Utilization Profile of Immunosuppressants for Graft-Versus-Host Disease Prophylaxis in Patients Submitted to Hematopoietic Stem Cell Transplantation

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Perfil de Utilização de Imunossupressores para Profilaxia de Doença Enxerto versus Hospedeiro em Pacientes Submetidos ao Transplante de Células-Tronco Hematopoiéticas

Perfil de Uso de Inmunosupresores para Profilaxis de Enfermedad Injerto *versus* Huésped en Pacientes Sometidos al Trasplante de Células Madre Hematopoyéticas

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Abstract

Introduction: Immunosuppressants have high toxicity associated to a narrow therapeutic range, and serum levels should be controlled. Thus, it is necessary to study the use of drugs in clinics that use them, providing an overview of their intake and rational use in a given population. **Objective:** Identify the profile of the use of immunosuppressants for prophylaxis of graft versus host disease in patients submitted to hematopoietic stem cell transplantation in a bone marrow transplant center. **Method:** It is a cross-sectional study performed at a Brazilian bone marrow transplant facility. The immunosuppressants used in 2017 were classified according to an international classification system, their intake expressed in defined daily dose and their protocols analyzed according to the "*Consenso da Sociedade Brasileira de Transplante de Medula Óssea"* of 2015. **Results:** The myeloablative conditioning regimen was the most frequent (51.7%). The most prescribed immunosuppressive protocol was cyclosporine with methotrexate (37.9%). Of the 29 eligible patients, 23 (79.3%) had protocols following the 2015 "Consenso" recommendations. Methotrexate, intravenous cyclosporine and mycophenolate were responsible for 85.64% of the intake. **Conclusion:** In this study, it was only possible to identify a profile of use of immunosuppressants and compare within the institution due to the scarcity of studies about the use of these drugs. Therefore, new studies should be conducted to promote their rational use and to develop public policies with access to these drugs.

Key words: Drug Utilization; Hematopoietic Stem Cell Transplantation; Graft vs Host Disease; Immunosuppressive Agents; Pharmacoepidemiology.

Resumo

Introdução: Imunossupressores apresentam alta toxicidade associada à estreita faixa terapêutica, devendo-se ter controle de níveis séricos. Assim, é necessário o estudo de utilização de medicamentos em clínicas que os utilizam, fornecendo uma visão geral de seu consumo e uso racional em uma dada população. **Objetivo:** Identificar o perfil de utilização de imunossupressores para profilaxia de doença enxerto *versus* hospedeiro em pacientes submetidos a transplante de células-tronco hematopoiéticas, em um centro de transplante de medula óssea. **Método:** Trata-se de um estudo transversal realizado em um centro de transplante de medula óssea brasileiro. Os imunossupressores utilizados em 2017 foram classificados segundo um sistema de classificação internacional; seu consumo, expresso em dose diária definida; e seus protocolos, analisados segundo as Diretrizes para profilaxia de doença do enxerto contra hospedeiro do *Consenso da Sociedade Brasileira de Transplante de Medula Óssea* de 2015. **Resultados:** O regime de condicionamento mieloablativo foi o mais frequente (51,7%). O protocolo de imunossupressão mais prescrito foi ciclosporina com metotrexato (37,9%). Dos 29 pacientes elegíveis, 23 (79,3%) tiveram protocolos seguindo as recomendações do Consenso de 2015. Metotrexato, ciclosporina intravenosa e micofenolato foram responsáveis por 85,64% do consumo. **Conclusão:** Neste trabalho, só foi possível identificar um perfil de uso de imunossupressores e realizar comparações dentro da instituição, em virtude da escassez de estudos de utilização desses medicamentos. Portanto, novos estudos devem ser realizados, a fim de promover seu uso racional e elaborar políticas públicas com acesso a esses medicamentos.

Palavras-chave: Uso de Medicamentos; Transplante de Células-Tronco Hematopoéticas; Doença Enxerto-Hospedeiro; Imunossupressores; Farmacoepidemiologia.

Resumen

Introducción: Inmunosupresores presentan una alta toxicidad asociada a la estrecha banda terapéutica, debiendo tener control de niveles séricos y alta vigilancia en cuanto a toxicidad y efectividad. Así, es necesario el estudio de uso de medicamentos en clínicas que los utilizan, proporcionando una visión general de su consumo en una determinada población. **Objetivo:** Identificar el perfil de uso de Inmunosupresores para profilaxia de enfermedad injerto contra huésped en pacientes sometidos al trasplante de células madre hematopoyéticas en un centro de trasplante de médula ósea. **Método:** Se trata de un estudio transversal realizado en un centro brasileño de trasplante de médula ósea. Los Inmunosupresores utilizados en 2017 se clasificaron según un sistema de clasificación internacional, su consumo expresado en Dosis Diaria Definida y sus protocolos analizados según el consenso de la sociedad brasileña de trasplante de médula ósea de 2015. **Resultados:** El régimen de condicionamiento mieloablativo fue el más frecuente (51,7%). El protocolo de inmunosupresión más prescrito fue ciclosporina con metotrexato (37,9%). De 29 pacientes elegibles, 23 (79,3%) tuvieron protocolos siguiendo recomendaciones del consenso de 2015. Metotrexato, ciclosporina intravenosa y micofenolato fueron responsables del 85,64% del consumo. **Conclusión:** En este trabajo, sólo fue posible identificar un perfil de uso de Inmunosupresores y realizar comparaciones dentro de la institución debido a la escasez de estudios de utilización de esos medicamentos. Por lo tanto, nuevos estudios deben ser realizados a fin de promover su uso racional y elaborar políticas públicas con acceso a esos medicamentos.

Palabras clave: Utilización de Medicamentos; Trasplante de Células Madre Hematopoyéticas; Enfermedad Injerto contra Huésped; Inmunosupresores; Farmacoepidemiología.

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INTRODUCTION

The hematopoietic stem cells transplantation (HSCT), or bone marrow transplantation (BMT) is a treatment performed in patients with benign and malignant hematological diseases, immunodeficiencies, inborn errors of metabolism, some solid tumors, in addition to self-immune diseases [1,2].

The HSCT presents significant low rates of morbidity and mortality. It is a high cost modality treatment involving complex pharmacological treatment[3]. Most of the conditioning protocols are myeloablative; they are regimens with elevated doses of chemotherapy and, because of this, myelotoxic. In case of patients with high risk of transplantation-related mortality, elder patients with severe comorbidities or receptors of the second transplant, this type of conditioning may not be essential to control the disease [4]. Thus, nonmyeloablative conditioning regimens and of reduced intensity, also called RIC – reduced intensity conditioning, were developed, with variable grades of myelosuppression effects to reduce the malignant cells and with less hematologic toxicities[4,5].

After the transplantation, because of the intense immunosuppression caused by the chemotherapics in the follow up phase, the patient presents medullary aplasia, where it occurs important immune deficiency that makes it vulnerable to bacterial, fungal, viral and parasitical infections, necessitating the use of innumerous antimicrobials [6].

Further to the infectious complications, the patients submitted to transplantation are subject to non-infectious diseases, such as hepatic veno occlusive disease (VOD), mucositis, lung injury, graft-versus-host disease (GVHD)GVHD, among others. Nevertheless, the most severe complication and potentially fatal in allogeneic transplantation is GVHD, characterized as a systemic syndrome that occurs with patients who receive immunocompetent lymphocytes. In this clinical condition, it occurs an immune reaction between the host tissue and the transplanted lymphocytes T[7].

Approximately 50% of the patients who undergo allogeneic transplantation may develop GVHD, despite the prophylaxis with immunosuppressants. The mortality may reach 20% and the disease can have several grades of severity[8]. Even after long periods after the transplantation, 60% to 80% of the patients submitted to HSCT present some degree of activity of the disease and indication of use of immunosuppressants agents[9]. Gender difference between the donor and receptor, age of the patient and conditioning regimen, protocol of prophylaxis utilized, source of progenitor cells, comorbidities pre -HSCT and compatibility with the human leukocyte antigen (HLA) are some of the risk factors for GVHD[9,10].

In the prophylaxis of GVHD, the patient is submitted to a clinical protocol with immunosuppressants aimed to control the actions of residual T cells originated from the donor's blood to avoid rejection. In the decade of the 80's, it was established a standard combination of immunosuppressants for the of GVHD where it was utilized inhibitor of calcineurin immunosuppressants (tacrolimus – TCL – or cyclosporine – CSA) in combination with metothrexate (MTX)[11]. Other combinations as sirolimus with TCL, CSA or TCL with mycophenolate (MMF) are also utilized and depend on the conditioning regimen (myeloablative, RIC or nonmyeloablative) and of the type of HSCT[9].

Because of their narrow therapeutic range-associated high toxicity, these drugs should have serum level control and high vigilance for toxicity and effectiveness. In addition, they present innumerous drug interactions leading to increase or reduction of the serum levels leading to possible toxicity or therapeutic failure. Consequently, it must be frequently monitored and adjusted properly, mainly for patient in HSCT, which utilizes complex therapeutic regimens with large number of drugs[12,13].

Therefore, in a hospital environment, it is necessary the drug utilization studies (DUS) DUS in clinics that use immunosuppressants prophylactic and therapeutically immunosuppressants. The DUS offer an overall view of the use of drugs in a certain population, in addition to clarifying methods, objectives and finalities [14]. They are useful for pharmaceutical and sanitary regulation because they allow the identification of vulnerable populational groups to the irrational use and therapeutic classes used inappropriately [15,16]. They are utilized to compare drugs and treatment, which can mean lower costs for the institution in addition to bringing a better return to the patient[17].

Based in the aforementioned, the present study has the objective to identify the profile of utilization of immunosuppressants for prophylaxis of GVHD in patients submitted to HSCT in a Brazilian reference site.

METHOD

Cross-sectional study in a Brazilian bone marrow transplantation center. It were utilized the institution's electronic data system containing medical prescriptions and patients' charts hospitalized for allogeneic HSCT (related and unrelated and haploidentical) from January 1 to December 31, 2017. It were excluded under or 18 years old patients.

For the analysis of sociodemographic variables utilized, it were considered: gender, age, religion, marital status and ethnicity. For the clinical variables of the patients,

it were used the baseline diseases considered according to the International Classification of Diseases (ICD). For the variables involving the choice of prophylaxis for GVHD, it were used the baseline disease that originated the transplant, the type of transplant and the conditioning regimen. For the evaluation of the conformity of use of protocols of immunosuppression, it were taken as basis the current standard recommendations for prophylaxis of GVHD of the GVHD"*Consenso da Sociedade Brasileira de Transplante de Medula Óssea*[9] (SBTMO)" of 2015, as follows :

> Allogeneic related transplantation and with myeloablative conditioning: association of a calcineurin inhibitor of (CSA or TCL) initiated in day (D) before the HSCT (D-1) plus MTX (D+1, D+3, D+6 e D+11).
>
> Allogeneic related transplantation and with RCI conditioning or not myeloablative: MMF from D+1 and CSA or TCL initiated in D-1[12].
>
> Unrelated myeloablative transplantations, RIC or nonmyeloablative: ATG demonstrates reduction of GVHD and improvement of the quality of life, therefore, can be included in these regimens and is administrated before the HSCT[18].
>
> Myeloablative RIC or nonmyeloablative haploidentical transplantations: the standard prophylaxis is the same of the related RIC and nonmyeloablative (CSA/TCL + MMF), but initiated from D+5 and addition to high doses of cyclophosphamide after the graft infusion (D3 and D4).

The standard immunosuppressants utilized in the study were those prescribed for prophylaxis of GVHD and classified according to the Anatomical Therapeutic Chemical Classification System – ATC created by the Norwegian Medical Depot (NMD), which organizes the available drug clearly and divided in groups and its consumption was expressed in Defined Daily Doses (DDD/100 beds/day). According to the World Health Organization (WHO), DDD is the average dose of maintenance assumed per day for a drug used for its main indication in adults with 70Kg[17,19]. The formula utilized is [20]: DDD/100 beds/days = [(quantity of drug consumed in g)/(DDD established for the drug (WHO) x period of observation in days x number of beds available rate of occupation)] x 100.

For the calculation of DDD, the data of consumption in grams of standard immunosuppressants were extracted from electronic prescriptions. The total patients-day was obtained through the electronic system of registration of hospitalization. According to the methodology ATC/DDD, recommended by the WHO Drug Utilization Research Group, the registries of consumption of drug could be used as source of data for these studies. The DDD of each drug established by WHO is listed in Table 1. The information about rate of occupation were obtained from the registry of hospitalization of the institution.

It was conducted an analysis of the categorical and dichotomic variables through descriptive statistics and relative and absolute frequencies with the software Statistical Package for the Social Sciences (SPSS 22).

The study was initiated only after the approval by the Institutional Review Board, report number CAAE 90590418.8.0000.5274.

RESULTS

During 2017, 211 patients were admitted in the institution; of these, 43 (20.4%) for allogeneic HSCT and after the exclusion criteria, (14 patients (32.6%) ≤ 18 years), 29 (13.7%) patients were eligible for the study. The other patients were admitted for autologous HSCT, donation of bone marrow and HSCT-related interim events.

Table 2 shows the description of the sociodemographic profile of the patients who underwent allogeneic HSCT

Table 1. Values of DDD established for immunosuppressants by WHO

Code ATC	Immunosuppressant	DDD	Unit of measure	Route of administration
L04AD01	Cyclosporine	0.25	g	Orally and IV
L04AA4	ATG	0.1	g	IV
L04AA06	Mycophenolate mofetil	2	g	**Orally and IV**
L04AD02	Tacrolimus	5	mg	Orally and IV
L04AX03	Metothrexate	2,5	mg	Orally and IV
L01AA01	Cyclophosphamide	NE	-	-

Captions: Orally =via oral; IV=via intravenosa; ATG=anti-thymocyte immunoglobulin (coelho); NE=not existing.
Source: ATC/DDD Index 2019/ WHO.

Table 2. Sociodemographic profile of the patients who underwent allogeneic HSCT, 2017

Variables	n	%
Gender		
Male	18	62.1
Female	11	37.9
Age (years)		
19-29	12	41.4
30-49	10	34.5
50-60	7	24.1
Race		
Caucasian	19	65.5
Brown	6	20.7
Black	3	10.3
Not informed	1	3.4
Education		
Elementary incomplete	7	24.1
Elementary complete	6	20.7
High school complete	6	20.7
High school incomplete	4	13.8
College complete	4	13.8
College incomplete	1	3.4
Illiterate	1	3.4
Marital status		
Single	15	51.7
Married	13	44.8
Divorced	1	3.4
Religion		
Catholic	14	48.3
Evangelic	13	44.8
Christian	1	3.4
Without religion	1	3.4

and the higher prevalence of the patients included were males, 18 (62.1%), 12 patients (41.4%) had between 19 and 29 years old, 19 (65%) were Caucasian, seven (24.1%), incomplete elementary school, 15 (51.7%), single and 14 (48.3%), catholic.

Of the evaluated sample of patients, the most prevalent diagnosis was acute myeloid leukemia (AML) with 13 patients (44.8%), followed by idiopathic aplastic anemia with seven cases (24.1%). The type of HSCT more performed was related allogeneic with 12 patients (41.4%) followed by 11 (37.9%) unrelated allogeneic and six (20.7%) haploidentical. Of the 29 patients, in only one hematopoietic stem cells (HSCs) were collected from peripheral blood (3.4%). The mortality rate in 100 days of transplantation was 13.8% with four patients. The others were from bone marrow, 28 (96.6%). The myeloablative conditioning regimen was the most frequent and it was performed in 15 patients (51.7%). All the patients underwent prophylaxis protocol for GVHD with at least two immunosuppressants: the most prescribed was the combination of CSA with MTX conducted in 11 patients (37.9%) (Table 3).

The protocols of immunosuppression utilized varied according to the conditioning regimen, type of HSCT and compatibility of the transplantation. Table 4 describes the patients according to the type of HSCT/conditioning regimen and protocol of immunosuppression. Of the total of eligible patients, 23 (79.3%) had the standard recommendations described in "*Consenso SBTMO 2015*" in their protocols of immunosuppression.

All the patients submitted to allogeneic related HSCT with myeloablative conditioning regimen and RIC (11 patients) utilized the association of CSA with MTX as prophylaxis of GVHD, and the only two who did the RIC regimen presented different recommendations of the "*Consenso SBTMO*" that suggest the protocol with CSA/TCL + MMF. Only one patient underwent

Table 3. Clinical and therapeutic profile of the patients (n=29)

Variables	n	%
Baseline disease		
C 92.0 Acute myeloid leukemia	13	44.8
D 61.3 Idiopathic aplastic anemia	7	24.1
D 46.2 Refractory anemia with excess blasts	3	10.3
C 91.0 Acute lymphoid leukemia	3	10.3
D 46.3 Refractory anemia with excess of blasts in transformation	1	3.4
D 61.0 Constitutional aplastic anemia	1	3.4
C 94.5 Acute myelofibrosis	1	3.4
Type of transplant		
Allogeneic-like	12	41.4
Unrelated allogeneic	11	37.9
Haploidentical	6	20.7
Source of the transplant		
Bone marrow	28	96.6
Peripheral blood	1	3.4
Conditioning Regimen		
Myeloablative	15	51.7
RIC	6	20.7
Nonmyeloablative	8	27.6
Protocol of immunosuppression		
CSA + MTX	11	37.9
CSA + MTX + ATG*	7	24.1
CSA + MMF + CY-post	5	17.2
TCL + MMF + CY-post	5	17.2
TCL+ MTX + ATG*	1	3.4

Captions: n = number of cases; RIC = reduced intensity regimen; CSA=cyclosporine; MTX=methotrexate; ATG=anti-thymocyte immunoglobulin; MMF=mycophenolate; CY-post=cyclophosphamide post-transplantation; TCL=tacrolimus; *in phase of conditioning.

Table 4. Distribution of patients according to the Type of HSCT, conditioning regimen and protocol of immunosuppression

Type of HSCT/Regimen of conditioning	Protocol of immunosuppression N					Total
	CSA + MTX	TCL + MMF + CY-post	TCL+ MTX + ATG	CSA + MMF + CY-post	CSA + MTX + ATG	
Unrelated allogeneic myeloablative	9	-	-	-	-	9
Related allogeneic nonmyeloablative	-	-	-	1	-	1
Related allogeneic RIC	2	-	-	-	-	2
Unrelated allogeneic myeloablative	-	-	1	-	5	6
Unrelated allogeneic nonmyeloablative	-	2	-	1	-	3
Unrelated allogeneic RIC	-	-	-	-	2	2
Haploidentical nonmyeloablative	-	1	-	3	-	4
Haploidentical RIC	-	2	-	-	-	2

Captions: HSCT = hematopoietic stem-cells transplantation; n=number of cases; CSA=cyclosporine; MTX=methotrexate; TCL=tacrolimus; MMF = mycophenolate; CY-post=cyclophosphamide post-transplantation; ATG= anti-thymocyte immunoglobulin; RIC = reduced intensity conditioning.

allogeneic related transplantation nonmyeloablative and utilized the association of CSA with MMF and cyclophosphamide post-transplantation (CY-post). The standard recommendations of "*Consenso SBTMO 2015*" suggest only the association of CSA/TCL + MMF.

Patients who underwent unrelated HSCT with myeloablative conditioning regimen utilized in their majority (5 patients – 83.3%) the association of CSA with MTX and anti-thymocyte immunoglobulin (ATG). However, one (16.7%) patient replaced CSA for TCL in this same protocol. In relation to the three unrelated patients of myeloablative conditioning, two utilized TCL + MMF and CY-post (66.7%) and one CSA + MMF + CY-post (33.7%), different from the standard guidelines for the treatment of GVHD according to "*Consenso SBTMO 2015*" where it is suggested CSA/TCL + MTX + ATG. The RIC conditioning for unrelated allogeneic had as prophylaxis protocol for GVHD the association CSA + MTX + ATG in its two patients.

Three patients who underwent nonmyeloablative haploidentical HSCT utilized HSCTCSA + MMF + CY-post (75%). Nonetheless, one (25.0%) replaced CSA for TCL in the same protocol. Only two haploidentical had the RIC regimen and all of them utilized TCL + MMF + CY-post.

Of the 29 patients, four (13.8%) had, for a brief period, the replacement of CSA for TCL (inhibitors of calcineurin).

A total of eight patients presented GVHD during the period of hospitalization (27.6%). The relations between the occurrence of GVHD and the protocols of immunosuppression were analyzed with the software SPSS. Four patients that utilized CSA + MTX presented GVHD, obtaining a total of 27.3% in this group. Of the seven patients who utilized CSA + MTX + ATG, three (42.9%) presented GVHD. None of the five patients who utilized the association of CSA + MMF + CY-post reported the occurrence of GVHD and only one (20%) of the five that utilized TCL + MMF + Cy-post had GVHD. The patient who utilized TCL + MTX + ATG presented GVHD, because it was not possible to know whether any reaction occurred with the protocol utilized, because only one patient utilized the association of these immunosuppressants, the exact test of Fisher showed a significance of P=0.294.

The quantitative study of the utilization of immunosuppressants was based in the comparison of DDD of these drugs along the year of 2017. Figure 1 shows the variation of the monthly consumption expressed in DDD/100 beds-day in the studied period. MTX, IV CSA and MMF were responsible for 85.6% of the consumption of immunosuppressants selected, and MTX had the bigger DDD (45.9 DDD/100 beds-day) along the year. It is possible to notice oscillations during the year and peaks of consumption in the months of June and October for these drugs, reflecting the months of great number of transplanted patients: four patients in June and four

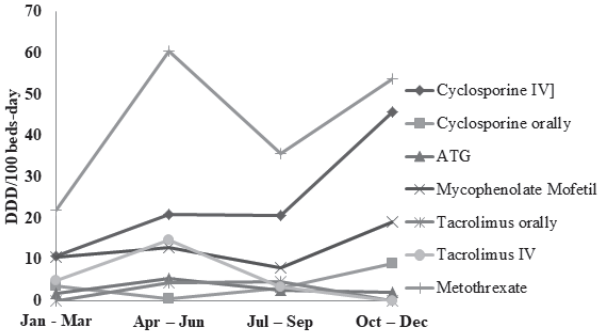

Figure 1. Variation of the month intake of immunosuppressants expressed in DDD per 100 beds-day, 2017

Captions: IV=intravenous; Orally; ATG = anti-thymocyte immunoglobulin.

in October. In the other months, the number of HSCT oscillated between one and three patients.

From January to March there were only four allogeneic HSCT where two were haploidentical and that overall there is no consensus for the use of the standard association of IV CSA + MTX therefore there was a drop of DDD of these drugs in this period. In April, there was only one unrelated HSCT whose protocol of immunosuppression included TCL + MTX. In this period, until mid-May, there was shortage of IV CS with replacement of IV TCL.

Between May and July, there were nine unrelated, related, allogeneic HSCT and haploidentical with larger utilization of the standard association of inhibitor of calcineurin (CSA/TCL) and MTX.

Still in June, 30.4% of the hospitalized patients used MTX (30.4 DDD/100 beds-day), while 13.7% of the patients used IV CSA (13.7 DDD/100 beds-day) and 8.4% used the standard dose of MMF (8.5 DDD/beds-day). In August and September, there was only two unrelated HSCT and from October to December, the number of related and unrelated allogeneic HSCT raised to nine, justifying the increase of the DDDs of CSA and MTX where peaks occurred in the month of October. In this month, 27.6%, 20.3% and 5.6% of the patients used the standard dose of MTX, IV CSA and MMF, respectively. ATG had its great consumption in May (2.3 DDD/100 beds-day). In relation to TCL orally, it was not noticed consumption from January to April as well as in August to December, and bigger consumption in July (4.6 DDD/100 beds-day). The consumption of IV TCL raised from January to June and a drop in July and no consumption in August and December.

The DDD for MMF, which is used in related nonmyeloablative regimens HSCT and RIC and haploidentical, followed the raises of DDD in the months of June and October because of the increase of the number of HSCT and an increase from October to December because of the haploidentical HSCT carried out in this period.

The DDD of CSA and TCL orally increases in the end of the year (interruption of the parenteral and moving to oral formulation).

It was not possible to calculate DDD for cyclophosphamide, because it does not present established DDD by ATC/DDD Index 2019/WHO.

DISCUSSION

It is a pioneer study of an oncology reference site that addresses the profile of utilization of immunosuppressants in patients who were submitted to HSCT.

The epidemiological profile encountered in this article presents similar results to other studies[21,22], such as the study of Abreu et al.[20], where the prevalence of the population who underwent allogeneic HSCT was of male patients (59%), catholic (38.5%), elementary school completed (33.35), average age of 31.3% and single (53,8%).

AML was the hematological malignant disease most frequent of allogeneic HSCT, which matches the results of the literature AMLHSCT[3,21]. Only one patient submitted to HSCT with collection of peripheral blood and presented AML as baseline disease, the others utilized bone marrow. Peripheral blood collection has the lower incidence of relapse and recovery of BM, called de "take", occurs more rapidly, but this can cause more frequency of chronic GVHD and more late mortality. The HSC of the peripheral blood are more prone to be used in more advance malignant diseases [23,24].

In relation to the types of HSCT, there is a balance between the related and unrelated and the majority of the conditioning are myeloablative, this means the prevalence of use of CSA/TCL + MTX, which is utilized in patients who undergo related and unrelated transplantations with myeloablative regimens[9].

It was not possible to relate the protocols of immunosuppression with the occurrence of GVHD because there was no statistical significance in the results encountered. One of the possible hypothesis may be the small number of study participants (n=29). In many centers of HSCT, it is used the standard protocol for prophylaxis of DECH in related and unrelated transplantations that consists in MTX associated to calcineurin inhibitors (CSA or TCL)[9,25,26]. This type of prophylaxis based in calcineurin inhibitors (CSA and TCL) is related to 25% to 40% of the appearance of acute GVHD and 40% to 60% of chronic GVHD, which suggests a good control [18]. Some studies show that the combination of CSA + MMF have the objective of reducing the toxicity related to the use of MTX in patients who do RIC conditioning and nonmyeloablative, mainly because of comorbidities [25,27-29].

Despite the protocol CSA + MTX presents good results for related and unrelated allogeneic HSCT, in the haploidentical it is associated to a bigger incidence of GVHD, even with the addition of ATG. Because of this, there was the necessity of developing new mechanisms of immunosuppression as, for instance, the addition of CY-post in high doses in D+3 and D+4. This strategy was well succeeded in haploidentical HSCT, which led to studies in related and unrelated HSCT [18,30]. Other studies suggest the combination of TCL + MMF + CY-post with similar results for haploidentical HSCT and allogeneic related and unrelated HSCT[18,31-33].

This is a descriptive study of utilization of drugs that had as objective to identify the profile of the use of immunosuppressants for the prophylaxis if GVHD in a quantitative way as well. To evaluate and measure the consumption of drugs in hospitals, several types of measures can be used; the most used is DDD recommended by WHO. It shows approximately the proportion of a population that received every day a standard pharmacological treatment and allows groups of drugs are standardized and its use compared among countries, regions and care-providing facilities and even within a certain institution[19,34].

The results obtained in the calculation of DDD are related to the type of HSCT and the conditioning performed. The curves of CSA IV, MTX and ATG were similar in the study, this tendency occurs because the patients who underwent myeloablative related allogeneic HSCT could use CSSA + MTX and the unrelated, CSA + MTX + ATG[35], therefore, the use of these drugs can fluctuate similarly because of the drug associations.

It is worth mentioning that, in myeloablative conditioning regimens, the patient has many chances of developing oral mucositis [36], and because of this, when the patient is hospitalized, IV drugs are utilized. The CSA orally, for instance, is only administered approximately one month after the transplantation, usually close to the release date, because the patient has already recovered of the mucositis and is able to swallow normally[9]. This can justify the fact that CSA orally has not been consumed in the month of January and its increase in February.

DDD for the drug ATG presents some small variations along the months. In some cases, it was replaced by CY-post in unrelated HSCT, which can justify a drop of DDD.

The paucity of studies that address DDD of immunosuppressants in HSCT was a justification to conduct this work in order to fill in the breaches of knowledge and contribute to the literature. In the study of Gardiner et al.[37], the pharmacy team of an Australian university conducted a study with some immunosuppressants utilizing DDD, where it shows that, between 2007 and 2013, the use of MMF, TCL and everolimus increased 2.7 times, 2.2 times and 2.3 times, respectively. The use of CSA and sirolimus decreased 20% and 30 % respectively. Based in this study of DDD, it was noticed that the use of immunosuppressants is increasing in Australia and Northern Europe and, therefore, with the increase of the survival of the transplanted patients, this consumption tends to increase [37].

A limitation was the small number of the population studied (n=29), further to the delimitation of not being possible to calculate DDD for cyclophosphamide, utilized as immunosuppressant after the transplant, since there is no established reference for this drug by the ATC/DDD Index 2019/WHO.

According to the *Guidelines for ATC classification and DDD assignment* 2019[19], DDD is defined as the mean dose of daily maintenance for a certain drug in its main prescription in adults (the weight reference is 70 Kg)". Likewise, Lee and Bergman in 1989 showed that the use of DDD in studies that involve pediatric patients causes discrepancies in the results because of the great difference of the magnitude of the dose. The situation can lead to an underestimation of the exposure of the population[34,38]. That said, only adult patients were included in this work because pediatric patients could underestimate the calculation of DDD, which justifies a reduction of 32.6% (14 pediatric patients) of the study population.

New measures like days of therapy – DOT are being adopted to improve the analysis of some classes of drugs like, for instance, the antimicrobials. This tool can be quite useful for the monitoring and analysis that, in some aspects, is better and more relevant than DDD[39]. In fact, DDD is arbitrary and does not take into consideration the range of doses per patient, since it considers a dose in grams, despite the weight. DOT/1000 patients-day does not underestimate or overestimate the use of drug, it describes the actual use per unit of time and, because of this, many authors believe this measure is more appropriate [40].

Another limitation of the study is the fact that the standard doses of immunosuppressants, like the doses of pediatric drugs are calculated per weight of the patient. In addition, the period of use of immunosuppressants for GVHD prophylaxis varies with the type of HSCT and can reach 180 days [9], which suggests that DOT could be a better option of measure in this analysis. In this cross-sectional study, it was evaluated only the intake of immunossuppresants while the patients that underwent allogeneic HSCT were hospitalized.

CONCLUSION

The current study evaluates the epidemiological profile and utilization of immunosuppressants in an oncological institution. The DUS allow the evaluation of tendencies of use of drugs, verification of its rational use and comparison of the data of the drugs internally and off the study sites. In this study, all the patients associated at least two immunosuppressants and the large majority followed the National Standard Recommendations. However, about the quantitative analysis of immunosuppressants it was only possible to identify the profile of its intake within the institution. The DDD has scarce data of

qualitative and quantitative studies with methods of DUS of immunosuppressants in HSCT and may not be the best measure of analysis of these drugs. With the increase of the number of person transplanted living with immunosuppressants, it can be expected that this class of drugs continue to consume an increasing portion of the expenses with drugs in the future. This is the relevance of this study. The results obtained suggest new studies for the choice of the better method of analysis of intake of these drugs, in order to ensure its rational use and offer results that contribute for the elaboration of public policies with access to these drugs.

CONTRIBUTIONS

Luna Clara França da Silva worked in the conception and planning of the study, data collection and final wording. Andrea Almeida Tofani and Carolina Lopes Martins worked in the conception and planning of the study and critical review of the manuscript. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There are no conflict of interests to declare.

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REFERENCES

1. Pasquini R, Coutinho E. Fundamentos e biologia do transplante de células-tronco hematopoiéticas. In: Zago MA, Falcão RP, Pasquini R. Tratado de hematologia. Rio de Janeiro: Atheneu: 2013. cap. 75, p. 711-729.
2. Vigorito AC, Souza CA. Transplante de células-tronco hematopoéticas e a regeneração da hematopoese. Rev Bras Hematol Hemoter. 2009;31(4):280-284. doi: http://dx.doi.org/10.1590/S1516-84842009005000057.
3. Gratwohl A, Baldomero H, Aljurf M, et al. Hematopoietic stem cell transplantation: a global perspective. JAMA. 2010;303(16):1617-24. doi: http://dx.doi.org/10.1001/jama.2010.491.
4. Martino R, Caballero MD, Canals C, et al. Allogeneic peripheral blood stem cell transplantation with reduced-intensity conditioning: results of a prospective multicentre study. Br J Haematol. 2001;115(3): 653-659. doi: http://dx.doi.org/10.1046/j.1365-2141.2001.03153.x.
5. Nakamura R, Forman SJ. Reduced intensity conditioning for allogeneic hematopoietic cell transplantation: considerations for evidence-based GVHD prophylaxis. Expert Rev Hematol. 2014;7(3):407-421. doi: http://dx.doi.org/10.1586/17474086.2014.898561.
6. Riul S, Aguillar OM. Contribuição à organização de serviços de transplante de medula óssea e a atuação do enfermeiro. Rev Latino-Am Enfermagem. 1997;5(1):49-57. doi: http://dx.doi.org/10.1590/S0104-11691997000100006.
7. Silva MM, Bouzas LFS, Filgueira AL. Manifestações tegumentares da doença enxerto contra hospedeiro em pacientes transplantados de medula óssea. An Bras Dermatol. 2005;80(1):69-80. doi: http://dx.doi.org/10.1590/S0365-05962005000100010.
8. Molldrem JJ, Komanduri K, Wieder E. Overexpressed differentiation antigens as targets of graft-versus-leukemia reactions. Curr Opin Hematol. 2002;9(6):503-508. doi: http://dx.doi.org/10.1097/00062752-200211000-00006.
9. Moreira MCR, Vigorito AC, Tavares RCBS, et al. Diretrizes para o diagnóstico, profilaxia e tratamento de doença do enxerto contra hospedeiro aguda. Rio de Janeiro: Sociedade Brasileira de Transplante de Medula Óssea; 2015. [acesso 2018 dez. 05]. III Reunião da SBTMO de Diretrizes Brasileiras em Transplante de Células Tronco Hematopoiéticas (TCTH). Disponível em: http://www.sbtmo.org.br/aula.php?id=22.
10. Dezern AE, Luznik L, Fuchs EJ, et al. Post-transplantation cyclophosphamide for GVHD prophylaxis in severe aplastic anemia. Bone Marrow Transplant. 2011;46(7):1012-1013. doi: http://dx.doi.org/10.1038/bmt.2010.213.
11. Cutler C, Logan B, Nakamura R, et al. Tacrolimus / sirolimus vs tacrolimus / methotrexate as GVHD prophylaxis after matched, related donor allogeneic HCT. Blood. 2014;124(8):1372-1377. doi: http://dx.doi.org/10.1182/blood-2014-04-567164.
12. Glotzbecker B, Duncan C, Alyea E, et al. Important Drug Interactions in Hematopoietic Stem Cell Transplantation: What Every Physician Should Know. Biol Blood Marrow Transplant. 2012;18(7):989-1006. doi: http://dx.doi.org/10.1016/j.bbmt.2011.11.029.
13. Corrêa PM, Zuckermann J, Fischer GB, et al. Immunosuppressive serum levels in allogeneic hematopoietic stem cell transplantation: pharmaceutical care contribution. Pharm Pract. 2016;14(2):683. doi: http://dx.doi.org/10.18549/PharmPract.2016.02.683.
14. Oliveira EA. Estudo da utilização de medicamentos em pacientes hipertensos e diabéticos: uma abordagem farmacoepidemiológica. Infarma. 2004;16(1-2):73-7.
15. Rozenfeld S, Valente J. Estudos de utilização de medicamentos - considerações técnicas sobre coleta e análise de dados. Epidemiol Serv Saúde. 2004;13(2):115-23. doi: http://dx.doi.org/10.5123/S1679-49742004000200005.
16. Storpirtis S, Mori ALPM, Yochiy A, et al. organizadores. Farmácia clínica e atenção farmacêutica. Rio de Janeiro: Guanabara Koogan; 2013.

17. Melo DO, Ribeiro E, Storpirtis S. A importância e a história dos estudos de utilização de medicamentos. Rev Bras Cienc Farm. 2006;42(4): 475-85.

18. Moiseev IS, et al. Risk-adapted GVHD prophylaxis with post-transplantation cyclophosphamide in adults after related, unrelated, and haploidentical transplantations. Eur J Haematol. 2018;100(5):395-402. doi: http://dx.doi.org/10.1111/ejh.13030.

19. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2019 [Internet]. 22nd ed. Oslo: World Health Organization; 2018 [cited 2018 Dec 26]. Available from: https://www.whocc.no/filearchive/publications/2019_guidelines_web.pdf.

20. Onzi PS, Hoffman SP, Camargo AL. Avaliação do consumo de antimicrobianos injetáveis de um hospital privado no ano de 2009. Bras Farm. 2011;2(2):20-25.

21. Abreu MHNG, Oliveira IR, Resende RG, et al. Análise sociodemográfica e clínica de pacientes submetidos ao transplante alogênico de células-troncos hematopoiéticas. Pesqui Bras Odontopediatria Clín Integr. 2012;12(3):345-350. doi: http://dx.doi.org/10.4034/PBOCI.2012.123.07.

22. Castro Júnior CG, Gregianin LJ, Brunetto AL. Análise clínica e epidemiológica do transplante de medula óssea em um serviço de oncologia pediátrica. J Pediatria. 2003;79(5):413-22. doi: http://dx.doi.org/10.1590/S0021-75572003000500008.

23. Pasquini R, Coutinho E. Fundamentos e biologia do transplante de células-tronco hematopoiéticas. In: Zago MA, Falcão RP, Pasquini R. Tratado de hematologia. São Paulo: Atheneu; 2013. p. 711-29.

24. Holtick U, Albrecht M, Chemnitz JM, et al. Bone marrow versus peripheral blood allogeneic haematopoietic stem cell transplantation for haematological malignancies in adults. Cochrane Database Syst Rev. 2014;20(4):CD010189. doi: http://dx.doi.org/10.1002/14651858.CD010189.pub2.

25. Ruutu T, van Biezen A, Hertenstein B, et al. Prophylaxis and treatment of GVHD after allogeneic haematopoietic SCT: a survey of centre strategies by the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant. 2012;47(11):1459-1464. doi: http://dx.doi.org/10.1038/bmt.2012.45.

26. Nash RA, Antin JH, Karanes C, et al. Phase 3 study comparing methotrexate and tacrolimus with methotrexate and cyclosporine for prophylaxis of acute graft-versus-host disease after marrow transplantation from unrelated donors. Blood. 2000;96(6):2062-8.

27. Piñana JL, Valcárcel D, Fernández-Avilés F, et al. MTX or mycophenolate mofetil with CsA as GVHD prophylaxis after reduced-intensity conditioning PBSCT from HLA-identical siblings. Bone Marrow Transplant. 2010;45(9):1449-56. doi: http://dx.doi.org/10.1038/bmt.2009.362.

28. Perkins J, Field T, Kim J, et al. A randomized phase II trial comparing tacrolimus and mycophenolate mofetil to tacrolimus and methotrexate for acute graft-versus-host disease prophylaxis. Biol Blood Marrow Transplant. 2010;16(7):937-947. doi: http://dx.doi.org/10.1016/j.bbmt.2010.01.010.

29. Weber T, Niestadtkötter J, Wienke A, et al. Enteric-coated mycophenolate sodium containing GvHD prophylaxis reduces GvHD rate after allogeneic HSCT. Eur J Haematol. 2016;97(3):232-238. doi: http://dx.doi.org/10.1111/ejh.12710.

30. Ringdén O. GVHD prophylaxis made safe, easy, and inexpensive. Blood. 2014;124(25): 3672-3673. doi: http://dx.doi.org/10.1182/blood-2014-10-607879.

31. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biol Blood Marrow Transplant. 2008; 14(6): 641–650. doi: http://dx.doi.org/10.1016/j.bbmt.2008.03.005.

32. Luznik L, Bolaños-Meade J, Zahurak M, et al. High-dose cyclophosphamide as single-agent, short-course prophylaxis of graft-versus-host disease. Blood. 2010;115(16):3224-3230. doi: http://dx.doi.org/10.1182/blood-2009-11-251595.

33. Luzni, L, Jalla S, Engstrom LW, et al. Durable engraftment of major histocompatibility complex-incompatible cells after nonmyeloablative conditioning with fludarabine, low-dose total body irradiation, and posttransplantation cyclophosphamide. Blood. 2001;98(12):3456-64. doi: http://dx.doi.org/10.1182/blood.v98.12.3456.

34. Castro CGSO. Estudos de utilização de medicamentos: noções básicas [Internet]. Rio de Janeiro: Editora Fiocruz; 2000 [acesso 2018 out. 01]. Disponível em: http://books.scielo.org/id/zq6vb.

35. Ruutu T, Gratwohl A, de Witte T, et al. Prophylaxis and treatment of GVHD: EBMT-ELN working group recommendations for a standardized practice. Bone Marrow Transplant. 2014;49(2):168-173. doi: http://dx.doi.org/10.1038/bmt.2013.107.

36. Cutler C, Li S, Kim HT, et al. Mucositis after allogeneic hematopoietic stem cell transplantation: a cohort study of methotrexate-and non-methotrexate-containing graft-versus-host disease prophylaxis regimens. Biol Blood Marrow Transplant. 2005;11(5):383-388. doi: http://dx.doi.org/10.1016/j.bbmt.2005.02.006

37. Gardiner KM, Tett SE, Staatz CE. Multinational Evaluation of Mycophenolic Acid, Tacrolimus, Cyclosporin, Sirolimus, and Everolimus Utilization. Ann Transplant. 2016;21:1-11. doi: http://dx.doi.org/10.12659/aot.895664.

38. Lee D, Bergman U. Studies of drug utilization. In: Strom BL, Kimmel SE, Hennessy S, editors.

Pharmacoepidemiology. Nova York: Churchilli Livingstone, 1989. Part. IV; p. 379.

39. Agência Nacional de Vigilância Sanitária; Gerência de Vigilância e Monitoramento em Serviços de Saúde; Gerência Geral de Tecnologia em Serviços de Saúde. Diretriz nacional para elaboração de programa de gerenciamento do uso de antimicrobianos em serviços de saúde[Internet]. Brasília, DF: ANVISA; 2017. [acesso 2018 nov. 10]. Disponível em: http://portal.anvisa.gov.br.
40. Guillot J, Lebel D, Roy H, et al. Usefulness of defined daily dose and days of therapy in pediatrics and obstetrics-gynecology: a comparative analysis of antifungal drugs (2000–2001, 2005–2006, and 2010–2011). J Pediatr Pharmacol Ther. 2014;19(3):196-201. doi: http://dx.doi.org/10.5863/1551-6776-19.3.196.

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