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ORIGINAL ARTICLE

Comparison of two different anti-infectious approaches after high-dose chemotherapy and autologous stem cell transplantation for hematologic malignancies in a 12-year period in British Hospital, Uruguay

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Abstract

Autologous stem cell transplant (ASCT) is a widely used and safe procedure to treat mostly hematologic diseases. These patients are at risk of infectious complications, which represents a major cause of morbidity and it is the second cause of mortality. This retrospective 12-year analysis of the incidence, type, and severity of infections in 266 consecutive unselected ASCT patients at our institution provides novel information addressing this issue. We included 266 ASCT procedures. Patients included in the 2006–2013 period are referred to as group 1 (ciprofloxacin prophylaxis and ceftazidime-amikacin as empirical antibiotics), and those in the 2013–2017 period are group 2 (levofloxacin prophylaxis and meropenem as empirical antibiotics). The incidence of febrile neutropenia was 72% in group 1 and 86.2% in group 2 ($p = 0.004$). The majority of infectious episodes were associated with fever of unknown origin: 55% in group 1 and 59% in group 2. Febrile of unknown origin episodes were 82.6% in group 1 and 80% in group 2. Significant differences between both groups were found in age, hypogammaglobulinemia, and advanced disease at ASCT. No differences were found between groups regarding the most common agent documented in positive blood cultures (Gram+ were 66.6% in group 1 and 69% in group 2 ($p = 0.68$)). Mortality within 100 days of transplant was low, 1.87%. Regardless of the prophylactic regimen used, most patients experience febrile episodes in the ASCT setting, fever of unknown origin is the most common infection complication, and Gram+ agents are prevalent in both groups. Mortality rates were low. According to our results, ASCT is a safe procedure and there is no clear benefit in favor of levofloxacin versus ciprofloxacin prophylaxis. Both anti-infectious approaches are acceptable, yielding similar outcomes.

Keywords Infection · Stem cell transplantation · Autologous · Risk factors · High-dose chemotherapy

Introduction

Autologous stem cell transplant (ASCT) plays a central role in the treatment of various diseases making it possible to administer high-dose anticancer drugs and/or radiation to eradicate malignant cells. The patient's own cryopreserved hematopoietic cells are infused to restore normal bone marrow function. This strategy has been increasingly adopted in the treatment of hematological malignancies, particularly lymphomas and multiple myeloma. In the last decades, advances in supportive care have improved the safety, efficacy, and outcome of ASCT. However, these patients are at risk of infectious complications, which represent a major cause of morbidity and significantly increase the cost of care [1]. Even when infection-related mortality in ASCT is reported to be low in most studies (< 2%) [2, 3], it represents the second cause of death (24%) after primary disease (69% of deaths), according to the 2016 report of the Center for International Blood and Marrow Transplant Research (CIBMTR) [4]. Thus, preventing infections is a major goal. The main risk factors for infections are the duration of the neutropenic phase, long-term placement of invasive devices (tunneled central venous catheters), and damaged mucocutaneous barriers [5]. No

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differences have been reported in the rate, epidemiology, and severity of infections in ASCT for hematological malignancies compared with solid tumors [6, 7].

The timeline for infections in ASCT differs from that of allogeneic transplant recipients. ASCT patients are at risk mostly during the aplasia. The incidence of febrile episodes varies from 60 to 100%; most of them are of unknown origin, and only one-third has a documented source of infection. Retrospective studies in adults have reported the predominance of Gram-positive bacterial infections, which are more common than Gram-negative infections. (3) It is to be noted that invasive fungal infections (IFI) and parasitic infections are rare. Bacteremia is detected in up to 20% [8–10].

Infections in the transplant setting in Latin America (LA) pose some particular challenges. Frequencies of prior viral infections including herpes viruses, hepatitis, cytomegalovirus (CMV), toxoplasmosis, and Epstein-Barr virus (EBV) are higher than in Europe and North America. Fungal infections are also more frequent in immunocompromised patients in Latin American countries. In addition, other diseases like tuberculosis and Chagas, uncommon in the northern hemisphere, are frequent in Latin America [11]. However, this is a very heterogeneous region with a wide economic, social and ethnic diversity, and a huge range of life expectancy at birth (55 years in Trinidad and Tobago to > 80 years in Costa Rica). Infrastructure and expertise are critical variables for transplant success [12–14].

Uruguay ranks second in Latin America and 28th in the world in terms of social progress according to the 2017 Social Progress Index ranking [15].

The first autologous stem cell transplant in Latin America was performed at our center in 1985. Since then, the number of transplants has steadily increased, with around 40 ASCTs per year in the last 5 years. Mortality rate of ASCT is < 2%. These results are in line with those published by North American and European centers [16, 17].

There are no publications concerning infections in ASCT in our country. This retrospective 12-year analysis of the incidence, type, and severity of infections in 266 consecutive unselected ASCT patients at our institution provides novel information addressing this issue.

Patients and methods

The primary objective of this retrospective single-center study was to compare the incidence of febrile neutropenia and the characteristics of infections of two different antibacterial approaches in the context of ASCT. Secondary objectives included evaluating the need of second-line antibiotic therapy, differences in intensive care unit (ICU) admission, analyzing predictive factors for febrile neutropenia and infections, and evaluating whether febrile neutropenia was associated with late engraftment.

Patients characteristics

From January 2006 to December 2017, 279 ASCTs were performed at the British Hospital Hematopoietic Stem Cell Transplantation Unit in Montevideo, Uruguay. The study included the patients who have the infectious episodes' complete data. This corresponds to 266 ASCT procedures performed to 249 patients; 17 patients received two transplants. Patients' characteristics are summarized in Table 1.

Transplantation procedures

After at least 5 days of stimulation with granulocyte colony-stimulating factor (G-CSF) at 10 mg/kg/day, repeated

Table 1 Population characteristics

	Median (range)	No. of patients (%)
Age, years	56 (18–72)	
Gender		
Male		154 (58%)
Female		112 (42%)
Disease		
MM		126 (47.4%)
NHL		86 (32.3%)
HL		34 (12.8%)
AML		13 (4.9%)
Solid tumors		4 (1.5%)
Renal amyloidosis		3 (1.1%).
CD34+ cell	4.87×10^6/kg (0.88–37)	
Serum Albumin	4.1 (1.5–5.15)	
Status before transplant		
In CR		101 (40%)
Not in CR		165 (60%)
Disease*		
Early disease		140 (52.6%)
Advanced disease		126 (47.4%)
Diabetes		19 (7.1%)
Mucositis		244 (97.1%)
Charlson CI score	2 (2–8)	
Baseline serum creatinine	0.92 mg/dL (0.5–3.84)	
Hypogammaglobulinemia		93 (35%)
Use of parenteral nutrition		27 (10.2%)

*All patients with 1st complete remission and patients in 1st PR immediately transplanted after initial diagnoses were designated as having early disease. All patients in second remission, or even more advanced states, for example, second or third relapse, were designated as having advanced disease. **NHL non Hodgkin lymphoma, *AML* acute myeloid leukemia, *MM* multiple myeloma, *HL* Hodgkin lymphoma, *CR* complete remission

leukaphereses were performed to obtain a minimum CD34+ cells of 2×10^6/kg recipient body weight. The median number of $CD34^+$ cells infused was 4.87 (0.88–37) $\times 10^6$/kg. Peripheral blood stem cells (PBSC) were frozen using a controlled-rate method and stored in liquid nitrogen at − 196 °C until use. Conditioning regimens were chosen according to the underlying disease: patients with multiple myeloma (MM) and amyloidosis (AL) ($n = 129$) were treated with high-dose melphalan (HDM). Patients with NHL and HL were treated with the following: BEAM (carmustine, etoposide, cytarabine, and melphalan) ($n = 68$ NHL and $n = 26$ HL), NEAM (mitoxantrone, etoposide, cytarabine, and melphalan) ($n = 15$ NHL and $n = 5$ HL), BEAC (carmustine, etoposide, cytarabine, and cyclophosphamide) ($n = 2$ NHL and $n = 2$ HL), and LACE (lomustine, cytarabine, cyclophosphamide, and etoposide) ($n = 1$ HL). Busulfan-cyclophosphamide (BuCy) was used in 12 AL and in 1 NHL, Carboplatin-etoposide in 4 solid tumors, and busulfan-melphalan (BuMel) in 1 AL. Harvested stem cells were infused 24 h after the discontinuation of chemotherapy, and G-CSF 5 mg/kg/day was administered subcutaneously until leukocyte recovery from day +5 after ASCT.

Definition criteria

Neutropenia was defined as an absolute neutrophil count (ANC) < 500/mL. Fever was defined as a single oral temperature measurement of > 38.3 °C or a temperature of > 38.0 °C sustained over a 1-h period [18]. Bacteremia refers as the isolation of a bacteria in blood cultures. Sepsis was defined following the definition of the Third International Consensus of Definitions for Sepsis and Septic Shock (Sepsis-3) [19]. The day of engraftment was defined as the first of 2 consecutive days of achieving an absolute neutrophil count > 500 cells/mL or L > 1000.Catheter-related infection was defined by clinical symptoms and/or positive catheter culture isolation.

Anti-infectious prophylaxis

Patients were admitted at the Transplantation Unit in a single-bed room with HEPA filters and positive pressure. A low germ diet was indicated. Anti-bacterial prophylaxis included ciprofloxacin (400 mg bid orally) from 2006 to 2013 starting on day 0 until neutrophil recovery and sulfamethoxazole-trimethoprim (480 mg bid orally) during the conditioning regimen. From 2013 to the present antibacterial prophylaxis has been levofloxacin 500 mg daily. In both periods, intravenous acyclovir (5 mg/kg bid) prophylaxis was administered from the beginning of the conditioning regimen until engraftment or 1 year in case of HSV or VZV positive serologies. For antifungal prophylaxis fluconazole 200 mg bid was administered from day 0 until engraftment.

Empirical antibiotic therapy

In case of febrile episodes, blood, throat, stool (if diarrhea), and urine culture were taken and empirical antibiotic therapy initiated. From 2006 to 2013 therapy consisted of ceftazidime 2 g IV each 8 h and amikacin 1 g day and from 2013 to present of meropenem 1 g IV each 8 h. In case of fever persistence for 3 days or hemodynamic instability, a glycopeptide was added, considering that all patients had a central line indwelling catheter, with the consequent risk of Gram-positive infection. If fever continued after 5 days, empirical antifungal treatment was added with an echinocandin. If the etiology of infection was identified, antibiotic treatment would be adapted if necessary.

Patients included in the 2006–2013 period are referred to as group 1 and those in the 2013–2017 period are group 2. All febrile episodes from admission to discharge were documented.

Statistical analysis

All data were analyzed using descriptive statistical methods, and statistical significance of differences between groups was calculated using test, t test for non-categorical variables and chi-square or Fisher's exact test for categorical variables. Factors affecting infection development were investigated using logistic stepwise analysis. Significance was established at $P < 0.05$.

Ethics

All procedures were in accordance and with the acceptance of the Hospital Britanico's Ethics Committee and with the Helsinki Declaration of 1975, revised in 2008.

Results

Two hundred sixty-six ASCTs performed between 2006 and 2017 in our Transplant Unit were included. Median age was 56 years (range 18–72), with a male-to-female ratio of 1.4:1. Most patients were transplanted because of MM and NHL (79.7%), and the majority were not in complete remission of their underlying disease (60%).

Patients were grouped according to the type of bacterial prophylaxis (ciprofloxacin and levofloxacin) shown in Table 2. The incidence of febrile neutropenia was 72% in group 1 and 86.2% in group 2 ($p = 0.004$). Culture-negative febrile episodes were 82.6% in group 1 and 80% in group 2. Significant differences between both groups were found in age, hypogammaglobulinemia, and advanced disease at ASCT.

Table 2 Characteristic of patients according to prophylactic regimens

	Group 1 2006–2013 (*N* = 121)	Group 2 2013–2017 (*N* = 145)	*P*
Males, *n* (%)	64 (53)	90 (62)	0.131
Age, median (range)	54 (18–71)	58 (23–72)	*0.020*
Underlying disease, *n* (%):			0.121
MM	69 (49.6)	66 (45.5)	
NHL	35 (29)	51 (35)	
HL	19 (15.7)	15 (10.3)	
Acute leukemia	7 (5.8)	6 (4.1)	
Solid tumor	0	4 (2.8)	
Amyloidosis	0	3 (2.1)	
CR, *n* (%)	49 (40.5)	52 (35.9)	0.438
Advanced disease, *n* (%)	46 (38)	80 (55.2)	*0.005*
Diabetes, *n* (%)	12 (10.2)	7 (4.8)	0.096
Mucositis, *n* (%)	106 (92.2)	140 (96.6)	0.140
Parenteral nutrition, *n* (%)	10 (9.2)	17 (11.7)	0.514
Hypogammaglobulinemia, *n* (%)	30 (27.3)	64 (44.5)	*0.016*
Charlson index (media ± SD)	3.06 ± 1.1	2.85 ± 1.2	0.64
Median CD34 + ×10*6/kg	5.8 ± 5.3	5.03 ± 2.39	*0.0001*
Conditioning regimen; *n* (%)			
Melphalan	60 (49.6)	69 (47.6)	0.74
BEAM	49 (40.5)	45 (31)	0.10
BUCY	7 (5.8)	6 (4.1)	0.53
NEAM	0	20 (13.8)	0.0001
BEAC	4 (3.3)	0	0.028
Carboplatin-etoposide	0	4 (2.8)	0.066
BuMel	0	1 (0.7)	0.36
LACE	1 (0.8)	0	0.27

NHL non Hodgkin lymphoma, *MM* multiple myeloma, *HL* Hodgkin lymphoma, *CR* complete remission. BEAM (carmustine, etoposide, cytarabine, and melphalan), NEAM (mitoxantrone, etoposide, cytarabine, and melphalan), BEAC (carmustine, etoposide, cytarabine, and cyclophosphamide), LACE (lomustine, cytarabine, cyclophosphamide, and etoposide), BuCy (busulfan-cyclophosphamide), BuMel (busulfan-melphalan)

Entries in italics reference the variables with statistically significant difference

Table 3 Epidemiology of culture isolation among groups

Isolation	Group 1 (*n* = 121)	Group 2 (*n* = 145)
Negative culture	100 (82.6%)	116 (80%)
Gram positives		
Clostridium difficile	3	5
Coagulase-negative staphylococci (CoNS) (not specified)	4	0
Staphylococcus epidermidis	2	5
Corynebacterium	2	2
Enterococcus	1	2
Pseudomona paucimobilis	1	0
Propionibacterium granulosus	1	0
Staphylococcus albus	1	0
Actinomyces odontolyticus	0	1
Streptococcus oralis	0	1
Staphylococcus aureus	0	1
Streptococcus mitis	0	1
SAMAR	0	1
Gram negatives		
Escherichia coli	5	4
Klebsiella pneumoniae	2	1
Achromobacter	0	1
Acynetobacter	0	1
Delftia acidovorans	0	1
Pseudomona aeruginosa	0	1
Serratia marcescens	0	1
Haemophylus b	0	1
Campylobacter spp.	0	1
Stenotrophomona maltophila	0	1
Fungi		
Candida albicans	1	1
Candida krusei	1	0
Candida glabrata	1	0

*Four patients in group 1 and 4 in group 2 had 2 different isolations in the same febrile episode

Characteristics of infections and evolution

Group 1

No febrile episodes were reported in 34/121 cases (28%). Considering the 87 patients who developed febrile neutropenia, median days of fever were 2 (1–19) and 55% had fever of unknown origin (FUO). Catheter-related infections and gastrointestinal were the most prevalent sites of infection in this group. Positive cultures were detected in 17.4% of the 87 patients. In blood positive cultures, Gram+ agents represented 66.6%. The isolations, site of infection, and evolution are listed in Tables 3, 4, and 5. Most patients (79, i.e., 91%) received ceftazidime+amikacin while 8 received ceftazidime-only in 3 cases, ceftazidime+vancomycin in 1, ceftazidime+metronidazol in 2, vancomycin+rifampicin 1, and imipenem+vancomycin 1. In 52 patients (60%) another antibiotic was indicated: meropenem in 45 (51.7%), vancomycin in 47 (54%), voriconazol in 7 (8%), caspofungin in 7 (8%), metronidazole in 8 (9.2%). The median administration of ceftazidime was 6 days (1–25), amikacin 6 (2–18), meropenem 9 (3–20), vancomycin 10 (3–20), voriconazol 12 (7–15), caspofungin 9 (3–10), and metronidazole 10 (2–15). Six (4.9%) patients required intensive care unit (ICU) admission, 3 due to pneumonia, 2 due to sepsis, and 1 because of a viral encephalitis. The

Table 4 Sites of infection

	Group 1 $N = 121$ (%)	Group 2 $N = 145$ (%)	P
None	80 (66.1)	92 (63.4)	NS
Catheter	20 (16.5)	13 (8.9)	NS
Pneumonia	8 (6.6)	17 (14)	NS
Colitis	13 (10.7)	13 (8.9)	NS
Urinary infection	4 (3.3)	7 (4.8)	NS
Sepsis	2 (1.6)	0	NS
Viral encephalitis	1 (0.8)	0	NS
Cellulitis	1 (0.8)	2 (1.3)	NS
Bacteremia without focus	4 (3.3)	9 (6.2)	NS
Alithiasis cholecystitis	0	1 (0.7)	NS
Folliculitis	0	1 (0.7)	NS
Parotitis	0	1 (0.7)	NS
Sinusitis	0	1 (0.7)	NS
Purulent tracheobronchitis	0	1 (0.7)	NS

*Twelve patients in group 1 and 2 had two or more evidenced focus

patients with sepsis died at the ICU; one died to a catheter-related infection with *Candida glabrata* and the other to a catheter-related infection and colitis.

Median days at neutrophil recovery with ANC > 500/mm^3 were 8 (4–17) and 11 (9–32) for ANC > 1000/mm^3. Median stay after transplantation was 17 (10–56) days for the whole group, 20.6 days for those who had febrile episodes, and 16.5 for those who did not ($p = 0.004$). There was no difference in days at neutrophil recovery > 500/mm^3 ($p = 0.13$) and > 1000/mm^3 ($p = 0.31$) in both groups.

Group 2

In this group 20/145 (13.8%) patients had no febrile episodes. Median days of fever were 2 (1–12); 59% had FUO. Catheter-related infections, pneumonia, and gastrointestinal were the most prevalent sites of infection, with 20% of positive cultures in this group. Gram+ blood cultures accounted for 69% of the positive blood cultures. Out of the 125 that experienced febrile neutropenia, 70 patients received an additional agent (56%), in 68 (54.4%) vancomycin was added, 5 (4%) voriconazole, 10 (8%) caspofungin, 16 (12.8%) metronidazole, and 20 patients received other plans (16%). Median days of meropenem were 10 (2–27), vancomycin 9 (2–25), voriconazole 8.5 (5–10), caspofungin 7 (1–19), and metronidazole 10 (5–14).

Six patients required ICU admission (4.1%), one because of pneumonia, 1 sepsis, 1 alithiasic cholecystitis, 1 catheter-related infection and pneumonia, and 2 due to arrhythmia. No deaths occurred in this group during their SCT stay.

Median day at neutrophil recovery > 500/mm^3 was 10 (6–21) and > 1000/mm^3 was 12 (9–21). Median day at discharge was +16 after stem cell infusion (12–62), being 19.8 for those who experienced febrile neutropenia and 17 days for those who did not ($p = 0.184$). No differences were found in the days at neutrophil recovery > 500 or 1000/mm^3 between both groups ($p = 0.08$ and 0.82).

Table 5 Sites, characteristics of isolations, and evolution

Outcomes	Group 1 ($n = 121$)	Group 2 ($n = 145$)	P
Fever and neutropenia	87 (72%)	125 (86.2%)	0.004
Bloodstream infections (BSI)			
Gram-positive bacteremia	9 (7.4%)	12 (8.3%)	NS
Gram-negative bacteremia	3 (2.5%)	6 (4.1%)	NS
Fungemia	3 (2.5%)	0 (0)	NS
Urinary infections			
Gram-positive	0 (0)	2 (1.4%)	NS
Gram-negative	4 (3.3%)	5 (3.5%)	NS
Fungemia	0 (0)	0 (0)	NS
Other sites			
Gram-positive	5 (4.1%)	6 (4.1%)	NS
Gram-negative	0 (0)	1 (0.7%)	NS
Fungemia	0 (0)	1 (0.7%)	NS
ICU admission	6 (4.9%)	6 (4.1%)	NS
Clostridium difficile infection within 30 days	3 (2.5%)	5 (3.4%)	NS
Mortality	4 (3.3%)	1 (0.7%)	NS
Within 30 days of transplant	1 (0.8%)	0 (0)	NS
Within 30–100 days of transplant	3 (2.5%)	1 (0.7%)	NS
Sepsis-related mortality	2 (1.65-%)	0 (0)	NS

ICU intensive care unit

No differences were found between groups regarding culture negativity (82.6% in group 1 and 80% in group 2) and the most common agent documented in positive blood cultures (Gram+ were 66.6% in group 1 and 69% in group 2 ($p = 0.68$)).

Mortality within 30 days of transplant was low, under 1%. By day 100, 4 patients had died in group 1 (2 sepsis, 1 Aspergillus, and 1 progression) and 1 in group 2 (arrhythmia), without statistical significance.

Discussion

Febrile neutropenia is a common complication in ASCT, and its incidence varies from 63 to 94% [3, 7, 20]. This complication implies longer hospitalization, use of diagnostic tools and antibiotics, and it increases the procedure's morbidity and mortality. Knowing the characteristics of the infections in each center helps to delineate better policies of prophylaxis and empirical treatment. This study retrospectively evaluated the

infectious complications of ASCT performed in a single center, over a 12-year period in a cohort of 266 patients, comparing two different prophylactic and antibiotic therapy approaches.

Current guidelines for prevention of infections in ASCT recommend antibacterial prophylaxis with a fluoroquinolone [21]. This is generally initiated at the time of stem cell infusion and stopped at the time of neutrophil recovery. Local epidemiological data must be considered, and quinolone resistance emergence should be monitored. Anti-Gram positive prophylaxis is not indicated; as an example, vancomycin prophylaxis has shown to increase the risk of emergence of resistant staphylococci. Herpes simplex virus prophylaxis is indicated: acyclovir or valacyclovir are used when the conditioning regimen is started, and it should be continued until engraftment and mucositis resolution. If the patient is VZV-positive, the prophylaxis should be maintained for 1 year. CMV prophylaxis is not recommended for CMV-seropositive autologous recipients [22]. Invasive fungal infections are remarkably infrequent in patients undergoing high-dose chemotherapy and ASCT. Gilbert et al. reported a fungemia rate of about 4% without using antifungal prophylaxis [23]. Reich et al. showed that 3 of 117 patients had invasive fungal infections [3]. Antifungal prophylaxis targeting *Candida* spp. and/or molds is recommended. Fluconazole at a dose > 200 mg/day is the drug of choice [24]. *Pneumocystis carinii* is a rare complication in ASCT. Prophylaxis with trimetoprim-sulfametoxazole (TMP-SMZ) should be considered for patients with particular risk factors, including hematologic malignancies treated with purine analogues or high-dose corticosteroids, with prophylaxis usually extended to 3–6 months after ASCT. Evaluation for latent or active tuberculosis is recommended in the transplant setting. Isoniazide prophylaxis should be administered to patients exposed to active infectious tuberculosis, patients with a positive tuberculin test or patients with a positive IGRA result with no previous treatment and no evidence of active tuberculosis [24].

The recommendation for prophylactic levofloxacin is based on a meta-analysis of 95 randomized, controlled trials comparing antibiotic prophylaxis with placebo or no intervention in neutropenia after chemotherapy. It showed that antibiotic prophylaxis significantly decreased the risk for death, fever, clinically documented infections, and microbiologically documented infections when compared with placebo or no treatment. This meta-analysis proposes that the benefits of antibiotic prophylaxis outweighed the potential side effects and the development of resistance since all-cause mortality was reduced [25–27]. Although fluoroquinolones are commonly used in ASCT, there is a concern of potentially increasing the risk of occurrence of resistant organisms and *C. difficile* infection. Levofloxacin prophylaxis is associated with decreased risk of bloodstream infection and febrile neutropenia in patients with myeloma undergoing ASCT [28]. However, its benefit compared with ciprofloxacin has not been extensively proved in this setting.

In 2013 our center adopted levofloxacin as standard prophylaxis and meropenem as the initial empiric antibiotic in the first febrile episode. This decision was made given the data of improvement of overall survival with levofloxacin in acute leukemia and the lower toxicity reported with the use of piperacillin tazobactam or meropenem as empirical antibiotic treatment versus ceftazidime amikacin. After 5 years, it was our interest to compare results of this approach with the previous scheme, to assess the worth of the change.

We found significant differences in the incidence of febrile neutropenia between groups, in favor of ciprofloxacin prophylaxis (72% vs 86.2% ($p = 0.004$)). The levofloxacin group included older patients with more advanced disease and hypogammaglobulinemia, which may explain this finding, at least partially. Gram positives were the most common microbes isolated in both groups. No differences were found in the incidence of all isolations (blood, urine, or other) between groups. These results are similar to those reported by other authors [25]. Although levofloxacin is more effective against Gram-positive agents, it did not result in a reduction in the incidence of febrile neutropenia or Gram-positive isolations in group 2. These findings differ from what was published recently by Copeland et al., who reported lower incidence of bloodstream infections in patients receiving levofloxacin prophylaxis compared with ciprofloxacin in multiple myeloma patients undergoing SCT [29]. Our cohort also included patients with other hematologic malignancies, and it is estimated that high rates of advanced disease and hypogammaglobulinemia in group 2 may have contributed to these findings.

The majority of infectious episodes in our study were associated with fever of unknown origin: 55% in group 1 and 59% in group 2, as reported internationally [7, 30, 31]. Catheter-related infections were less frequent in group 2, whereas pneumonia was more frequent. Considering results of isolations, we cannot infer that the choice of prophylactic regimen has influenced these outcomes. Perhaps, a more extensive evaluation of the site of infection, including more precise imaging techniques in the last 5 years, may explain the latter. No increase in resistant bacteria nor *Clostridium difficile* infection was found in group 2. Fungi infection was low (1.8%), including 3 cases of bloodstream candidemia: 1 *C. albicans*, 1 *C. krusei* and 1 *C. glabrata* and 1 lung aspergillosis in group 1 and 1 patient with *Candida albicans* in folliculitis in group 2.

Sixty percent of patients needed the addition of a second-line empirical antibiotic in group 1 and 56% in group 2, without significant differences ($p = 0.47$). The median of neutrophil recovery was day 8 in group 1 and day 10 in group 2 ($p = 0.0001$). Not having infectious complications was associated to earlier discharge in both groups. Patients in group 2 were older, with more advanced disease and immunosuppression;

they also had a lower count of CD34+ infused cells; we propose that all these factors contribute to this difference.

Most ICU admissions were due to infections. Two patients died from sepsis in the ICU in group 1. No deaths occurred in group 2 during hospitalization. The global mortality rate was low (1.87%), similar to international reports [28, 32].

This study has limitations, mainly due to its retrospective nature and difference in clinical characteristics of patients, as there were more advanced diseases in group 2. These differences do not allow us to define equality between levofloxacin and ciprofloxacin. Regarding the empirical antibiotic plan, even though ceftazidime-amikacin theoretically is a more toxic plan, we have to point it out that meropenem usage could develop multiresistant bacterial infection. As this is a retrospective analysis, the toxicity of the initial empirical antibiotics (ceftazidime-amikacin vs meropenem) was not detailed. Costs of both anti-infectious approaches were not evaluated.

Conclusions

Most patients experience febrile episodes in the ASCT setting and more than 50% are FUO. More than 50% require the use of more than one empirical antibiotic approach, regardless of the prophylactic regimen. Gram+ agents are prevalent and mortality rates were low. According to our results, there is no clear benefit in favor of levofloxacin versus ciprofloxacin prophylaxis, or between ceftazidime-amikacin versus meropenem; therefore, both anti-infectious approaches are acceptable, yielding similar outcomes.

Compliance with ethical standards

All procedures were in accordance and with the acceptance of the Hospital Britanico's Ethics Committee and with the Helsinki Declaration of 1975, revised in 2008.

Conflict of interest The authors declare that they have no conflict of interest.

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