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Artículos originales

Therapeutic pathways of allogeneic and autologous hematopoietic stem cell transplantation recipients: a hospital pharmacist's perspective

Trayecto terapéutico de receptores de trasplante de células madre hematopoyéticas: una perspectiva de farmacéuticos hospitalarios

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Resumen

Introducción: Pacientes de trasplante de células madre hematopoyéticas autólogo y alogénico (Alo-TCMH y Auto-TCMH) enfrentan riesgos farmacoterapéuticos.

Objetivo: Detallar el perfil terapéutico y la evolución de biomarcadores de disfunción renal, hepática e inflamatoria en pacientes de Alo- y Auto-TCMH desde su ingreso hasta el alta hospitalaria, ofreciendo una perspectiva detallada del manejo farmacológico.

Método: Se extrajeron datos retrospectivos de las historias clínicas de 20 pacientes de Alo-TCMH y 20 de Auto-TCMH. Se describió el trayecto terapéutico mediante el cambio de tratamientos farmacológicos, los medicamentos potencialmente inapropiados utilizando la escala GO-PIM, y la carga anticolinérgica (CA). Se evaluaron las variaciones fisiopatológicas afectando órganos de eliminación, mediante niveles de proteína C reactiva (PCR), puntuación para la enfermedad hepática en etapa terminal (puntuación MELD) y filtración glomerular (FG).

Resultados: Alo-TCMH pacientes tuvieron un mayor número de fármacos iniciados durante la estancia hospitalaria, lo que llevó a una hiperpolifarmacia durante la estancia y al alta. Un 35% de los medicamentos usados eran metabolizados por CYP3A4. CA aumentó al alta en pacientes de HSCT. Los pacientes de Auto-TCMH ≥ 65 años tomaban al menos un PIM. Se informaron niveles altos de CRP en los receptores de TCMH. Puntuación MELD aumentó y la GFR disminuyó en pacientes de Alo-TCMH mientras que la FG aumentó ligeramente en pacientes de Auto-TCMH.

Conclusión: El farmacéutico clínico debe enfocarse en la polifarmacia, PIM y CA, y evaluar la inflamación y las funciones renales y hepáticas para evaluar de manera reflexiva el potencial de depuración de los pacientes y sugerir dosificaciones individualizadas.

Palabras clave: Trasplante de células madre hematopoyéticas; Proteína C reactiva; Insuficiencia hepática, Lista de medicamentos potencialmente inapropiados.

Abstract

Introduction: Patients undergoing allogeneic and autologous hematopoietic stem cell transplantation (Allo-HSCT and Auto-HSCT) are at risk of pharmacotherapy-related problems.

Objective: To describe in Allo-HSCT and Auto-HSCT patients from admission to hospital discharge, their therapeutic profile, and the time-course of biomarkers of renal and liver dysfunction, and of inflammation to display a more specific overview of drug therapy in HSCT patients.

Method: Data were retrospectively extracted from the charts of 20 Allo-HSCT and 20 Auto-HSCT patients. The therapeutic pathway was described by the turn-over of drug treatments, the potentially inappropriate medications by using the GO-PIM scale, and the anticholinergic burden. Patho-physiological variations affecting clearance organs were characterized by the C-Reactive Protein (CRP) levels, and the hepatic and renal impairment evaluation tools (Model for End-stage Liver Disease score: MELD score, and glomerular filtration rate: GFR).

Results: Compared to Auto-HSCT patients, Allo-HSCT patients had a higher number of drugs initiated during hospital stay leading to hyper-polypharmacy during the stay and at discharge. Around 35 % of drugs used were metabolized by CYP3A4 in HSCT patients. Anticholinergic burden increased at discharge in HSCT patients. Auto-HSCT patients ≥ 65 years were taking at least one PIM. High CRP levels were reported in HSCT recipients. MELD score increased and GFR decreased in Allo-HSCT patients while GFR slightly increased in Auto-HSCT patients.

Conclusion: Clinical pharmacist should target polypharmacy, PIM and anticholinergic burden, and evaluate inflammation and both renal and hepatic functions in order to thoughtfully assess the clearance potential of patients and to suggest individualized dosing.

Keywords: hematopoietic stem cell transplantation; C-reactive protein; Hepatic Insufficiency; list of potentially inappropriate medications.

Highlights

Beyond general guidelines and recommendations that have defined the role of hospital pharmacists in caring for hematopoietic stem cell transplantation (HSCT) patients, this study investigated specific pharmacotherapeutic and biological features in both allogeneic and autologous HSCT patients from admission to discharge.

This study emphasizes that anticholinergic burden, potentially inappropriate medication (according to the GO-PIM scale), and hepatic impairment (by using MELD-score) should be evaluated throughout the

hospitalization stay. Elevated levels of C-reactive protein raise concerns since inflammation induces metabolic down-regulation, and noteworthy of CYP3A4 which is very frequently involved in the elimination of drugs used in these patients.

Clinical pharmacist should consider specificities of drug treatment and of patho-physiological variations affecting clearance organs to thoughtfully assess the clearance potential of patients and to suggest individualized dosing.

Introduction

Patients with hematological malignancies, especially those undergoing hematopoietic stem cell transplantation (HSCT), face a high risk of pharmacotherapy-related problems due to complex drug regimens and patho-physiological variations affecting clearance organs. Potential drug-drug interactions (DDIs) are particularly common among HSCT patients in the bone marrow transplantation unit[1]. The identification and resolution of drug-related problems (DRP) constitute a very important role of the clinical pharmacist in managing drug therapy, and several general guidelines and recommendations have been provided to define the role of hospital pharmacists in caring for HSCT patients[2-6].

Besides general guidelines and recommendations, clinical pharmacists should pay close attention to specific aspects of drug treatments, as exposure to polypharmacy (PP), hyper-polypharmacy (HPP, > 10 drugs), potentially inappropriate medications (PIM) including drugs with anticholinergic properties. Recently, a list of PIM specific to geriatric oncology has been proposed (Geriatric Oncology Potentially Inappropriate Medications, GO-PIM scale) based on the NCCN Clinical Practice Guidelines in Oncology for Older Adult Oncology[7]. Some of these features of drug treatments (PP, HPP or PIM) have been associated with negative clinical outcomes in older adults with blood cancers[7]. in patients with acute myeloid leukemia[8-9], non-Hodgkin's lymphoma[10], or in patients undergoing allogeneic HSCT[11-12].

Furthermore, kidney and liver impairment should be evaluated as HSCT patients are at an increased risk of developing early and late complications[13-14]. Recently, Model for End-stage Liver Disease score (MELD score) has been proposed as a screening tool to identify patients with hepatic impairment (HI) who are at risk of drug safety issues[15]. Inflammation has been recognized as a relevant factor that inhibits the metabolic activities of CYP450s isoforms, especially CYP3A4 and CYP2C19 thereby potentially influencing hepatic clearance and intestinal/hepatic first-pass effect[16].

The purpose of this study was to describe in allogeneic and autologous HSCT patients, from admission to hospital discharge, the therapeutic profile of patients with regard to PP, HPP, GO-PIM and anti-cholinergic burden, as well as the time-course of biomarkers of renal and liver dysfunction, and inflammation status in order to bring to hospital pharmacists a more specific overview of drug therapy in these patients.

Methods

Study design, setting and population

This retrospective, observational, single-center study (from January 2020 to December 2021) involved adult inpatients of the Clinical Hematology department of our University Hospital. Clinical data were extracted from electronic health records (EHR) using the computerized physician order entry database (CPOE, DxCare Software). Given that there was no aim of statistical comparison between allogeneic and autologous patients, clinical data 20 allogeneic and 20 autologous HSCT patients were considered representative for the descriptive study and were randomly retrieved from the database of patients. All allogeneic and autologous patients registered in the JACIE (Joint Accreditation Committee ISCT-Europa & EBMT) database were assigned unique identification numbers ranging from 1 to 127. To select a representative subset of allogeneic and autologous patients for the study, a randomization procedure was conducted for each group using Microsoft Excel's random number generation function to random-

ly choose 20 patients. Following the selection of patient records, de-identification was performed to ensure confidentiality.

The study received approval from the Institutional Research Ethics Committee of our University Hospital (agreement n° 23.84). It was conducted in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki and its subsequent amendments, or comparable ethical standards. Due to the retrospective and non-interventional nature of the study, utilizing data from a database, a consent waiver was granted. The principles of ethical research, such as confidentiality and anonymity, were strictly followed.

Patient data collection

Drug treatments were documented upon hospital admission, throughout the hospital stay, and at discharge. PIM were assessed using the cancer-specific Geriatric Oncology Potentially Inappropriate Medications (GO-PIM) scale based on the NCCN Clinical Practice Guidelines in Oncology for Older Adult Oncology[7]. This scale includes a list of medications commonly used for supportive care that are of concern for older adults (NCCN). The anticholinergic burden was evaluated using the Anticholinergic-Cognitive-Burden Scale (ACBS,[17]), and the Anticholinergic-Impregnation Scale (AIS,[18]) which estimates potential peripheral anticholinergic adverse effects. Information on the metabolic pathways of the drugs used was obtained from Drugbank 5.0[19] or relevant literature through PubMed when not available.

The following laboratory parameters were retrieved upon hospital admission, the day after the bone marrow transplantation (BMT), and at discharge.

• Serum creatinine levels (SCrea) for estimating glomerular filtration rate (GFR) using the CKD-EPI equation.

• SCrea, bilirubin and International Normalized Ratio (INR) for calculation of the Model for End-stage Liver Disease score (MELD score), a screening tool to identify patients with hepatic impairment (HI) who are at risk of drug safety issues[15].

$$MELD_{score} = 3.78 \times \ln\left(bilirubin\ \left[\frac{mg}{dL}\right]\right) + 11.2 \times \ln(INR) + 9.57 \times \ln\left(SCrea\ \left[\frac{mg}{dL}\right]\right) + 6.43$$

• C-reactive protein (CRP) for estimating of the degree of inflammation.

Statistical analysis

No statistical comparison between allogeneic and autologous HSCT patients was performed. To assess the differences before and after allogeneic or autologous HSCT, paired t-tests were employed allowing for the comparison of means between two measurements taken on the same individuals, accounting for individual variability. A p-value less than 0.05 was considered statistically significant. All statistical analyses were performed using Microsoft Excel.

Results

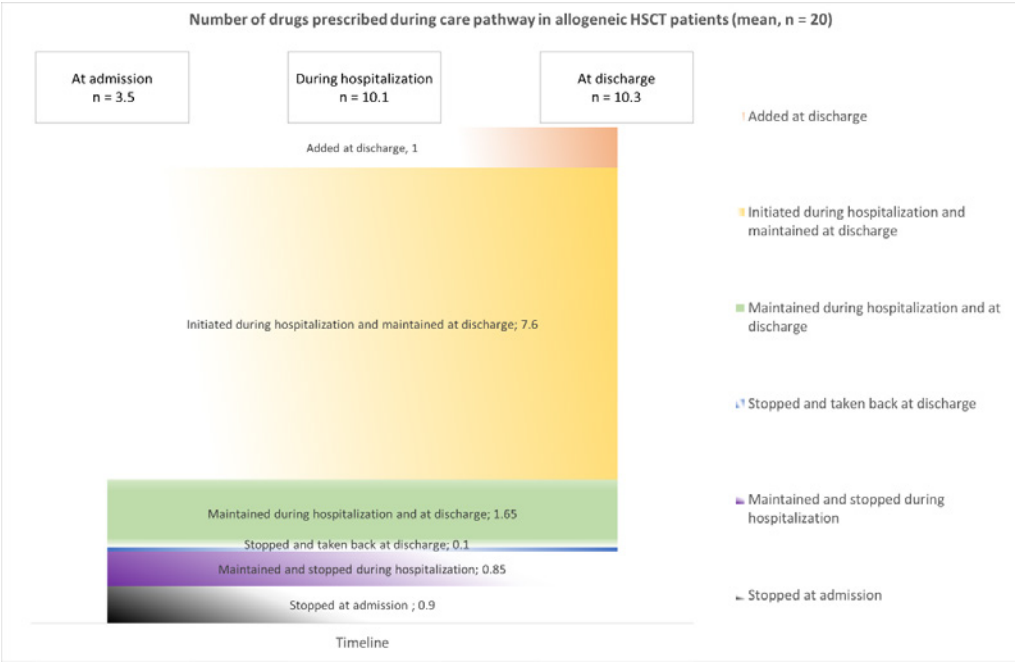
The patient characteristics of allogeneic and autologous HSCT patients are presented in Table 1. Both myeloablative conditioning (MAC) and reduced intensity conditioning (RIC) were employed in allogeneic HSCT patients, using various drugs, which led to a high degree of heterogeneity in terms of treatment intensity and associated toxicities. In contrast, autologous patients typically received a one-drug regimen involving melphalan (140 mg/m² n=7, or 200 mg/m² n= 8) as their conditioning treatment.

Table 1. Characteristics of allogeneic and autologous HSCT patients.

	Allogeneic HSCT	Autologous HSCT
Patient demographics		
Number of patients	20	20
Median age (years, median (range))	53.5 (25 - 67)	58.5 (19 - 69)
Female	7	9
Male	13	11
Cancer type		
Acute Myeloid Leukemia (AML)	12	-
Acute Lymphoid Leukemia (ALL)	1	-
Multiple Myeloma (MM)	-	15
T-Lymphoma	1	-
Myelofibrosis	3	-
Hodgkin Lymphoma	1	5
Chronic Myelomonocytic Leukemia (CMML)	1	-
Refractory Anemia with Excess Blasts (RAEB)	1	-
Conditioning treatment		
Myeloablative conditioning (MAC)	6	-
Reduced intensity conditioning (RIC)	14	-
Melphalan		15
Carmustine, Etoposide, Cytarabine, Melphalan +/- rituximab (BEAM or R-BEAM)	-	3
Thiotepa, Busulfan	-	2
Hospitalization		
Length of stay, (days, median (range))	40.9 (28 - 82)	18.6 (13 - 36)
Duration of aplasia (days, median (range))	13 (6 - 33)	6 (4 - 11)
Time from admission to BMT (days, median)	9.1	4.9
Time from BMT to discharge (days, median)	31.8	13.8

Therapeutic pathway

The therapeutic pathway, excluding anticancer drug conditioning treatment, for allogeneic and autologous HSCT patients from admission to discharge, is depicted in Figure 1. HSCT patients at discharge can be categorized as having polypharmacy (PP, 5-9 drugs, $n_{Allogeneic}$ = 4 [20 %], $n_{Autologous}$ = 9 (45 %]) or hyper-polypharmacy (HPP, 10 or more drugs, $n_{Allogeneic}$ = 15 [75%], $n_{Autologous}$ = 8 [40 %]).



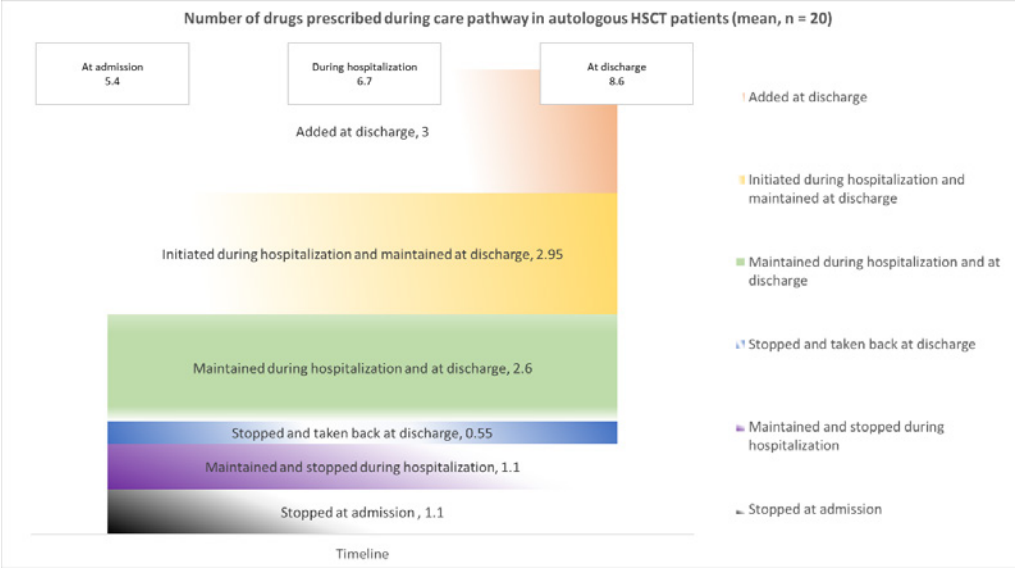


Figure 1. Therapeutic pathway of allogeneic (top) and autologous (bottom) HSCT patients from admission to discharge (mean number of drugs, n = 20 in each group).

Renal function

In patients undergoing autologous HSCT renal function significantly improved throughout the hospital stay in all patients (mean increase + 17.5 %) from admission to discharge (94.9 ± 18.7 ml/min vs 109.9 ±

17.3 ml/min, P-value: 1.66E-06). On the other hand, allogeneic HSCT patients renal function decreases from admission to discharge by 16.3 % (104.4 ± 11.4 ml/min vs 87.8 ± 24.0 mL/min, P = 2,01E-03, Figure 2).

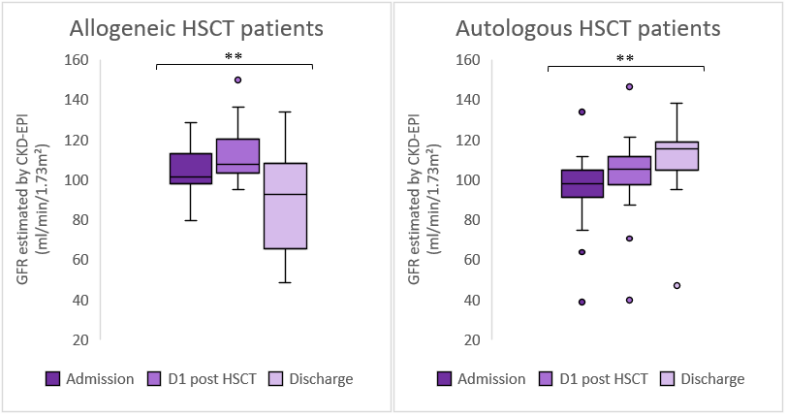


Figure 2. Evolution of glomerular filtration rate (GFR, ml/min/1.73 m^2) in allogeneic (left) and autologous (right) HSCT patients at admission, the day after the BMT, and at discharge (median, Q1-Q3, and min-max, n = 20 in each group).

Inflammation

Allogeneic and autologous HSCT recipients had CRP levels peaking around 131 mg/L and 117 mg/L, respectively, after transplantation. At discharge, CRP levels were 10 to 4-times lower than peak levels in allogeneic and autologous HSCT recipients but they remained 2 to 6-times higher than levels at admission (Fig. 3). Two patients in the autologous group had CRP levels > 100 mg/L at discharge (Figure 3).

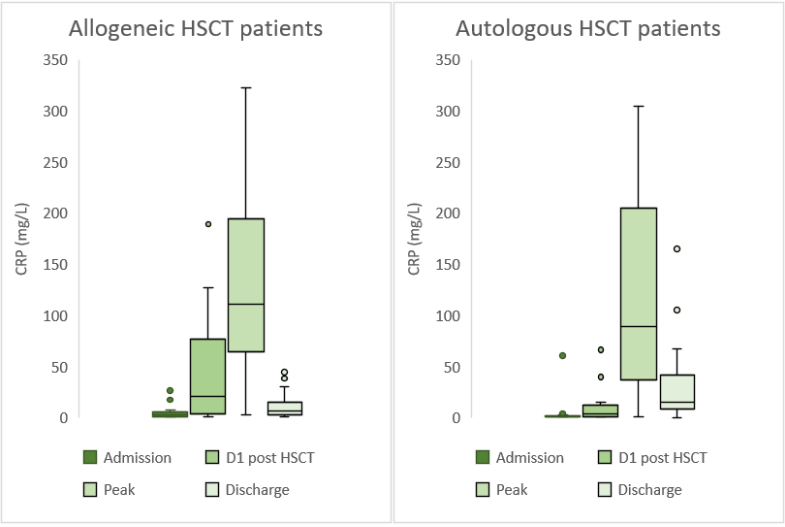


Figure 3. Evolution of C-reactive protein (CRP in mg/L) in allogeneic (left) and autologous (right) HSCT patients at admission, the day after the BMT, at the peak during hospitalization, and at discharge (median, Q1-Q3, and min-max, n = 20 in each group).

Liver function & MELD score

The mean MELD score was lower than 7.5 in both allogeneic and autologous HSCT patients at admission. It was not significantly different from admission to discharge for autologous HSCT patients. On the other hand, the mean MELD score significantly increased to 9.0 for allogeneic patients (P = 2,89E-03) with one third of patients having a MELD score above 10 (corresponding to a Child Pugh Score B, Figure 4).

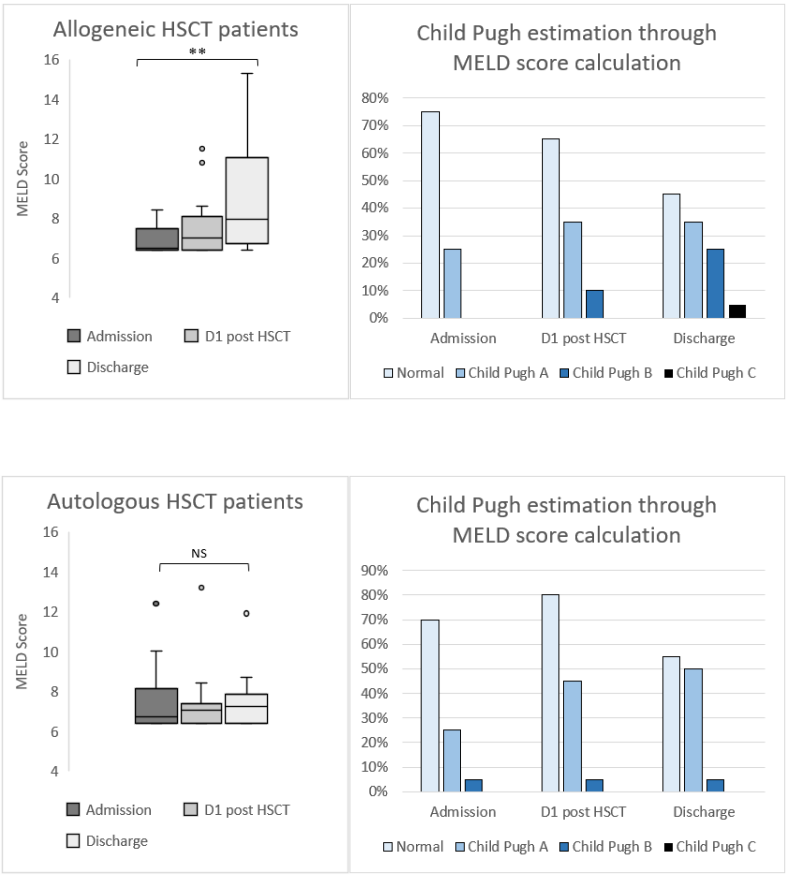
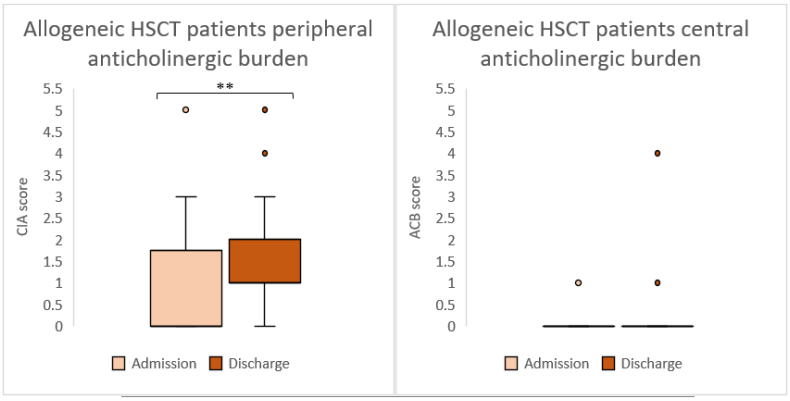


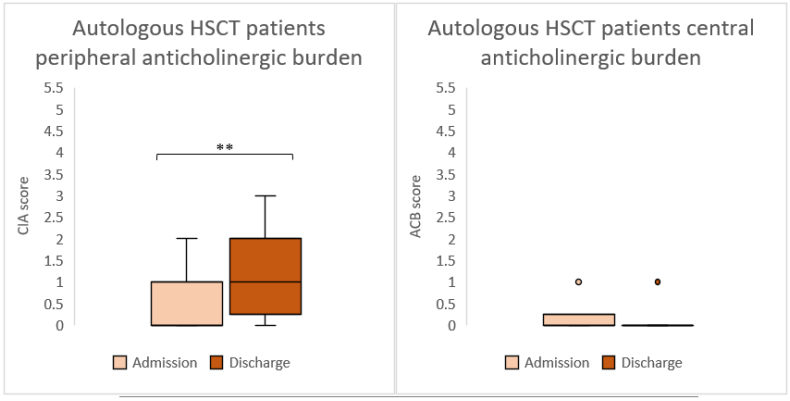
Figure 4. Evolution of model for end-stage liver disease (MELD) score in allogeneic (top) and autologous bottom) HSCT patients at admission, the day after the BMT, and at discharge (median, Q1-Q3, and min max, n = 20 in each group) and Child Pugh liver function estimation through MELD score.

Anticholinergic burden

The central anticholinergic burden, measured by ACB scores, at admission and discharge for allogeneic and autologous HSCT patients, is low and doesn't show any differences throughout hospitalization. The peripheral anticholinergic burden (AIS scale) is higher at discharge compared to admission in both allogeneic (P-value: 6,13E-03) and autologous (P-value: 4,33E 03) HSCT patients. It is slightly higher in allogeneic HSCT patients compared to autologous HSCT patients (Figure 5, Table 2).



Allogeneic HSCT patients	Peripheral (AIS)		Central (ACB)	
Anticholinergic burden	Admission	Discharge	Admission	Discharge
Low risk	85%	80%	100%	95%
High risk	15%	20%	0%	5%
Mean score	0,80	1,80	0,05	0,35
High Risk: AIS or ACB ≥ 3				



Autologous HSCT patients	Peripheral (AIS)		Central (ACB)	
Anticholinergic burden	Admission	Discharge	Admission	Discharge
Low risk	100%	90%	100%	100%
High risk	0%	10%	0%	0%
Mean score	0,40	1,20	0,21	0,20
High Risk: AIS or ACB ≥ 3				

Figure 5. Anticholinergic burden estimated according by the anticholinergic-impregnation scale (AIS for peripheral effects) and by the ACB score (anticholinergic cognitive burden, central effects) measured at admission and at discharge in allogeneic (top) and autologous (bottom) HSCT patients.

Table 2. Anticholinergic burden scale of allogeneic and autologous HSCT patients at admission and discharge

Anticholinergic burden Admission		Peripheral (AIS)		Central (ACB)	
		Discharge	Admission	Discharge	
Allogeneic HSCT patients	Low risk	85 %	80 %	100 %	95 %
	High risk	15 %	20 %	0 %	5 %
	Mean score	0.80	1.80	0.05	0.35
Autologous HSCT patients	Low risk	100 %	90 %	100 %	100%
	High risk	0 %	10 %	0 %	0%
	Mean score	0.40	1.20	0.21	0.20
High Risk: AIS or ACB ≥ 3					

Inappropriate medications (GO-PIM)

The prevalence of potentially inappropriate medications (GO-PIM) was assessed in autologous HSCT patients aged 65 years and older (n = 8), while it was not assessed in allogeneic HSCT patients due to the small number of patients aged 65 years and older (only 2 patients). All autologous HSCT patients aged 65 years or older, were found to be taking at least one PIM according to the GO-PIM scale. GO-PIM drugs accounted for 6.8 %, 25 %, and 11.6 % of the medications administered to these patients at admission, during hospitalization, and at discharge, respectively. The most frequently observed GO-PIM drugs among autologous HSCT patients were ranked as follows: alprazolam > morphine > zopiclone > tramadol > metoclopramide > chlorpromazine and dexchlorpheniramine.

Discussion

Therapeutic pathway

Therapeutic pathway of HSCT patients from admission to discharge (Fig. 1) reveals distinct patterns between allogeneic and autologous recipients. Allogeneic HSCT patients have a higher number of drugs initiated during their hospital stay leading to HPP during the stay and at discharge, while autologous HSCT patients have a higher number of drugs added at discharge but were less prone to HPP. This observation raises concerns because HPP is known to increase the risk of inappropriate prescribing practices, particularly in older adults[20]. HPP has been associated with various adverse health consequences, including increased healthcare expenses, adverse drug events, drug interactions, medication non-compliance, reduced functional capacity, and geriatric syndromes[21]. Specifically, among older patients with blood cancers, PP has been strongly associated with frailty[7]. These findings emphasize the importance of evaluating the appropriateness of medication regimens for elderly patients with blood cancers who are exposed to PP and HPP at discharge, in order to ensure the safety and effectiveness of their treatment.

Out of the 60 different drugs prescribed for systemic use in HSCT patients, 58% were common to both allogeneic and autologous recipients. These shared drugs mainly included anti-infectives for systemic use (ATC J), opioid analgesics (ATC NO2A), and psycholeptics including anxiolytics (ATC N05B) (see supplementary Table 1 and Table 2). It is noteworthy that a similar percentage of drugs metabolized by CYP3A4 were used in both allogeneic and autologous HSCT patients (34.9 % and 35.3 % respectively). This is concerning because drugs metabolized by CYP3A4 are known to have potential interactions with other medications. Although the current study did not examine DDI, a previous study reported that DDIs in HSCT patients primarily resulted from pharmacokinetic mechanisms rather than pharmacodynamic interactions[1].

Inappropriate medications (GO-PIM)

All autologous HSCT patients aged 65 years or older were taking at least one PIM according to the GO-PIM scale. This prevalence is higher compared to older patients (≥75 years) with blood cancers, where

44 % were reported to be taking at least one GO-PIM[7]. These results emphasize the frailty of the HSCT patients.

Given the prevalence of potentially inappropriate medication (PIM) use in older autologous HSCT patients and the potential for treatment-related adverse effects, interventions should be implemented to identify safer alternatives to GO-PIM drugs. This shift in medication choice can contribute to reducing the risk of adverse events and optimizing the safety and efficacy of medication regimens in this patient population.

Renal function

Both allogeneic and autologous HSCT patients exhibited normal renal function upon admission, making systematic drug adjustment regimens seemingly unproblematic. Autologous HSCT patients experienced a significant improvement in GFR during hospitalization (P-value: 1.66E-06), echoing findings in multiple myeloma patients. This enhanced renal function may expand transplant eligibility, potentially allowing transplantation for patients in end-stage renal failure. However, vigilance is crucial as this improvement may be transient, potentially indicating an early relapse with a poor prognosis.

Contrarywise, allogeneic HSCT patients displayed a different pattern, with a decrease in GFR after transplantation (P=2,01E-03). Pre-transplant renal dysfunction is a recognized risk factor for mortality following allogeneic HSCT and is included in risk scoring indices to estimate post-transplant mortality. The decrease in GFR observed in allogeneic HSCT patients is related to the toxic effects of conditioning regimens and the use of immunosuppressant drugs for graft-versus-host disease (GVHD) prophylaxis. Chronic kidney disease (CKD) has a cumulative incidence of up to 50%, developing from 6 months to 10 years post-transplantation, significantly impacting the long-term prognosis, and increasing mortality risk[22]. These results emphasize the importance of monitoring GFR after discharge, and clinical pharmacists should be aware of the potential worsening of renal function.

Inflammation

Beyond DDI that are easily detected by most software used in our hospitals, variations in CRP levels have the potential to lead to drug-disease interactions. In vitro and in vivo studies have demonstrated that inflammation plays a significant role in the regulation of metabolic enzymes and drug transporters, contributing to intra- and interindividual variability in drug pharmacokinetics[23]. Notably, in severe COVID-19 patients, increased CRP levels ranging from 50-150 mg/L were associated with 30% CYP3A4 decreased activity[24]. Therefore, during the hospital stay, it is important to consider checking CRP levels in patients taking drugs metabolized by CYP3A4 with a low or intermediate extraction ratio, such as ciclosporin or midazolam. Indeed, IL-6 levels have been associated with an increase in ciclosporin blood levels in a series of 6 patients given ciclosporin intra-venously[25]. The significant increase in CRP in allogeneic HSCT patients suggests that for oral ciclosporin drug-disease interactions potentially related to inflammation may be of greater concern during the hospital stay. Hence, further research on the impact of inflammatory reactions on ciclosporin blood after oral dosing may allow a more comprehensive understanding of the pharmacokinetics of ciclosporin in allogeneic HSCT. Given the significant prevalence of drugs metabolized by CYP3A4 (around 40 %, see supplementary Table 1 and Table 2) inflammation induced-downregulation of CYP3A4 may also be of concern for several drugs in both allogeneic and autologous HSCT patients, especially for drugs with narrow therapeutic index.

Liver function & MELD score

Screening for drug safety risk factors, including hepatic impairment, is an important task during medication reconciliation at hospital admission. While estimating renal impairment is relatively straightforward, hepatic impairment is more complex due to the multifaceted nature of liver function. The Child-Pugh Score (CPS) is a widely used scoring system that considers laboratory parameters as well as clinical to categorize patients into classes A, B, and C. The MELD score, calculated from only the laboratory parameters has been proposed as an alternative to CPS (score 7.5 - < 10 corresponding to CPS-A, 10 - < 15 corresponding to CPS-B and ≥ 15 corresponding to CPS-C)[15].

The significant increase in MELD score in allogeneic patients (P=2,89E-03) is likely due to hepatic injury caused by the conditioning regimen, acute Graft-Versus-Host Disease (aGVHD), and potentially hepatotoxic drugs. These findings suggest the need for careful attention to drug dosage regimen adjustment in allogeneic HSCT patients, particularly for drugs that are highly cleared by the liver and/or have concerns of liver toxicity, such as certain antifungal agents like voriconazole[26-27]. This easy-to-calculate score is a useful tool for the clinical pharmacist to assess liver function and since it can be related to corresponding CPS classes, individualized dosing based on hepatic function should thus be considered to optimize drug safety and efficacy in these patients.

Anticholinergic burden

The assessment of anticholinergic burden using the ACBS and AIS revealed considerable variability among allogeneic and autologous HSCT patients (Fig. 5). A cumulative anticholinergic burden score of ≥ 3 is considered high and has been independently associated with the development of delirium during hospitalization in patients aged 65 years and older.

The issue of anticholinergic burden should also be considered in autologous HSCT patients since it can have implications for future healthcare services such as readmission and emergency room revisits, particularly in older patients[28]. The problem of anticholinergic-related adverse drug events (ADEs) is particularly relevant in older patients, and a specific scale called the Anticholinergic Risk Scale (ARS) has been proposed for patients aged 65 years and older[29]. In a cohort of patients aged 75 years and older with blood cancers, the ARS scale was used and showed that 9% had an ARS score of 1, 10% had a score of 2, 5% had a score of 3, and 3% had a score of 4[7]. In our cohort of HSCT patients, when considering those aged 65 years and older (10 out of the total cohort of 40 patients, including 2 allogeneic and 8 autologous HSCT patients), similar percentages were observed (at admission: 10% had an ARS score of 2, and at discharge, 20% had an ARS score of 1).

These findings highlight the importance of pharmaceutical interventions aimed at reducing the anticholinergic burden through pharmacotherapeutic substitutions. Such interventions can help mitigate the risk of anticholinergic-related ADEs during hospitalization and at discharge in HSCT patients.

Strengths and weaknesses

The study provides a comprehensive analysis of various pharmacotherapeutic and biological features in allogeneic and autologous HSCT patients, including therapeutic pathways, drug utilization, anticholinergic burden, inflammation, and renal and liver function. By addressing the pharmacotherapy challenges in HSCT patients, the study contributes to the knowledge base for improving patient care. The current study did not analyze DDIs but highlighted that drug-disease interaction through the potential metabolic down-regulation induced by inflammation should be considered especially for CYP3A4 substrates and deserve to be studied prospectively.

The study was conducted at a single site, with a relatively small sample size, which may limit the generalizability of the findings to other healthcare settings. The results may not fully represent the diversity and variability that can exist across different institutions. The study relied on retrospective data collection, which may introduce limitations such as incomplete or missing data, potential bias in data selection, and limited ability to establish causality.

Conclusion

This preliminary study sheds light on various specific pharmacotherapeutic and biological features in allogeneic and autologous HSCT patients. Patients displayed polypharmacy and even hyper-polypharmacy, as well as anticholinergic and potentially inappropriate drugs as evidenced by anticholinergic burden scales, and the recently developed GO-PIM list specific to oncology patients. Patients exhibit signs of liver dysfunction, highlighted by the automatic screening tool for hepatic impairment MELD score, indicating the need for careful consideration of the dosage regimen for drugs that are extensively metabolized by the liver and/or have potential liver toxicity concerns. Furthermore, HSCT patients have elevated levels of C-reactive protein, raising concerns about the impact of inflammation-induced met-

abolic down-regulation on the dosing regimen of drugs metabolized by CYP3A4 that were evidenced in these patients.

These findings highlight the importance of considering drug-disease interactions through inflammation, optimizing drug treatments, and preventing drug-related problems in this vulnerable patient population. Further research, including prospective studies and interventions, is warranted to build upon these findings and improve the care of HSCT patients.

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Appendix

Table 2. Ranking of drugs administered to allogeneic HSCT patients during hospitalization estimated by the frequency of patients that received the drugs, and their metabolic pathways (Informations retrieved from Drugbank (*), and when not available retrieved from literature).

Drugs	Frequency (%)	Metabolic pathway	Reference
CICLOSPORINE	100	3A4	*
VALACICLOVIR	100	esterase	*
TRAMADOL	100	extensive CYP2D6 and CYP3A4, CYP2B6	*
ACIDE URSODEOXYCHOLIQUE	100	non CYP450	*
PHYTOMENADIONE	100	CYP4F2	*
PENTAMIDINE ISETHIONATE	100	CYP1A1	Li 2003
ONDANSETRON	100	CYP1A2, CYP2D6 and CYP3A4	*
NEFOPAM	100	CYP1A2, CYP2C19 and CYP2D6	Mittur 2018
FLUCONAZOLE	100	minimal	*
RACECADOTRIL	95	ND	*
CEFEPIME	95	minimal	*
ALPRAZOLAM	95	3A4 extensive	*
MACROGOL	95	not metabolized	*
MYCOPHENOLIQUE ACID	90	esterase	*
ALIZAPRIDE	90	ND	*
SULFAMETHOXAZOLE and TRIMETHOPRIME	90	NAT and CYP2C9 // CYP2C9, CYP3A4 and CYP1A2	*
ZOPICLONE	85	CYP3A4 and CYP2C8	Becquemont 1999
AMOXICILLINE	85	ND	*
PARACETAMOL	80	conjugation and CYP2E1	*
PHLOROGLUCINOL	55	ND	*
OXYCODONE	55	CYP3A4 and CYP2D6 extensive	*
AMLODIPINE	55	3A4	*

Drugs	Frequency (%)	Metabolic pathway	Reference
VANCOMYCINE	50	almost not metabolized	*
FUROSEMIDE	50	CYP2C11, 2E1, 3A1, and 3A2	Yang 2009
METOCLOPRAMIDE	50	CYP2D6, CYP3A4 and CYP1A2	*
MORPHINE	50	UGT2B7	*
LANSOPRAZOLE	45	CYP3A4 and CYP2C19	*
LETERMOVIR	35	UGT1A1 and UGT1A3: Minimal	*
FILGRASTIM	35	non CYP450	*
ACICLOVIR	35	minimal, via alcohol dehydrogenase and aldehyde dehydrogenase	*
CETIRIZINE	35	minor	Renwick 1999
POSACONAZOLE	30	primarily glucuronidation	*
HYDROXYZINE	30	hydrolysis and N-acetylation	*
METHYLPREDNISOLONE	30	ND	*
PANTOPRAZOLE	30	CYP2C19, sulfation and CYP3A4	*
PREDNISONE	30	ND	*
DEXCHLORPHENIRAMINE	25	CYP2D6, CYP3A4, and glucuronidation or sulfation	*
CLORAZEPATE POTASSIQUE	25	CYP 2C19 and 3A4	Riss 2008
CHLORPROMAZINE	20	CYP2D6 (major pathway), CYP1A2 and CYP3A4	*
VORICONAZOLE	15	Extensive via CYP2C19, CYP2C9 and CYP3A4	*
CASPOFUNGINE	15	independent of CYP450, hydrolysis and N-acetylation	*
NICARDIPINE	15	extensive via CYP2C8, CYP2D6, and CYP3A4	*
VALGANCICLOVIR	15	esterases	*

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Table 3. Ranking of drugs administered to autologous HSCT patients during hospitalization estimated by the frequency of patients that received the drugs, and their metabolic pathways (Informations retrieved from Drugbank (*), and when not available retrieved from literature).

Drugs	Frequency (%)	Metabolic pathway	Reference
VALACICLOVIR	100	esterase	*
PENTAMIDINE ISETHIONATE	95	CYP1A1	Li 2003
NEFOPAM	95	CYP1A2, CYP2C19 and CYP2D6	Mittur 2018
CEFEPIME	95	almost not metabolized	*
ALIZAPRIDE	90	ND	*
ALPRAZOLAM	90	3A4 extensive	*
RACECADOTRIL	90	ND	*
ZOPICLONE	90	CYP3A4 and CYP2C8	Becquemont 1999
MACROGOL	80	not metabolized	*
PEGFILGRASTIM	80	non CYP450	*
ONDANSETRON	65	CYP1A2, CYP2D6 and CYP3A4	*
TRAMADOL	65	extensive CYP2D6 and CYP3A4, CYP2B6	*
SULFAMETHOXAZOLE and TRIMETHOPRIME	60	NAT and CYP2C9 // CYP2C9, CYP3A4 and CYP1A2	*
ACICLOVIR	50	minimal, alcohol dehydrogenase and aldehyde dehydrogenase	*
FLUCONAZOLE	50	minimal	*
MORPHINE	50	UGT2B7	*
PHLOROGLUCINOL	50	ND	*
PHYTOMENADIONE	50	CYP4F2	*
AMOXICILLINE or AMOXICILLINE/CLAVULANATE	40	ND but minimal	*

Drugs	Frequency (%)	Metabolic pathway	Reference
FILGRASTIM	40	non CYP450	*
AMPHOTERICINE B	35	not metabolized	*
CHLORPROMAZINE	35	CYP2D6 (major pathway), CYP1A2 and CYP3A4	*
METOCLOPRAMIDE	25	CYP2D6, CYP3A4 and CYP1A2	*
DEXCHLORPHENIRAMINE	25	CYP2D6, CYP3A4,and glucuronidation or sulfation	*
LANSOPRAZOLE	25	CYP3A4 and CYP2C19	*
VANCOMYCINE	25	almost not metabolized	*
CLORAZEPATE POTASSIQUE	20	CYP 2C19 and 3A4	Riss 2008
MEROPENEM	20	almost not metabolized	*
OXYCODONE	15	CYP3A4 and CYP2D6 extensive	*
PANTOPRAZOLE	15	CYP2C19, sulfation and CYP3A4	*
PARACETAMOL	15	conjugation and CYP2E1	*
PREGABALINE	15	almost not metabolized	*
APREPITANT	10	CYP3A4 major and CYP1A2 and CYP2C19	*
VORICONAZOLE	5	CYP2C9, CYP2C19, and CYP3A4	*

Li XQ, Björkman A, Andersson TB, et al. Identification of human cytochrome P(450)s that metabolise anti-parasitic drugs and predictions of in vivo drug hepatic clearance from in vitro data. Eur J Clin Pharmacol. 2003;59(5-6):429-42. doi: 10.1007/s00228-003-0636-9.

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