

Antimicrobial prophylaxis in patients after hematopoietic cell transplantation: results of a survey of the Polish Federation of Bone Marrow Transplant Centers

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Introduction

Infection is a major cause of morbidity and one of the major causes of death after hematopoietic cell transplantation (HCT). Since infection may compromise the benefit of transplantation, each infectious complication remains a clinical challenge in patients after transplantation. In European Group for Blood and Marrow Transplantation (EBMT) analysis of 114,491 patients with 5-year follow-up, a total of 55,668 patients were reported dead [1]. In 22.3% of all deaths, the cause was infection. The rate of deaths from infections varied over calendar time and posttransplant phase. Overall the rate of infectious deaths decreased in all phases after autologous HCT (auto-HCT), and up to day 100 and beyond after allogeneic HCT (allo-HCT) which was the second cause of death after auto-HCT and third after allo-HCT.

With respect to the risk of infectious complications, posttransplant period is usually divided into the following intervals: very early (up to day 30 and beyond), early (between days 30 and 100), late (between day 100 and 1 year), and very late (beyond 1 year). Alternatively, the phases can be divided into pretransplant phase, neutropenic phase, and immunosuppression phase; in allo-HCT setting, additional phase of immunosuppressive prophylaxis and graft-versus-host disease (GVHD) is distinguished. The risk of infections is particularly high during very early phase due to the toxicity of conditioning and neutropenia, as well as immunosuppressive therapy

in case of allo-HCT; additionally, immunosuppression can be continued for many months after hematological recovery, especially in patients diagnosed with GVHD. Incidence of infections is particularly high during very early and early posttransplant phase [2-6]; however, the patient remains at risk of infectious complications from the beginning of conditioning regimen through the entire posttransplant period.

All Polish hematopoietic cell transplant centers were invited to participate in the survey on proposed prophylactic pharmacological approach for patients undergoing auto- or allo-HCT, both in pediatric and adult settings. This report presents the results of the survey.

Methods

During Transplant Workshop of Polish Federation of Bone Marrow Transplant Centers in Poznan, dated October 12, 2019, a survey on proposed antimicrobial prophylaxis was distributed, and one questionnaire per center was prepared. Based on their own experience, the centers were asked to suggest antibacterial, antifungal, and antiviral prophylaxis in auto- and allo-HCT settings, with respect to the pretransplant phase, neutropenic phase, immunosuppressive prophylaxis phase and in case of GVHD. Additional questions were related to other supportive therapies and key diagnostic tests. Both pediatric and adult centers answered the same questionnaire. Vaccinations were not included in the survey.

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Five adult and one pediatric centers perform auto-HCT only; however, they partially answered the allo-HCT section, as the survey questions were about the recommended approach.

No Bioethical Committee agreement was necessary for this study, as no patients were involved. All participants of the survey are coauthors of this manuscript and they gave their agreement for publication.

Results and Discussion

A total number of 23 centers participated, including 6 for pediatric and 17 for adult patients. The summary of prophylaxis proposed by the centers with respect to auto- and allo-HCT and with respect to pre- and posttransplant phases in allo-HCT setting is shown in table I.

Prophylaxis in auto- and allo-HCT settings

Antibacterial prophylaxis

More than half of adult centers both in auto- and allo-HCT patients prefer to use quinolones (ciprofloxacin or levofloxacin). Some of the adult centers are in favor of use of oral penicillins (amoxicillin ± clavulanate or V-cyllin) mainly in allo-HCT setting. The choice of prophylaxis in pediatric centers is split between ciprofloxacin and amoxicillin, both in allo- and auto-HCT settings. Additionally, half of the centers are willing to use V-cyllin after allo-HCT. The prophylactic use of other antibacterial compounds is rare both in pediatric and adult centers.

Antifungal prophylaxis

All pediatric and adult centers use fluconazole in patients after auto-HCT, and selection of antifungals in allo-HCT patients is variable and it includes posaconazole, voriconazole, fluconazole, and micafungin, with the exception of general avoidance of prophylactic use of voriconazole in pediatric centers. One adult center uses caspofungin during conditioning before allo-HCT with antithymocyte globulin (ATG). More than half adult centers perform regular weekly testing for galactomannan (GM) in all allo- and auto-HCT patients. It is also the rule for allo-HCT, but not for auto-HCT pediatric patients.

Antiviral prophylaxis

All adult centers use acyclovir in allo- and auto-HCT settings, and all pediatric centers use acyclovir in allo-HCT patients while only exceptionally in auto-HCT setting. One adult center uses ganciclovir during conditioning before allo-HCT with ATG. Almost all adult and pediatric centers perform regular weekly testing for Cytomegalovirus (CMV) DNA and Epstein-Barr virus (EBV) DNA in allo-HCT patients. Some adult centers emphasize the necessity of use of letermovir in CMV-seropositive recipients.

Other antimicrobial prophylaxis

Almost all centers use cotrimoxazole in prophylaxis against pneumocystodosis and toxoplasmosis. Almost all pediatric and a few adult centers perform regular intravenous immunoglobulin (IVIG) supplementation, mainly in allo-HCT patients.

Prophylaxis in various phases of allo-HCT

Antibacterial prophylaxis

Antibacterial prophylaxis in allo-HCT setting is rarely used during conditioning period by the centers, while virtually all pediatric and adult centers use prophylaxis both during neutropenia and immunosuppressive treatment and/or GVHD phase.

Antifungal prophylaxis

Antifungal prophylaxis in allo-HCT setting is very rarely used by adult centers during conditioning period, while virtually all pediatric and adult centers use antifungal prophylaxis both during neutropenia and immunosuppressive treatment and/or GVHD phase. Additionally, more than half pediatric centers also use antifungal prophylaxis during conditioning. None of the centers use voriconazole during conditioning. Itraconazole tablets are used exceptionally in one center only.

Antiviral prophylaxis

Acyclovir is recommended for prophylaxis both before HCT and during neutropenia and immunosuppressive treatment by almost all centers.

Other antimicrobial prophylaxis

Cotrimoxazole in prophylaxis is used both during neutropenia and immunosuppressive therapy periods in almost all centers, and also in part of the centers before HCT. Supplementation of IVIG to maintain concentration 4 g/L is performed both during neutropenia and immunosuppressive therapy in almost all centers.

Clinical implications of the survey

The results of this survey underline the value of antimicrobial prophylaxis in patients undergoing HCT and good awareness of this issue in all transplant centers. Virtually all pediatric and adult centers use antibacterial, antifungal, antiviral, and anti-pneumocystodosis prophylaxis both in allo- and auto-HCT patients. There are some differences regarding specific drugs, especially with respect to the lower use of quinolones in pediatric patients. The most preferred combinations of drugs are: quinolones and penicillins, fluconazole and posaconazole, and acyclovir and cotrimoxazole. Posaconazole and voriconazole are used exclusively in allo-HCT patients in primary and secondary prophylaxis as a result of reimbursement program of these drugs in Poland. This is also in line with international guidelines of antimicrobial prophylaxis.

The results of this survey reflect pharmacological antimicrobial prophylaxis practices used in Polish transplant centers. They also reflect drug availability and reimbursement in Poland, since letermovir, a new anti-CMV compound, recommended for CMV-seropositive allo-HCT recipients is not used in Poland.

This survey may be used to create universal national guidelines for Polish HCT centers which are compatible with international guidelines

Table I. Proposed anti-infective prophylaxis

	Pediatric (n = 6)		Adult (n = 17)		Total (n = 23)				
	Auto	Allo	Auto	Allo	Auto	Allo			
Antibacterial									
Quinolones: Ciprofloxacin	2	4	9	8	11	12			
Levofloxacin	-	-	6	6	6	6			
Penicillins: Amoxicillin ± Clavulanian	3	4	1	5	4	9			
V-cyllin	-	3	1	8	1	11			
Cephalosporines: Cefuroxime	1	1	1	-	2	1			
Aminoglycosides (oral)	1	1	-	-	1	1			
Macrolides: Azithromycin	-	1	-	-	-	1			
Rifaximin	-	-	1	1	1	1			
Antifungal									
Posaconazole	-	4	-	12	-	16			
Voriconazole	-	1	-	10	-	11			
Fluconazole	6	5	17	10	23	15			
Itraconazole	-	1	1	1	1	2			
Mycamine	-	3	-	7	-	10			
Galactomannan testing ≥ 1/week	1	4	8	12	9	16			
Other: Mannan or BDG	-	-	2	2	2	2			
Antiviral									
Acyclovir	1	6	17	16	18	22			
Other	-	-	-	-	-	-			
CMV DNA ≥ 1/week	-	6	-	14	-	20			
EBV DNA ≥ 1/week	-	6	-	12	-	18			
Other antimicrobial prophylaxis									
Cotrimoxazole	4	6	17	13	21	19			
IVIG supplementation	3	5	-	6	3	11			
Other: pentamidine	1	1	-	-	1	1			
Prophylaxis in allo-HCT patients with respect to transplant phase									
	Pediatric (n = 6)			Adult (n = 17)			Total (n = 23)		
	Pre HCT	Neutropenia	GVHD IST	Pre HCT	Neutropenia	GVHD IST	Pre HCT	Neutropenia	GVHD IST
Antibacterial									
Quinolones: Ciprofloxacin	2	4	4	1	8	6	3	12	10
Levofloxacin	-	-	-	3	7	7	3	7	7
Penicillins: Amoxicillin ± Clavulanian	1	4	4	1	2	6	2	6	10
V-cyllin	-	1	4	-	1	8	-	2	12
Cephalosporines: Cefuroxime	-	-	-	-	1	-	-	2	-
Aminoglycosides (oral)	1	-	-	-	-	-	1	-	-
Macrolides: Azithromycin	-	1	1	-	-	-	-	1	1
Rifaximin	-	-	-	-	1	-	-	1	-
Antifungal									
Posaconazole	3	3	4	1	3	12	4	6	16
Voriconazole	-	1	1	-	5	9	-	6	10
Fluconazole	4	5	4	4	15	6	8	20	10
Itraconazole	-	-	1	-	-	-	-	-	1
Mycamine	2	2	2	1	5	2	3	7	5
Galactomannan testing ≥ 1/week	1	4	4	3	10	8	4	14	12
Other: Mannan or BDG	-	-	-	-	2	1	-	2	1
Antiviral									
Acyclovir	3	6	6	13	15	14	16	21	20
Other	-	-	-	-	-	-	-	-	-
CMV DNA ≥ 1/week	4	6	6	2	7	11	6	13	17
EBV DNA ≥ 1/week	4	6	6	-	5	10	4	11	16
Other antimicrobial prophylaxis									
Cotrimoxazole	4	5	6	7	11	11	11	16	17
IVIG supplementation	1	5	5	1	2	6	2	7	11
Other: pentamidine	1	1	1	-	-	-	1	1	1

BDG – beta-d-glucan; GVHD – graft-versus-host disease; IST – immunosuppressive therapy; IVIG – intravenous immunoglobulin

[7-15]. It may also serve as a useful tool for any local or multicenter epidemiological analyses.

Authors' contributions

JS, LG – involved in design of the study. JS, LG – wrote manuscript. JS, LG, AŁ, KC – performed survey. MU, AC, LG, KC – involved in critical review. All authors approved the final manuscript.

Conflict of interest

All authors have nothing to disclose with respect to this paper.

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Ethics

The work described in this article has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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