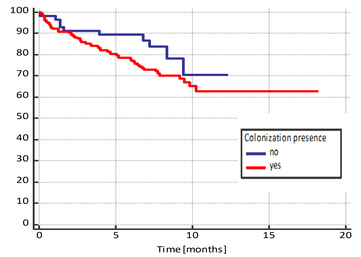


Figure 1. OS comparison depending on absence/presence of colonization.

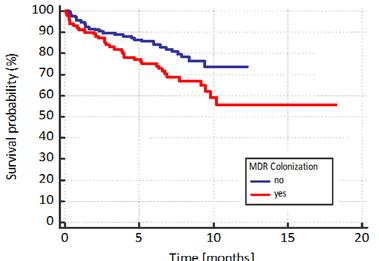


Figure 2. OS comparison depending on absence/presence of MDR pathogen colonization.

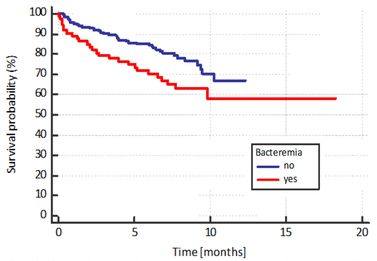


Figure 3. OS comparison depending on absence/presence of bacteremia. Log-rank p=0.03.

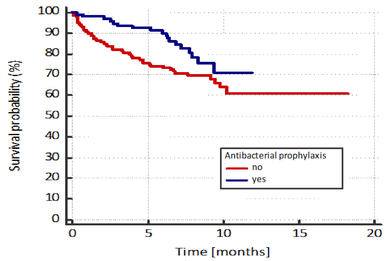


Figure 4. OS comparison according to the use/non-use of antimicrobial prophylaxis. Log-rank p=0.04.

Survival analysis

- The median overall survival (OS) from date of alloHSCT was not reached.
- Death within 100 days after alloHSCT occurred in 13% of patients, 52% of these patients died in the course of bacterial septic shock.
- The presence of colonization before alloHSCT was associated with shorter OS compared to non-colonized patients (p=0.03) (Figure 1).
- MDR pathogen colonization influenced the shortening of overall survival (OS) compared to non-MDR pathogen colonization (p=0.03) (Figure 2).

Analysis of prognostic factors

- In a multivariate Cox regression model for OS bacteremia (HR 2.02 95%CI: 1.03-3.96, p=0.04) was independent predictor of shorter survival, and the use of antibacterial prophylaxis was associated with longer survival (HR 0.24 95%CI: 0.08-0.69 p=0.01) (Table 2), (Figure 3, 4). In addition, the presence of fungal infection was a factor shortening OS (p=0.02).
- The initial presence of colonization and duration of neutropenia <1.0 G/l significantly increased the risk of infection (p=0.018; p=0.004, respectively), while reduced-intensity conditioning and ciprofloxacin prophylaxis significantly decreased infection incidence (p=0.018; p=0.02, respectively).

	Coefficient	p	HR	95% CI	
				lower	upper
Age	0.03	0.01	1.03	1.01	1.05
WBC level at allo-HSCT	0.89	0.01	2.45	1.30	4.62
ANC level at allo-HSCT	-1.07	0.00	0.34	0.16	0.71
G-CSF days	0.10	0.00	1.10	1.04	1.16
Bacteremia	0.70	0.04	2.02	1.03	3.96
CMV infection	-0.86	0.02	0.43	0.21	0.88
Antibacterial prophylaxis	-1.45	0.01	0.24	0.08	0.69

Table 2. Prognostic factors for OS in alloHSCT recipients estimated by multivariate analysis, using Cox regression.

CONCLUSIONS

- The presence of colonization is associated with an increased incidence of infection, while colonization with MDR pathogens influences shorter survival in alloHSCT recipients.
- In 25% of originally colonized patients, the presence of infection with colonizing pathogen was detected. Thus, knowledge of the colonizing pathogen may allow more effective implementation of targeted treatment in case of infection.
- The use of antimicrobial prophylaxis reduces the risk of infection and affects longer survival.

ACKNOWLEDGEMENTS

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Table 1. Characteristics of infections caused by a colonizing pathogen in alloHSCT recipients.

Number of patients colonized before alloHSCT				n=180
Number of patients with at least one infection with colonizing pathogen (%)				45/180 (25%)
Etiology	**Location of colonization**		**Location of infection**	**Number of secondary infections**
***Klebsiella pneumoniae* ESBL (+)**	anus	→	vascular bed	7
	anus	→	gastrointestinal tract	2
	anus	→	urinary tract	1
	anus	→	sputum	1
	urinary tract	→	vascular bed	1
	throat	→	vascular bed	1
***Escherichia coli* ESBL (-)**	anus	→	vascular bed	3
	urinary tract	→	urinary tract	3
	urinary tract	→	vascular bed	1
	anus	→	gastrointestinal tract	1
	throat	→	vascular bed	1
***Escherichia coli* ESBL (+)**	anus	→	vascular bed	3
	anus	→	urinary tract	2
	anus	→	gastrointestinal tract	2
Enterococcus faecium	urinary tract	→	urinary tract	4
	anus	→	urinary tract	2
	anus	→	vascular bed	1
***Klebsiella pneumoniae* ESBL (-)**	throat	→	vascular bed	2
	throat	→	sputum	1
	anus	→	gastrointestinal tract	1
	urinary tract	→	urinary tract	1
	urinary tract	→	vascular bed	1
	urinary tract	→	skin near the central-line	1
***Enterococcus faecium* VRE**	anus	→	vascular bed	3
	anus	→	gastrointestinal tract	2
	urinary tract	→	skin near the central-line	1
Pseudomonas aeruginosa VIM	anus	→	skin near the central-line	3
	anus	→	vascular bed	1
	anus	→	urinary tract	1
	anus	→	cellulitis	1
Pseudomonas aeruginosa	throat	→	lungs	1
Enterococcus faecalis	anus	→	vascular bed	1
***Klebsiella pneumoniae* VIM**	anus	→	vascular bed	1
Enterobacter cloacae	urinary tract	→	skin near the central-line	1

alloHSCT - *allogeneic hematopoietic stem cell transplantation;* ESBL - *extended-spectrum beta-lactamase;* VRE - *Vancomycin-Resistant Enterococcus;* VIM - *Verona integron-encoded metallo-ß-lactamas*

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