Bacteremia During Early Post-allogeneic Hematopoietic Stem Cell Transplantation Period: A Single Center Experience

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Received: 24 September 2015 / Accepted: 24 June 2016 / Published online: 29 June 2016
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Abstract Bacteremia is a significant complication of allogeneic hematopoietic stem cell transplantation (HSCT). We aimed to study bacteremia occurring during early post-transplant period at Bone Marrow Transplantation Unit of Ain Shams University regarding its risk factors and impact on survival. Patients performing allogeneic HSCT were followed up for occurrence of bacteremia. Survival status was assessed at 180 days post-transplant. Bacteremia occurred in 53.3 % of patients. On univariate analysis, CD34 +ve cell dose ($P = 0.004$), duration of neutropenia ($P = 0.018$), time interval between day of stem cell infusion and day of neutrophil engraftment ($P = 0.043$) and > 1 apheresis days ($P = 0.040$) were associated with higher rates of bacteremia. On multivariate analysis, CD34 +ve cell dose ($P = 0.002$) and apheresis day number ($P = 0.038$) remained significant. There was significant difference between patients who developed bacteremia and those who did not regarding overall survival (OS) ($P = 0.042$). Patients developing bacteremia caused by Gram negative bacteria (GNB) had lower OS than Gram positive bacteria (GPB) ($P < 0.001$). In conclusion, stem cell dose and apheresis day number influence bacteremia risk. Also, Gram negative bacteremia has negative impact on allogeneic transplant recipient survival rates.

Keywords Allogeneic hematopoietic stem cell transplantation · Bacteremia · Early post-transplant period · Risk factors · Overall survival

Introduction

Despite all the advances in the field of allogeneic hematopoietic stem cell transplantation (HSCT), it does remain to be a procedure with several potential complications, infections being of the major ones [1]. Bacteremia may result in dramatic complications such as septic shock, multi-organ failure or even death [2]. Also, it can result in extension of admission period and increased costs of antimicrobial therapy against target organisms [3]. Approximately 20–44 % of HSCT recipients develop an episode of bacteremia [4–8]. Before engraftment, bacteremia is often related to central venous catheters (CVC) and/or severe mucositis. Following engraftment, despite normalization of white blood cell counts, compromised granulocyte functions and primarily impairment of chemotaxis and phagocytosis may persist [9].

The causative organisms have changed over time due to the wide use of long-term CVC, use of prophylactic antibiotics, administration of initial empiric broad-spectrum antibiotics for neutropenic fever, improvement in adjuvant therapies, e.g. use of hematopoietic growth factors, and increased awareness of the importance of infection control [10–12]. In turn, a possible change of microbial impact on survival over the years may have occurred. In this study, we will study bacteremia occurring in our transplant unit during the early post-transplant period and their impact on survival.

Patients and Methods

Transplant Procedures and Follow Up

All patients who were planned to perform allogeneic peripheral blood (PB) HSCT from a matched sibling donor

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at Bone Marrow (BM) Transplantation Unit of Ain Shams University from January 2009 to December 2014 were included consecutively in this study. All recruited patients had no signs of active bacterial infection at time of admission and during the preceding week. Patients were admitted in isolated single rooms ventilated with high efficiency particulate air filtration system and were scheduled to receive a low-microbial diet without food sterilization procedures. Hygienic hand washing was followed in all cases. All personnel used protective gowns, gloves and masks when nursing patients or being in their rooms. All patients had a CVC inserted before conditioning and removed at discharge. Antimicrobial prophylaxis with oral levofloxacin 500 mg once daily was given to patients from the start of admission till neutrophil engraftment (defined as the first of three consecutive days post-transplant with neutrophil counts $>500/\text{mm}^3$ [13]) or occurrence of fever and initiation of empirical antibiotic therapy (Pipercillin/Tazobactam and Amikacin). Neutropenia was graded according to the Common Toxicity Criteria of the National Cancer Institute [14]. All patients received granulocyte colony stimulating factor starting from day +6 till 3 days after neutrophil engraftment. Graft versus host disease (GVHD) prophylaxis was with methotrexate and cyclosporine (CSP). CSP has been substituted by mycophenolate mofetil (MMF) in case of CSP toxicity. Acute GVHD was treated with methylprednisolone. Those who had cytomegalovirus (CMV) infection by quantitative real-time PCR received preemptive treatment with ganciclovir. State of survival was assessed at 180 days post-transplant.

Microbiology

During the first 100 days post-transplant, in case of fever $>38.3^\circ\text{C}$ once or $>38^\circ\text{C}$ on 2 consecutive measurements, sampling for blood culture were performed before the patient started empirical antimicrobial therapy. A 3–5 ml blood sample was taken under aseptic measures from a peripheral vein in a 5 cc disposable sterile syringe and was added to a blood culture bottle. BACTEC 9240 system (Becton–Dickinson, Cockeysville, Md., USA) was used for obtaining bacterial growth after incubation for 7 days and a complete record of causative organisms was performed. A blood culture was considered positive when an organism grew in one or more bottles, with the exception of coagulase-negative *Staphylococci* (CoNS) which required 2 separate positive blood cultures with the same antibiogram to be considered a true bacteremia.

End Points and Statistical Methods

Overall survival (OS) was defined as the time from study entry to the time of death from any cause. Patients with no

reported event at the time of analysis were censored at the most recent assessment date. Descriptive statistical analysis of the main characteristics of the patients was done (mean, standard deviation (SD), range, number and percentage). Univariate analysis of risk factors has been performed using unpaired *t* test (for continuous variables) and Chi square test (for categorical variables). Survival probabilities were estimated using the Kaplan–Meier method and survival curves were compared by the log-rank test. Binary logistic regression model has been used for multivariate analysis of significant risk factors obtained from univariate analyses. Statistical significance was determined at the 0.05 level. All *P* values were 2-sided. Standard computer program SPSS for Windows, release 17.0 (SPSS Inc, USA) was used for data entry and analysis.

Results

Patient Characteristics

Seventy five patients were included in this study. The mean age was 28 ± 11 years (range = 4–52). There were 37 males (49.3 %) and 29 patients (38.7 %) had comorbidities. Their indications for HSCT were acute myeloid leukemia (AML) in 41 patients (54.7 %), acute lymphoblastic leukemia (ALL) in 16 (21.3 %), biphenotypic acute leukemia (BAL) in 3 (4 %), chronic myeloid leukemia (CML) in 5 (6.7 %) and severe aplastic anemia in 10 (13.3 %). All acute leukemia patients were in complete hematological remission (CR). Forty five of them (75 %) were in CR1 whereas 15 (25 %) were in $>\text{CR1}$. All CML patients were resistant to two lines of tyrosine kinase inhibitors and were in chronic phase. Forty three patients (57.3 %) received busulfan (BU)/fludarabine (FLU) conditioning regimen, 9 (12 %) received total body irradiation (TBI)/cyclophosphamide (CY), 13 (17.3 %) received BU/CY and 10 (13.3 %) received FLU/CY/antithymocyte globulin (ATG).

Incidence of Bacteremia and Causative Organisms

Bacteremia occurred in 40 patients (53.3 %). All patients had a single episode of bacteremia. Twenty one (52.5 %) were due to Gram positive bacteria (GPB) which included 14 (38.9 %) due to CoNS, 5 (13.9 %) due to *Staphylococcus Aureus* and 2 due to *Streptococcus Viridans*. Regarding Gram negative bacteria (GNB), they occurred in 19 (47.5 %) patients and they were caused by *Acinetobacter Baumannii* in 9 (23.7 %), *Pseudomonas Aeruginosa* in 5 (14.3 %), *Klebsiella Pneumoniae* in 3 (7.9 %), *Stenotrophomonas Maltophilia* in 1 (2.8 %) and *Proteus Mirabilis* in 1 (2.8 %). MRS accounted for 50 % of GPB (number = 10), whereas extended spectrum β -lactamase

Table 1 Univariate and multivariate analyses of risk factors

Risk factor		Univariate analysis		Multivariate analysis			
		+ve bacteremia (N = 40)	−ve bacteremia (N = 35)	P	OR	95 % CI	P
		Mean ± SD (Range)	Mean ± SD (Range)				
Age, years		27.82 ± 12.53 (4–52)	28.09 ± 9.19 (10–52)	0.919			
CD34 +ve cell dose, x 10 ⁶ cells/Kg body weight		5.88 ± 1.08 (3.74– 9.1)	6.54 ± 0.78 (4.8–8)	0.004*	0.560	0.389–0.806	0.002*
Duration of grade 4 neutropenia, days ^a		11.8 ± 6.17 (3–35)	8.83 ± 4.12 (1–18)	0.018*	1.166	0.964–1.410	0.113
Duration between day of stem cell infusion and day of neutrophil engraftment, days		14.68 ± 5.26 (8–39)	12.69 ± 2.37 (8–19)	0.043*	0.994	0.776–1.273	0.959
N (%)		N (%)					
Sex							
Male	19 (47.5 %)	18 (51.4 %)	0.734				
Female	21 (52.5 %)	17 (48.6 %)					
Comorbidities							
+ve	16 (40 %)	13 (37.1 %)	0.800				
−ve	24 (60 %)	22 (62.9 %)					
Diagnosis							
AML	19 (47.5 %)	22 (62.9 %)	0.401				
ALL	8 (20 %)	8 (22.9 %)					
BAL	2 (5 %)	1 (2.9 %)					
CML	3 (7.5 %)	2 (5.7 %)					
SAA	8 (20 %)	2 (5.7 %)					
Conditioning regimen							
BU/FLU	20 (50 %)	23 (65.7 %)	0.298				
TBI/CY	5 (12.5 %)	5 (11.4 %)					
BU/CY	7 (17.5 %)	6 (17.1 %)					
FLU/CY/ATG	8 (20 %)	2 (5.7 %)					
D/R sex							
F/F	13 (32.5 %)	5 (14.3 %)	0.227				
M/M	10 (25 %)	11 (31.4 %)					
M/F	8 (20 %)	12 (34.3 %)					
F/M	9 (22.5 %)	7 (20 %)					
Apheresis days							
1	32 (80 %)	34 (97.1 %)	0.040*	8.062	1.117–58.202		0.038*
>1	8 (20 %)	1 (2.9 %)					
≥grade II acute GVHD ^b							
+ve	8 (20 %)	10 (28.6 %)	0.386				
−ve	32 (80 %)	25 (71.4 %)					
Use of MP therapy ^b							
+ve	13 (32.5 %)	11 (31.4 %)	0.921				
−ve	27 (67.5 %)	24 (68.6 %)					
Use of GCV therapy ^b							
+ve	6 (15 %)	11 (31.4 %)	0.090				
−ve	34 (85 %)	24 (68.6 %)					
Use of MMF							
+ve	3 (7.5 %)	6 (17.1 %)	0.200				

Table 1 continued

	N (%)	N (%)
–ve	37 (92.5 %)	29 (82.9 %)

AML acute myeloid leukemia, *ALL* acute lymphoblastic leukemia, *BAL* biphenotypic acute leukemia, *CML* chronic myeloid leukemia, *SAA* severe aplastic anemia, *BU* busulfan, *FLU* fludarabine, *TBI* total body irradiation, *CY* cyclophosphamide, *ATG* antithymocyte globulin, *D* donor, *R* recipient, *F* female, *M* male, *GVHD* graft versus host disease, *MP* methylprednisolone, *GCV* ganciclovir, *MMF* mycophenolate mofetil, *N* number, *SD* standard deviation, *OR* odds ratio, 95 % *CI* 95 % confidence interval

* Significant

^a Grade 4 neutropenia = Absolute neutrophil count < 0.5 × 10⁹/L

^b Preceding or concurrent

(ESBL)-producing organisms accounted for 52.6 % of GNB (number = 10). During the follow up periods 2009–2010, 2011–2012 and 2013–2014, the incidence rates for GPB were 45, 21.4 and 22.2 % respectively, whereas for GNB they were 20, 14.3 and 40.7 % respectively (GPB/GNB = 2.25, 1.5, 0.55 respectively). Thirty one bacteremia episodes (77.5 %) occurred before engraftment whereas 9 (22.5 %) occurred after it. Twenty one bacteremia (52.5 %) occurred between day 0 and day +9 after stem cell transfusion. Median time from stem cell transfusion to bacteremia was 7 days (range = 0–88 days).

Risk Factors for Occurrence of Bacteremia

On univariate analysis, CD34 +ve cell dose ($P = 0.004$), duration of grade 4 neutropenia ($P = 0.018$), duration between day of stem cell transfusion and day of neutrophil engraftment ($P = 0.043$) and >1 apheresis days ($P = 0.040$) were associated with higher rates of occurrence of bacteremia (Table 1). On multivariate analysis, both CD34 +ve cell dose ($P = 0.002$) and number of apheresis days ($P = 0.038$) remained significant statistically (Table 1).

Impact of Bacteremia on Outcome

After median follow up period of 180 days (range 10–180 days), there was significant difference between patients who developed bacteremia during early post-transplant period and those who did not develop them as regards OS (62.5 vs 82.9 %; mean OS = 145.5 vs 166.6 days respectively; $P = 0.042$) [Fig. 1a]. Patients who developed bacteremia caused by GNB had lower OS in comparison to GPB (36.8 vs 85.7 %, mean OS = 116.5 vs 170.5 days respectively, $P < 0.001$) [Fig. 1b]. The most fatal organism was *Acinetobacter Baumannii* as it was associated with 6 deaths (28.6 %).

Discussion

This study investigated bacteremia that occurred in recipients of allogeneic transplants at Bone Marrow Transplantation Unit of Ain Shams University during early post-transplant period. Bacteremia prevalence rate was 53.3 % which was lower than that reported in France (73.9 %) [15], more or less similar to that reported in USA (55 %) [2], and higher than that observed in Sweden (33 %) [16]. The higher prevalence in the French study can be attributed to the infrequent use of hematopoietic growth factors which shortens the duration of neutropenia [14], and the lower prevalence in the Swedish study can be attributed to the use of multiple blood culture bottle sets each designed in a different laboratory [16]. In our study, the incidence of bacteremia caused by GPB was declining and that caused by GNB was increasing throughout the study years despite the use of quinolone prophylaxis and these results were in agreement with those reported by two American studies [2, 17]. In contrast, an Italian study reported rising GPB/GNB ratios throughout the study period which can be attributed to the prolonged application of CVC (more than 6 months) [18]. The most commonly isolated organism in our study was CoNS which, in general, have been known to be the most commonly isolated bacteria from the blood of patients with cancer and febrile neutropenia [19]. Our result was consistent with many studies performed on allogeneic HSCT recipients [15, 18, 20–22]. However, other studies reported other organisms as the most commonly encountered ones, e.g. *α-Streptococci* [2, 16], *Pseudomonas Aeruginosa* [23], *Enterococci* [24] and *Escherichia Coli* [25].

Median time from stem cell transfusion to bacteremia was more or less similar to that reported by two European studies [16, 18]. Most episodes occurred between 0 and 9 days post-transplant which is in agreement with an American study [2]. Most bacteremia episodes occurred

Fig. 1 **a** Kaplan–Meier curves for overall survival (OS) of patients who developed bacteremia during early post-transplant period (dashed line) and those who did not (continuous line) (62.5 vs 82.9 %; mean OS = 145.5 vs 166.6 days respectively; $P = 0.042$). **b** Kaplan–Meier curves for OS of patients who developed bacteremia caused by GNB (dashed line) in comparison to GPB (continuous line) (36.8 vs 85.7 %, mean OS = 116.5 vs 170.5 days respectively, $P < 0.001$)

before engraftment which was similar to a Brazilian study [24]. In contrast, another study showed more or less equal frequencies of bacteremia before and after engraftment and this difference can be attributed to the use of a broader definition of blood stream infection which involved occurrence of one or more positive blood cultures for CoNS [21].

Many factors were associated with increased risk of bacteremia in univariate analysis, e.g. unrelated donor [16, 24], mismatched donors [24], umbilical cord blood and duration of neutropenia [18]. Ninin et al. failed to find significant risk factors [14]. However, most of the studies

did not perform multivariate analysis of the risk factors [15, 16, 18]. We agreed with Cappellano et al. [24] in that number of stem cell transfused is significantly associated with increased risk of bacteremia. However, CD34 +ve cell dose remained significant in multivariate analysis in our study but lost its significance in the other study. Such effect of CD34 +ve cell dose can be explained by the faster neutrophil engraftment, shorter duration of neutropenia and even faster immunologic recovery that associate high CD34 +ve cell doses which in turn can result in lower risk of bacteremia [26, 27]. Unfortunately, higher CD34 +ve cell dose administered is associated with higher risk of chronic GVHD [28]. Another significant risk factor for bacteremia in both univariate and multivariate analyses was number of apheresis days. To our knowledge, this variable has not been previously included in analysis for risk of bacteremia in allogeneic HSCT patients. It has been previously assumed that frequent stem cell manipulation, including frequent apheresis sessions, especially in the setting of autologous HSCT is associated with increased risk of bacterial contamination of grafts [29, 30]. However the risk of bacterial contamination is lower with the use of PB stem cell products compared with BM due to use of closed apheresis system and avoidance of multiple punctures through the skin [30]. This result should be interpreted with caution owing to the small number of patients who required more than one apheresis.

There was significant difference as regards OS between patients who developed bacteremia during early post-transplant period and those who did not which is in agreement with two other studies [23, 24]. The risk of death among patients with GNB bacteremia was higher than in those with GPB bacteremia which is in concordance with Collin et al. [2]. GNB have often been implicated in the pathogenesis of severe sepsis and septic shock [31]. Our finding suggests that differences in virulence mechanisms of different pathogenic microorganisms should be considered in treatment of bacteremia.

The present study has the following limitations. First, it was a single-center study in which it is difficult to rule out the possibility of bias in bacterial species identified and in patients' characteristics. Second, it did not correlate bacteremia with other sites of infection which may have had also an impact on OS. In conclusion, despite the powerful infection control measures applied in our and many HSCT centers, they are still unsatisfactory for lowering the prevalence of bacteremia in allogeneic transplant recipients and more strict protocols are needed. Second, the incidence of Gram negative bacteremia is rising in our center and they have a negative impact on survival rates of allogeneic transplant recipients during early post-transplant period. Finally, the impact of apheresis days on the risk of bacteremia occurrence following allogeneic HSCT should be

investigated in larger studies with emphasis on performing cultures from apheresis bags.

Compliance with Ethical Standards

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

Ethical Standards All procedures performed were in accordance with the ethical standards of the research committee of Faculty of Medicine of Ain Shams University and with the 1964 Helsinki declaration and its later amendments.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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