Bloodstream infection in hematopoietic stem cell transplantation outpatients: risk factors for hospitalization and death

Rachel Russo1, Elisa Teixeira Mendes1,2, Anna Sara Levin1,3, Frederico Dulley4, Maura S. Oliveira1, Maria Aparecida Shikanai-Yasuda1, Silvia Figueiredo Costa1,3

ABSTRACT

We described 235 bloodstream infection (BSI) episodes in 146 hematopoietic stem cell transplantation (HSCT) outpatients and evaluated risk factors for hospitalization and death. Records of outpatients presenting with positive blood cultures over a 5-year period (January 2005 to December 2008) were reviewed. Variables with p < 0.1 in bivariate analysis were used in a regression logistic model. A total of 266 agents were identified, being 175 (66.7%) gram-negative, 80 (30.3%) gram-positive bacteria and 9 (3.4%) fungi. The most common underlying disease was acute leukemia-40 (27.4%), followed by lymphoma non-Hodgkin 26 (18%) and 87 patients (59.6%) were submitted to allogeneic hematopoietic stem cell transplant (HSCT). BSI episodes were more frequent during the first 100 days after transplantation (183 or 77.8%), and ninety-one (38.7%) episodes of BSI occurred up to the first 30 days. Hospitalization occurred in 26% of the episodes and death in 10% of cases. Only autologous HSCT was protector for hospitalization. Although, central venous catheter (CVC) withdrawal and the Multinational Association of Supportive Care in Cancer (MASCC) score up to 21 points were protector factors for death in the bivariate analysis, only MASCC remained as protector.

KEYWORDS: Bacteremia. Hematopoietic stem cell transplantation. Outpatients. Outcome. Resistance.

INTRODUCTION

Bloodstream infection (BSI) is the most relevant infections in patients undergoing hematopoietic stem cell transplant (HSCT) with high morbidity and mortality1. Until recently, gram-positive bacteria (GPB) were the most common agents causing BSI in these patients; moreover, in the last years there has been an increase of gram-negative bacteria (GNB) in several hospitals2.

Despite the increase in the number of allogeneic (allo) HSCT patients with early discharge and outpatient autologous (auto) transplantation programs; there is a lack of studies evaluating the safety of treating infections in HSCT outpatients.

The objective of this study was to evaluate the etiological agents causing BSI in HSCT outpatients as well as the risk factors associated with hospitalization and 30-day mortality.

METHODS

The Hospital das Clínicas is a teaching hospital with 2,200-beds and is a reference...
center for auto and allo- HSCT in Brazil. The outpatient unit is open from 7 am to 7 pm, every day of the week, including weekends. All patients submitted to HSCT were hospitalized at the time of transplantation.

Records of outpatients presenting with positive blood cultures over a 5-year period (January 2005 to December 2008) were reviewed. This study was approved by the Ethics Committee of the Hospital das Clínicas of University of São Paulo.

The BSI definition used were patients with positive blood culture collected through the central venous catheter (CVC) or a peripheral access during a period in which patients had fever and physicians had described antibiotics. The end points evaluated were hospitalization and 30-day mortality BSI onset. Clinical and demographic variables at the time of BSI, such as gender, age, underlying disease, length of hospitalization, type of HSCT, CVC (type and withdrawal), the presence of mucositis or graft-versus-host disease (GVHD) and Multinational Association of Supportive Care in Cancer (MASCC) risk index score were evaluated. Hospitalizations depended on the clinical status, and when possible, the treatment was administered in the outpatient unit in which blood cultures were indicated in the presence of fever, hemodynamic instability or any infectious symptoms.

Microorganism identification and antimicrobial susceptibility test was performed using Vitek® (laboratory BioMérieux) and disk diffusion test followed the updated recommendations of CLSI (Clinical and Laboratory Standards Institute).

Data were analyzed using the softwares Epi Info version 3.5.1 and STATA. The two-tailed Fisher’s exact test was used for categorical variables and the Wilcoxon test was used for continuous variables. Logistic regression models were developed to identify factors associated with hospitalization within 21 days onset of BSI and 30-day mortality onset BSI. All non-overlapping variables with p < 0.1 on bivariate analysis were entered into a stepwise forward model. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 743 HSCT outpatients were evaluated during the study period and the records of 146 of them were analyzed. A total of 235 BSI episodes were identified among the 146 patients evaluated, being 207 (88%) monomicrobial and 28 (12%) polymicrobial. The hospitalization occurred in 61 (26%) episodes, the more frequent reason was septic shock, 18/61 (31%) (Table 1). A total of 266 agents were isolated, being 175 (66.7%) gram-negative bacteria (GNB), 80 (30.3%) gram-positive bacteria (GPB) and 9 (3.4%) fungi (Table 1).

Resistance to cefepime in *P. aeruginosa* was identified in only 2/15 (13%) of the isolated agents, to imipenem in 2/14 (14%), and to meropenem in 3/10 (27%). Among *Enterobacter cloacae*, resistance to cefepime occurred in 3/11 (27%) cases, no carbapenem resistance was identified. Among *Acinetobacter spp*, resistance to cefepime occurred in 3/24 (14%) and resistance to imipenem in 2/24 (8%). Resistance to levofloxacin occurred in 1/39 (3%) and to trimethoprim-sulfamethoxazole in 3/39 (8%) of *S. maltophilia* isolates. Resistance to vancomycin was identified in 7/9 (78%) of *E. faecium* BSI. Gram-negative bacteria accounted for 72% of bloodstream infections in allogeneic transplants and 62% of autologous ones (p=0.12). The mean time between transplantation and BSI was higher among allogeneic than autologous HSCT patients (145.5 and 44.1 days, respectively), probably because allogeneic patients remain hospitalized for longer periods after transplantation and at higher risk of infection after discharge. Death in 30 days were 8.5% in autologous and 15.2% in allogeneic HSCT (p=0.17). Median time between positive culture and death in days were 56 days in gram-negative and 27 days in gram-positive infections.

The bivariate analysis showed that previous use of levofloxacin, MASCC score higher than 21 and autologous (auto)-HSCT were protector factors and neutropenia was a risk factor for hospitalization. Moreover, only auto-HSCT remained as protector in the multivariate analysis (Table 2). The bivariate analysis showed that the CVC withdrawal, and MASCC higher than 21 points were protector factors for death (Table 2). Moreover, only MASCC score remained as protector (Table 2).

DISCUSSION

We observed a high proportion of GNB-BSI in our HSCT outpatient unit. The predominance of GNB has been reported by Brazilian studies that evaluated HSCT inpatients. In our casuistic, BSI episodes occurred mainly in the first 100 days after the transplantation, similarly to other studies in the literature and *S. maltophilia* was the most frequent agent in both monomicrobial and polymicrobial BSI. In general, this agent causes outbreaks in BMT settings. Moreover, as in our hospital, a recent study has shown that *S. maltophilia* and *P. aeruginosa* were the most commonly isolated GNB in HSCT patients. We observed a high frequency of infection caused by waterborne bacteria (18%). Infection by these agents is rare even in neutropenic patients. However, our service recommends the protection of the CVC’s lumen with a
plastic dressing to prevent exposure to tap water, a potential source of waterborne agents but it was not possible to assess patients’ compliance with this recommendation. Thus, inappropriate care of CVC at home during baths might explain this finding⁷.

In our study the 30-day mortality onset BSI was 10% and hospitalization occurred in 26% of patients. Moreover, the multivariate analysis showed that autologous HSCT was the only independent protector factor for hospitalization. MASCC score and CVC withdrawal were protective factors for death in the bivariate analysis. In addition, only MASCC score higher than 21, remained as protector factor in the multivariate analysis. Unfortunately, in our study the catheter removal was not carried out as recommended in the literature because of the difficulty of venous access.

In the literature the presence of infection is a major cause of death in HSCT patients¹. Ortega et al showed that 10% of HSCT inpatients with infection evolved to death⁶.
Therefore, the proportion of deaths in the present study in outpatients was similar to that described in BSI HSCT inpatients. Vancomycin-resistant enterococcus (VRE) mortality in HSCT patients ranges from 7% to 34% similar to our findings. In contrast, authors have reported a high mortality of BSI caused by carbapenem-resistant GNB in HSCT.

In conclusion, GNB were the most frequent agents causing BSI in HSCT outpatients in our hospital; hospitalization rate was low and auto-HSCT was a protector factor for hospitalization and the MASCC score higher than 21 points for 30-day mortality.

**FUNDING**

No funding of any kind has been received.

**CONFLICT OF INTERESTS**

None to declare.

---

Table 2 - Risk factors for hospitalization and death in 30 days among 235 episodes of BSI in HSCT outpatients patients.

| Variables                          | Hospitalization N (%) | Bivariate Analysis | Multivariate Analysis | p-value | Multivariate Analysis | p-value |
|------------------------------------|-----------------------|--------------------|-----------------------|---------|-----------------------|---------|
|                                    | No (N) | Yes (N) | P- value | RR (CI 95%) | P- value | OR (CI 95%) | p-value |
| Previous usage of levofloxacin (%) | 44 (85) | 8 (16) | 0.030 | 0.82 (0.70-0.97) | 0.56 (0.23-1.40) | 0.22 |
| Autologous BMT (%)                 | 74 (88) | 10 (12) | 0.0001 | 0.75 (0.65-0.86) | 0.23 (0.11-0.68) | 0.005 |
| Bacteremia due to gram-positive* (%) | 46 (66) | 24 (34) | 0.050 | 1.17 (0.97-1.41) | 1.16 (0.51-2.65) | 0.71 |
| Mucositis (%)                      | 43 (68) | 20 (32) | 0.16 | 1.11 (0.91-1.33) |          |         |
| Severe neutropenia (%)             | 38 (60) | 25 (40) | 0.007 | 1.28 (1.02-1.60) | 1.67 (0.71-3.92) | 0.24 |
| CVC withdrawn (%)                  | 52 (79) | 14 (21) | 0.19 | 0.91 (0.77-1.07) |          |         |
| Length of BMT until bacteremia, median (range) (days) | 174 | 61 | 0.21 | 60 (6-746) |          |         |
| ANC. median (range) cels/mm³       | 164 | 61 | 0.12 | 220 (0-23,400) |          |         |
| MASCC. median                      | 174 | 59 | < 0.0001 | 18 (8-26) |          |         |
| MASCC score higher than 21 (%)     | 101 (82) | 23 (18) | 0.008 | 0.82 (0.70-0.96) | 0.55 (0.27-1.13) | 0.10 |

| Variables                          | Death N (%) | Bivariate Analysis | Multivariate Analysis | p-value | Multivariate Analysis | p-value |
|------------------------------------|-------------|--------------------|-----------------------|---------|-----------------------|---------|
|                                    | Yes (N) | No (N) | P- value | RR (CI 95%) | p-value | OR (CI 95%) | p-value |
| Age. (median)                      | 32 | 38 | 0.29 |          |         |          |         |
| Previous usage of levofloxacin (%) | 26 (93) | 2 (7) | 0.17 | 0.89 (0.77-1.03) |          |         |
| Autologous BMT (%)                 | 54 (92) | 5 (8) | 0.17 | 0.93 (0.86-1.01) | 3.73 (0.90-15.28) | 0.06 |
| Bacteremia Gram- positive* (%)     | 39 (81) | 9 (19) | 0.10 | 1.11 (0.95-1.29) |          |         |
| Bacteremia Gram-negative (%)       | 81 (90) | 19 (9) | 0.15 | 0.91 (0.79-1.0) |          |         |
| Fungi                              | 4 (100) | 0 | 0.58 | 0.87 (0.81-0.92) |          |         |
| Mucositis (%)                      | 38 (83) | 8 (17) | 0.41 | 1.02 (0.92-1.12) |          |         |
| GVHD (%)                           | 34 (83) | 7 (17) | 0.21 | 1.07 (0.92-1.25) |          |         |
| Severe neutropenia (%)             | 32 (82) | 7 (18) | 0.28 | 1.06 (0.90-1.23) |          |         |
| CVC withdrawal (%)                 | 34 (97) | 1 (3) | 0.32 | 0.87 (0.79-0.97) | 40 (0.07-2.38) |         |
| ANC, median (range) cels/mm³       | 2,350 | 1,250 | 0.54 |          |         |          |         |
| Duration of neutropenia. (days, mean) | 3.4 | 4.5 | 0.43 |          |         |          |         |
| MASCC. median                      | 21 | 16 | 0.001 | 0.78 (0.68-0.90) |          |         |
| MASCC score higher than 21 (%) **  | 127 (88) | 18 (12) | 0.07 | 0.90 (0.83-1.02) |          |         |
| Shock                              | 11 (27) | 29 (73) | 0.34 | 1.70 (0.43-6.69) |          |         |

CVC: central venous catheter; MASCC: Multinational Association for Supportive Care in Cancer Risk Index. GVHD: Graft-Versus-Host Disease.
REFERENCES

1. Schuster MG, Cleveland AA, Dubberke ER, Kauffman CA, Avery RK, Husain S, et al. Infections in hematopoietic cell transplant recipients: results From the Organ Transplant Infection Project, a multicenter, prospective, cohort study. Open Forum Infect Dis. 2017;4:cof050.

2. Averbuch D, Tridello G, Hoek J, Mikulsk M, Akan H, Yanez San Segundo L, et al. Antimicrobial resistance in Gram-negative rods causing bacteremia in hematopoietic stem cell transplant patients: intercontinental prospective study of Infectious Diseases Working Party of the European Bone Marrow Transplantation group. Clin Infect Dis. 2017;65:1819-28.

3. Mendes ET, Dulley F, Basso M, Batista MV, Coracin F, Guimaraes T, et al. Healthcare-associated infection in hematopoietic stem cell transplantation patients: risk factors and impact on outcome. Int J Infect Dis. 2012;16:e424-8.

4. Labarca JA, Leber AL, Kern VL, Territo MC, Brankovic LE, Bruckner DA, et al. Outbreak of Stenotrophomonas maltophilia bacteremia in allogenic bone marrow transplant patients: role of severe neutropenia and mucositis. Clin Infect Dis. 2000;30:195-7.

5. Girmenia C, Bertaina A, Piciocchi A, Perruccio K, Algarotti A, Busca A, et al. Incidence, risk factors and outcome of pre-engraftment gram-negative bacteremia after allogeneic and autologous hematopoietic stem cell transplantation: an Italian prospective multicenter survey. Clin Infect Dis. 2017;65:1884-96.

6. Ortega M, Rovira M, Almela M, Marco F, de la Bellacasa JP, Martinez JA, et al. Bacterial and fungal bloodstream isolates from 796 hematopoietic stem cell transplant recipients between 1991 and 2000. Ann Hematol. 2005;84:40-6.

7. Toscano CM, Bell M, Zukerman C, Shelton W, Novicki TJ, Nichols WG, et al. Gram-negative bloodstream infections in hematopoietic stem cell transplant patients: the roles of needleless device use, bathing practices, and catheter care. Am J Infect Control. 2009;37:327-34.

8. McDiarmid S, Hutton B, Atkins H, Bence-Bruckler I, Bredeson C, Sabri E, et al. Performing allogeneic and autologous hematopoietic SCT in the outpatient setting: effects on infectious complications and early transplant outcomes. Bone Marrow Transplant. 2010;45:1220-6.

9. Tavadze M, Rybicki L, Mossad S, Avery R, Yurch M, Pohlman B, et al. Risk factors for vancomycin-resistant enterococcus bacteremia and its influence on survival after allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2014;10:1310-6.

10. Forcina A, Baldan R, Marasco V, Cichero P, Bondanza A, Noviello M, et al. Control of infectious mortality due to carbapenemase-producing Klebsiella pneumoniae in hematopoietic stem cell transplantation. Bone Marrow Transplant. 2017;52:114-9.