Quinolone Prophylaxis Prevents the Development of Carbapenem-Resistant Infection in Patients Undergoing Hematopoietic Stem Cell Transplant

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Introduction

Hematopoietic stem cell transplant (HSCT) is an important treatment modality for patients with both benign and malignant hematological diseases [1].Tremendous advances have occurred in the field of stem cell transplant with the use of mismatched and haploidentical donors and improved supportive care to prevent graft versus host disease enabling more patients to undergo transplant safely. Patients undergoing stem cell transplant are at an increased risk of bacterial, viral and fungal infections [2]. Patients have severe neutropenia in the immediate peri-transplant period and are at highest risk of bacterial infections [3, 4]. Infection is the most common cause of morbidity and mortality in patients undergoing transplants [5,6]. There can be several reasons for high rates of infections in these patients [7]. Bacteremia occurs in as high as 20% of patients [8].Multiorgan dysfunction and mortality ensues in complicated cases. Some studies have reported that gram-positive cocci (GPC) blood stream infections (most commonly coagulase negative staphylococcus) occur more commonly than gram-negative bacilli (GNB) infections. However, gram-negative infections contributed to as high as 45% mortality in these patients [9].

Measures to decrease the incidence of infections like isolation, HEPA filter fitted rooms [10] and gut decontamination have been used in transplant patients. Antibiotic prophylaxis with fluoroquinolone has been recommended by the IDSA and ASCO for patients who are expected to have a profound ($<$ 100 neutrophils/uL) and prolonged neutropenia ($>$ 7 days) [11]. In a recent meta-analysis antibiotic prophylaxis significantly reduced the all-cause mortality in neutropenic patients [8]. However, it has been shown to alter the gut microbiome increasing chance of clostridium difficile infections [12]. There are concerns regarding subsequent emergence of fluroquinolone resistance increasing need for therapy with carbapenem antibiotics. Many authors have argued against using prophylactic antibiotics and advocate well-structured sepsis care bundles that focuses on timely identification and treatment of neutropenic sepsis [13]. There is also a concern around rising carbapenem resistant enterobacteracae (CRE) around the world [14]. In this study we evaluate the role of antibiotic prophylaxis in patients undergoing stem cell transplant at our center.

Materials and Methods

This is a retrospective observational study. A total of 219 patients were included in the study over a period of 2012 to 2019. Patients were nursed in HEPA filtered air-conditioned single rooms in isolation with reverse barrier nursing. All persons entering the room used gowns, shoe covers, face mask and cap, and washed their hands thoroughly or used antiseptic handwash. The initial 100 patients who underwent HSCT had received oral antibiotic prophylaxis with oral levofloxacin. Levofloxacin was started at the time of admission and was continued till day + 28 and it was similar for both autologous or allogeneic transplant during the study period. Fluconazole and valacyclovir were given as antifungal and antiviral prophylaxis, respectively. Fluconazole and valacyclovir were stopped on day 28. In view of concerns around rising incidence of CRE in

our unit and around the world, antibiotic prophylaxis was discontinued after first 100 BMTs. At present we stop antibiotic prophylaxis at the time of neutrophil engraftment. Caps are no longer used in our transplant unit now.

Fever was defined as a single temperature of [?] 101 F or >100.4 F lasting for more than 1 hour.[3]Any febrile episode was taken as infective episode and treated accordingly. First-line antibiotic consisted of piperacillin–tazobactam or cefoperazone-sulbactum and amikacin. This was modified later depending on microbiological information or clinical evolution. A severe or life-threatening/fatal infection was defined according to the Blood and Marrow Transplant Clinical Trials Network criteria [15]. A severe bacterial infection was defined as any bacterial organ infection and/or bacteremia by any bacterial organism in a febrile patient [16]. We analyzed in detail all bacterial infections that occurred in the first 30 days post-transplant that led to the patient's death.

Hematopoietic stem cell source was peripheral blood and all products were unmanipulated. Neutrophil engraftment was defined as the first of 3 consecutive days with achievement of absolute neutrophil count of [?] 500/mm3 and no subsequent decline. Platelet engraftment was defined as the first of 3 consecutive values of platelet count [?] 20,000/cm3 with transfusion independence. All patients remained hospitalized until engraftment and until the time deemed clinically suitable for discharge. Discharge criteria were neutrophil engraftment, absence of infection and ability to eat and drink [17]. Primary objective of study was to identify carbapenem resistant gram negative infection. Secondary outcome measures included documented infections, blood stream infections (BSI), incidence of gram positive, gram-negative sepsis, infection related mortality and duration of hospital stay.

Statistical Analysis

Data analysis was done with SPSS v 23.0. Description of patients at presentation was presented as number (%) for qualitative variables and as either mean ± standard deviation or median (range) for continuous variables. The baseline characteristics were compared between various subcategories by chi-square test or Fisher exact test for categorical variables and by Kruskal-Walis or Mann Whitney test for continuous variables. P value [?] 0.05 was taken as significant

Results

A total of 219 patients were included in the study. One hundred and twenty-four patients had undergone autologous stem cell transplant (ASCT) and 95 patients underwent allogeneic stem cell transplant (AlloSCT). The first 100 patients undergoing transplant received antibiotic prophylaxis and the next 119 patients did not receive antibiotic prophylaxis. All patients received levofloxacin as prophylaxis except 11 children less than 7 year of age who received amoxicillin prophylaxis. The median age of the patients in 'no-prophylaxis group' was 45 years (range- 2 to 68 years) and in the 'prophylaxis group' it was 34.5 years (range -1 to 68 years). In both cohorts, myeloma was the most common diagnosis of patients undergoing ASCT. In AlloSCT group most common diagnoses were leukemia and hemoglobinopathy. The median CD34 dose was comparable in both the cohorts (5x 10^6 /kg vs 3.91 x 10^6/kg; p=0.111). Median neutrophil engraftment occurred at 11 days in the no prophylaxis group and at 12 days in prophylaxis group (Table 1). There was no difference in the median duration of hospital stay. There was no significant difference in other baseline characteristics (Table 1).

Both groups had comparable duration of fever. However, documented infection were significantly lower in patients who received antibiotic prophylaxis (29% vs 42.9%; p=0.034). The patients who did not receive antibiotic prophylaxis had higher rates of gram negative (34.5% vs 22%; p=0.043) and CRE sepsis (21% vs 1%; p=0.001) but there was no difference in the rates of gram-positive sepsis or BSI (Table 2). We did not observe any clostridium difficile infection.

In patients undergoing ASCT, number of febrile episodes, duration of fever, documented infections, BSI and gram-positive BSI were not different in prophylaxis vs no- prophylaxis group. However, GNB infection and carbapenem resistance were significantly lower in prophylaxis group. Despite this, overall mortality remained

same in both groups.

In patients undergoing AlloSCT, number of febrile episodes, duration of fever, documented infections, gram-positive or gram-negative BSI was not different in prophylaxis vs no-prophylaxis group. However, carbapenem resistance was significantly lower in prophylaxis group (2% vs 23.9%). This contributed to major mortality difference in AlloSCT group (vs ASCT) in patients who did not receive antibiotic prophylaxis.

Transplant related mortality (TRM) was 8.2% for all patients. In ASCT group 7 (5.6%) patients died while in Allo SCT group 11 (11.5%) patients died. Antibiotic prophylaxis was not associated with reduction in mortality (p=0.258) in both ASCT and Allo SCT groups (Table 2).

Discussion

Patients undergoing HSCT are particularly prone for infections in the period preceding engraftment [18]. Neutrophils are important first defence against bacterial infections. Both severity and duration of neutropenia are important for risk assessment. AGIHO regards patients with expected neutrophil count of <0.5 for more than 7 days to be high risk [19]. Patients undergoing BMT are at high risk for complicated infections [20]. Prevention of febrile neutropenia is of utmost importance as after onset it is associated with 25 to 30% rate of major complications like hypotension, renal failure along with 11% mortality [21]. Antibiotic prophylaxis has been shown to reduce the risk of life-threatening infections in neutropenic patients albeit with the risk of developing antimicrobial resistance, alteration of gut microbiome, drug toxicity and increased cost [22].

IDSA /ASCO guidelines published in 2018, suggest antibiotic prophylaxis in patients undergoing myeloablative conditioning regimen [11]. Zeigler et al reported reduction in central line related blood stream infections from 18.4% to 6.0% with levofloxacin prophylaxis [23].

Overall incidence of blood stream infections in our study was 22.8%. This is similar to most published literature. In most studies published, gram-positive BSI has been the most common cause of bacteremia [24]. In our study, we found an overwhelming majority of GNB infection seen in 28.7% of all patients. Gram-positive infection was observed in 9.13% of all patients. In a single center retrospective study, gram-positive bacteria accounted for 57% and gram-negative rods bacteria for 37% of bacteremia [25]. Over time the author had been a decrease in GPC/GNB ratio with use of fluroquinolone prophylaxis.

In a randomised study done by GIMEMA group, the duration of fever, microbiologically documented infections, BSI and single-agent gram-negative BSI were significantly lower in the levofloxacin group than in the placebo group. This, however, did not include HSCT patients. Mortality and tolerability were similar in the two groups [26].Similar to our results, Clemmons et al reported reduced incidence of bacteremia in both autologous and allogeneic HSCT with flouroquinolone prophylaxis. They reported no difference in mortality in autologous subgroup with trend towards lower mortality in AlloSCT patients [27]. Modi et al also reported reduction in the incidence of neutropenic fever and antibiotic use in ASCT group with fluoroquinolone prophylaxis without any impact on mortality or morbidity [28]. In our study antibiotic prophylaxis was found to reduce gram negative sepsis and carbapenem resistance without any impact on mortality. However, the incidence of bacteremia, gram positive sepsis and duration of fever was not affected. Increasing rates of CRE over time is related to stopping antibiotic prophylaxis is non-intuitive as these outcomes are likely to be influenced by time. This association has been matched with greater antibiotic utilization over the past decade [29]. Fever could be due to a lot of non-infectious causes in a transplant patient. On the other hand, Heindenrech et al reported day 100 mortality and BSI in their cohort of 47 patients undergoing allogeneic HSCT and concluded that bacterial prophylaxis was not required [30].

Averbuch et al reported more MDR infections in allogeneic BMT group vs autologous BMT [31]. They also reported a high 18% mortality in CRE group vs 4% in carbapenem sensitive GNB. A multicenter Italian study reported CRE infection-related mortality rates of 16% and 64.4% in autologous and allogeneic groups respectively [32]. Multidrug resistant (MDR) GNB infection are associated with high mortality. A recent study reported 79% mortality in post HSCT setting and MDR pseudomonas infection [33]. Our findings are somewhat surprising as we noted more carbapenem resistant gram-negative bacteria in no-prophylaxis

group. This is difficult to explain. It is possible that during the study period (2012-2019) overall incidence of CRE was rising. Even though CRE did not impact mortality in ASCT group, it was a major contributor to mortality in allogeneic BMT group. Increased mortality in no-prophylaxis group in our study was largely driven by mortality in AlloSCT group. Median age in this group was higher compared to prophylaxis group. Even if mortality in HSCT was not affected, antibiotic prophylaxis is likely to reduce use of carbapenem antibiotics and thereby reduce cost.

Quinolones have been shown to be associated with Clostridium difficile diarrhea, tendinopathy, decrease in seizure threshold and QT prolongation. We did not observe any such adverse effect in our study. Retrospective nature of our study may have led to under-reporting of these adverse effects. In children less than 7 years old quinolones are contraindicated as they may cause cartilage damage [34]. In our study we used amoxicillin as an antibiotic prophylaxis to overcome these effects. Overall, we did not observe any significant toxicity due to quinolones in our patients.

Resistance to fluoroquinolones have been reported in 50% of gram-negative isolates in patients receiving fluoroquinolone prophylaxis. In a study by Miles-Jay A et al, the rates of fluoroquinolone resistance has been found to be static over 10 years of prophylaxis [35].

Limitations of present study are that to some extent such data are available in literature. However, data on correlation with carabapenem resistance are not easily available. Our study was limited by retrospective nature performed on patients treated over a period of 8 years. The inclusion of both autologous and allogeneic patients, heterogeneity of underlying diseases and transplantation type (matched related, matched unrelated, haploidentical) does take away some shine from the analysis of total patients compared to the non-prophylaxis group. One may argue that results may differ based on these factors. However, we are reliably able to document role of antibiotic prophylaxis in prevention of gram-negative infection and carbapenem resistance in this high-risk population.

Based on results of this data, we now routinely use antibiotic prophylaxis for all our HSCT patients. This paper contributes to scientific literature by provide data from India which is scarce.

Conclusion : Antibiotic prophylaxis reduces documented bacterial infections and incidence of carbapenem resistance. Antibiotic prophylaxis does not reduce mortality in patients undergoing hematopoietic stem cell transplant.

Table 1: General Characteristics of patients

	No-Prophylaxis	Prophylaxis	P value
Number of patients	119 73 46	100 51 49	0.124
Autologous Allogeneic			
Age Median(range)	45 years (2 to 68 years)	34.5 (1 to 68years)	0.005
Diagnosis	Diagnosis	Diagnosis	Diagnosis
Autologous Myeloma	51 14 4	35 11 1	
Lymphoma Others			
Allogeneic Leukemia	24 3 2 13 5 3	15 3 1 15 8 8	
MDS MPN			
Haemoglobinopathies			
Aplastic Anemia Others			
Conditioning regimen	95 (79.8%) 24 (20.2%)	86 (86%) 14 (14%)	
Myeloablative Reduced intensity			
Allogeneic transplant	46 31 (67.4%) 5 (10.9%)	49 40 (81.6%) 4 (8.2%) 5	
Matched Sibling Donor	10 (21.7%)	(10.2%)	
Matched unrelated Donor			
Haploidentical			

CD 34 dose Median (range)	5.10 x 10^6/kg (2.0 to 23.0x 10^6/kg)	3.91x 10^6/kg (1.0 to 17.0x 10^6/kg)	0.111
Neutrophil engraftment Median(range)	11 Days (12 to 31 Days)	12 Days (9 to 35 Days)	0.024
Platelet engraftment Median(range)	11 Days (12 to 25 Days)	12 (10 to 117 Days)	0.004
Hospital stay Median (range)	23 Days (12 to 71)	25 Days (13 to 149)	0.132

Table 2: Infection related outcomes in study group

	No Prophylaxis	Prop
Fever Mean Duration (Days) Autologous Allogeneic	2.94 + 0.87 2.98 + 0.84 2.87 + 0.92	2.93
No. of febrile patients Autologous Allogeneic	106 67 39	92 46
Documented Infection Autologous Allogeneic	51 (42.9%) 31 (42.46%) 20 (43.47%)	29 (2
Bacteremia Autologous Allogeneic	29 (24.4%) 15 (20.54%) 14 (30.43%)	21 (2
Gram Negative Bacteria Autologous Allogeneic D30 mortality	41 (34.5%) 24 (32.87%) 17 (36.95%) 10 (24.3%)	22 (2
Carbapenem Resistance Autologous Allogeneic D30 mortality	21 (17.6%) 10 (13.69%) 11 (23.9%) 7 (33.3%)	1 (1%
Gram Positive Autologous Allogeneic D30 mortality	11 (9.2%) 8 (10.95%) 3 (6.52%) 2 (18.1%)	9 (9%

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