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Infectious complications after second allogeneic hematopoietic cell transplant in adult patients with hematological malignancies

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We conducted a retrospective review of the infectious complications and outcomes over a 2-year follow-up period of adult patients who received a second allogeneic hematopoietic cell transplant (2nd allo-HCT) during a five-year period at two cancer centers in Michigan. Sixty patients, of whom 44 (73%) had acute leukemia or myelodysplastic syndrome, were studied. The majority ($n = 37$,62%) received a 2nd allo-HCT because of relapsed leukemia. Infection episodes after the 2nd allo-HCT totaled 112. Bacteria were identified in 76 episodes, the majority of which occurred pre-engraftment. The most common infecting organisms were *Enterococcus* species and *Clostridioides difficile*. Viral infections, predominantly cytomegalovirus, accounted for 59 infection episodes and occurred mostly in pre-engraftment and early post-engraftment periods. There were 16 proven/probable fungal infections, of which 9 were invasive aspergillosis or candidiasis. Mortality was 45% ($n = 27$) at one year and 65% ($n = 39$) at 2 years after transplant, and 16 deaths (41%) were due to infection. Of those 16 infection deaths, 8 were bacterial, 4 fungal, 2 both bacterial and fungal, and 2 viral. Failure to engraft neutrophils or platelets was significantly associated with decreased survival, $p < 0.0001$ and $p < 0.001$, respectively. Infections are common after a 2nd allo-HCT and are associated with a high mortality rate.

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) is a common procedure for the management of certain hematological malignancies, including acute myeloid leukemia and myelodysplastic syndrome. However, failure to achieve engraftment and remission is not uncommon. Between 33 and 42% of allo-HCT recipients experience a relapse of their primary malignancy and 4–6% fail to engraft the transplanted cells [1, 2]. For these patients, a second allo-HCT can be performed. This approach has been most successful in children, patients who have relapsed after a longer interval from the initial allo-HCT, and those who have achieved remission of relapsed leukemia at the time of the second transplant [3]. Most reports of outcomes and complications after a second allo-HCT focus on issues such as graft versus host disease (GVHD), relapse of leukemia, and leukemia-free survival; the majority of these reports are in children [4–8]. Few studies specifically address the infectious complications following a second allo-HCT, and adult patients are typically underrepresented. We sought to characterize the infectious complications and outcomes of adult patients who underwent a second allo-HCT at our two institutions in Southeast Michigan over the 5-year period from 2010 to 2015.

METHODS

Patients and setting

This retrospective cohort study was conducted at the University of Michigan Health System (UMHS) in Ann Arbor, Michigan and the Karmanos Cancer Center (KCC) in Detroit, Michigan. All adult patients ≥18 years of age who underwent a second allo-HCT from January 1, 2010 through December 31, 2015 were enrolled in this study. Information was collected for 2 years after receiving a second allo-HCT unless death occurred prior to that time. Approval to carry out this study was granted by the institutional review board at each medical center.

Data collection

Data related to both the first and second allo-HCT were collected from the electronic medical record. Information collected included demographics, underlying hematological cancer, reason for and time interval to second allo-HCT, type/match of allo-HCT, time to neutrophil and platelet engraftment, development of graft versus host disease (GVHD), treatment and outcome of infections, and hematologic-related and infection-related mortality. Study data were entered into a database using REDCap electronic data capture tools.

Definitions

The time of successful neutrophil and platelet engraftment following transplant was defined as the first of 3 consecutive days when the absolute

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neutrophil count was >500 neutrophils/μL and the platelet count was >50,000/μL, respectively. GVHD, veno-occlusive disease, and other complications related to the transplant were defined according to NCCN guidelines [9]. Reduced intensity conditioning regimens were defined using criteria proposed by Bacigaluopo et al. [10].

Infection episodes were defined as episodes of fever or hemodynamic instability for which antimicrobial therapy was initiated, but no pathogen was identified OR episodes in which specific microorganisms were identified. Day of episode was counted as the first day of antimicrobial administration. Timing of infection episodes after the second allo-HCT was separated into 3 periods to reflect pre-engraftment (<30 days after transplant), early post-engraftment (30–100 days after transplant), and late post-engraftment (>100 days after transplant).

EORTC/MSGERC criteria were used for the definition of proven/probable invasive fungal disease [11]. CMV infection, end-organ disease, and factors placing patients at high risk were defined by current consensus definitions [12]. Screening with plasma CMV PCR was performed in high-risk patients starting on day 21 and day 30 after transplantation at UMHS and KCC, respectively. Screening for CMV was continued until day 100 post second allo-HCT or longer if T-cell immunodeficiency persisted. PCR testing for possible CMV, HHV-6, or EBV infection was performed with febrile episodes.

Deaths were attributed to infection if there was an active infection at the time of death and if no other cause was found, as adjudicated by 4 of the authors.

Prophylactic regimens

Primary antibacterial prophylaxis, typically with an anti-pseudomonal fluoroquinolone, was begun on the day of the second transplant and continued until neutrophil engraftment. Prophylaxis was again given if graft versus host disease developed or if severe neutropenia recurred. Acyclovir was used as prophylaxis against viral infections, beginning on the day of transplant and continuing for at least one year but specific cytomegalovirus (CMV) prophylaxis was not given. Antifungal prophylaxis was started on day 5 post-transplant with an antifungal chosen by the clinician; thus, fluconazole or a mold-active azole or an echinocandin could be used and was continued until day +100. If GVHD occurred, the prophylaxis was continued or restarted. *Pneumocystis* prophylaxis with pentamidine or an anti-folate agent was begun after neutrophil and platelet engraftment was achieved, but no earlier than day 30 and continued for 6 months; *Pneumocystis* prophylaxis was restarted or continued if the patient required treatment for GVHD.

Statistical analysis

We conducted descriptive data analyses for all variables. Student's *t* test, Fisher's exact test, and one-way analysis of variance were used to determine differences between groups. Statistical significance was defined as p value < 0.05. The Kaplan–Meier survival analysis was used to estimate the effect of neutrophil and platelet engraftment on survival. All statistical analyses were completed using SPSS software, version 26.0 (SPSS, Inc., Chicago, IL).

RESULTS

Patients

A total of 60 patients received a second allo-HCT from January 2010 through December 2015; this included 29 from KCC and 31 from UMHS. The mean age at first allo-HCT was 46.2 ± 14.1 years and at second allo-HCT was 48.9 ± 13.6; sixty percent ($n = 36$) were men. In most patients ($n = 44$, 73%) the first allo-HCT was given for acute leukemia or myelodysplastic syndrome (Table 1). The mean number of mononuclear cells infused was $6 \pm 3.7 \times 10^6$ and the mean number of CD34 + cells infused was $6.2 \pm 3.5 \times 10^6$ cells with the first allo-HCT. The mean time to engraftment for neutrophils was 13 ± 4 days and for platelets was 24 ± 24 days after the first allo-HCT.

The known reasons for the second allo-HCT included relapse of the original malignancy in 37 (62%), graft failure in 16 (27%), and development of a new malignancy in 6 (10%) (Table 2). Median time from first allo-HCT to second allo-HCT was 344 (range 32–8248) days. Conditioning regimens for the second allo-HCT were fludarabine-based in 43 (72%), and 14 (23%) were reduced intensity regimens. Total body irradiation was used in 30 patients (50%). Neutrophil engraftment occurred in only 50 (83%) of second allo-HCT recipients, with time to engraftment of 13 ± 4 days. Platelet engraftment occurred in 41 (68%) of second allo-HCT, with time to engraftment of 23 ± 23 days (Table 2).

Table 1. Demographics and underlying conditions of 60 patients undergoing second allo-HCT.

Feature	No.	%
Age at second transplant (years, mean ± std dev)	48.9 ± 13.6	
Sex		
Female	24	40
Male	36	60
Race		
White	48	80
Black	9	15
Asian	2	3
Not specified	1	2
Comorbid conditions		
Solid malignancy[a]	7	12
Diabetes mellitus	5	8
Autoimmune disease	3	5
Chronic kidney disease	2	3
Coronary artery disease	1	2
Chronic obstructive pulmonary disease	1	2
Hematological disease		
Acute leukemia or myelodysplastic syndrome	44	73
Myelofibrosis	6	10
Lymphoma	5	8
Chronic leukemia	2	3
Aplastic anemia	2	3
Plasma cell dyscrasia	1	2

[a]includes breast ($n = 2$), testicular ($n = 1$), skin ($n = 1$), prostate ($n = 1$), labia ($n = 1$), colon ($n = 1$).

Infection episodes

A total of 112 documented infection episodes were identified after the second allo-HCT among 56 of the 60 patients. Additionally, there were 14 episodes (12 pre-engraftment and 2 in the early post-engraftment period) of febrile neutropenia for which no specific organism was identified; these episodes were not further analyzed.

The greatest number of documented infection episodes ($n = 41$, 37%) was seen in the pre-engraftment period <30 days after transplant, but infections continued to occur in the early post-engraftment period 30–100 days after transplant ($n = 33$, 29%) and in the late post-engraftment period >100 days after transplant ($n = 38$, 34%). For 11 of the 112 episodes, infection was clinically diagnosed as follows: cellulitis ($n = 3$), cholecystitis ($n = 2$), sinusitis ($n = 2$), pneumonia ($n = 2$), typhilitis ($n = 1$), and mediastinitis ($n = 1$). A bacterial pathogen was assumed to be the cause for these cases, but an infecting organism was not identified. Of the 112 episodes, 43 (38%) involved more than one organism, including concomitant bacterial/viral infections ($n = 15$), bacterial/fungal infection ($n = 4$), two or more concomitant bacterial infections ($n = 17$), two or more concomitant viral infections ($n = 5$), and concomitant bacterial/fungal and viral infection ($n = 2$). In the pre-engraftment period after the second allo-HCT, 7 patients experienced the infection with the same pathogen that

Table 2. Characteristics of second allo-HCT in 60 patients.

Characteristic	N	%
Reason for second allo-HCT		
Relapse of original malignancy	37	62
Graft failure	16	27
New malignancy	6	10
Not known	1	2
Conditioning regimen		
Fludarabine	43	72
Busulfan	27	45
Melphalan	13	22
Clofarabine	10	17
Cytarabine	8	13
Rituximab	2	3
Total lymphoid irradiation	30	50
Anti-thymocyte globulin	19	32
Reduced intensity conditioning	14	23
Specifics of transplant		
Matched Related	20	33
Matched Unrelated	31	52
Unmatched	3	5
Not known	6	10
CD34 + cells infused (mean + std dev)	$7.7 \pm 5.0 \times 10^6$	
Mononuclear cells infused (mean + std dev)[a]	$8.0 \pm 5.2 \times 10^6$	
Engraftment		
Neutrophil engraftment occurred (N, %)	50	83
Time to engraftment, days (mean ± std dev)	13 ± 4	
Platelet engraftment occurred (N, %)	41	68
Time to engraftment, days (mean ± std dev)	23 ± 23	

[a]Data were missing for 5 patients.

had occurred after the first allo-HCT. The pathogens were *Clostridioides difficile* ($n = 4$), vancomycin resistant *Enterococcus* (VRE) ($n = 1$), CMV ($n = 1$), and *Staphylococcus aureus* ($n = 1$).

Bacterial infections. There were 76 infection episodes in which specific bacterial pathogens were implicated. This included 35 of 41 (85%) infections that occurred in the pre-engraftment period, 21 of 33 (64%) infections in the early post-engraftment period, and 20 of 38 (53%) infections in the late post-engraftment period (Table 3). The most common pathogen identified was *Enterococcus*, both VRE ($n = 12$, 16%) and vancomycin-susceptible ($n = 8$, 11%). *C. difficile* infection accounted for 15 infection episodes (20%) (Table 3). Enterococcal and *C. difficile* infections were most common pre-engraftment but continued to occur throughout all time periods. The most common type of bacterial infection was bacteremia, the majority of which were primary without an identifiable source. Urinary tract infections and pneumonias occurred less commonly.

Viral infections. Viral pathogens were identified in 59 infection episodes. The most common viral infections were those due to CMV ($n = 21$, 36%). Infections with BK virus ($n = 10$, 17%), and various respiratory viruses ($n = 11$,19%) were less common. CMV and BK virus infections occurred predominantly pre-engraftment and early post-engraftment (Table 4). With the exception of 2 patients who had biopsy-proven CMV colitis, all episodes of CMV infection were characterized by viremia with no end-organ disease. In contrast, BK virus caused significant end-organ disease with 7 of 10 infections characterized as hemorrhagic cystitis.

Of the total of 41 infection episodes that occurred pre-engraftment, viruses were implicated in 18 (44%); infections in this period were predominantly due to CMV and BK virus. In the early post-engraftment period, viruses were found in 24 of 33 (73%) infection episodes, and in the late post-engraftment period, in 17 of 38 (45%) infection episodes. Late infections were predominantly due to respiratory viruses and varicella zoster virus.

Fungal infections. A total of 16 proven or probable fungal infection episodes were identified in 12 patients (Table 5). The most common fungal infections were invasive pulmonary aspergillosis ($n = 5$, 31%), of which 2 had concomitant brain involvement, and *Candida glabrata* fungemia ($n = 4$, 25%). Of the total of 41 infection episodes that occurred pre-engraftment, 6 (15%) involved fungi. In the early post-engraftment period, fungi were isolated in 4 of 33 (12%) infection episodes, and in the late post-engraftment period, fungi were implicated in 6 of 38 (16%) infection episodes.

Alternaria spp., *Fusarium* spp., and *C. parapsilosis* were isolated only in the pre-engraftment period (Table 5). *Rhizopus* spp. and *Pneumocystis jirovecii* were identified only in the late post-engraftment period. Invasive pulmonary aspergillosis was seen throughout all periods post-transplantation.

All patients had received antifungal prophylaxis through day 100, and 5 of the 6 patients who had invasive fungal infections at >100 days had GVHD and were continued or restarted on antifungal prophylaxis after GVHD was confirmed. The patient who developed *Pneumocystis* pneumonia was no longer on prophylaxis for *Pneumocystis* when this fatal infection occurred more than a year after transplant. Other prophylactic agents included voriconazole in 5 patients, fluconazole in 4, and micafungin in 4; there were no clear trends of certain invasive fungal infections occurring in patients on specific antifungal agents.

Non-infectious complications

A total of 32 patients had GHVD. Of these 32, 21 had GHVD that had begun after the first allo-HCT, and 11 developed GVHD only after the second allo-HCT. Median time to development of GVHD after the second allo-HCT was 23 days (range 10–232 days). Six patients (10%) had graft failure and 20 (33%) had relapse of leukemia. Other complications included veno-occlusive disease ($n = 4$), Idiopathic pneumonia syndrome /engraftment syndrome ($n = 3$), diffuse alveolar hemorrhage ($n = 4$), and transfusion-associated lung injury ($n = 1$).

Outcomes

All-cause mortality in the first year after receiving a second allo-HCT was 45% ($n = 27$), and the 2-year mortality was 65% ($n = 39$). Sixteen (41%) of the 39 deaths were attributed to infection, and 16 (41%) were attributed to hematologic causes (Table 6). Failure to engraft neutrophils was very significantly associated with decreased survival over time ($p < 0.0001$) (Fig. 1a), as was failure to engraft platelets ($p = 0.001$) (Fig. 1b).

The number of deaths due to infectious causes was similar across all post-transplant periods, while most deaths due to hematologic causes occurred in the early or late post-engraftment periods ($p < 0.001$). Of the 16 deaths attributed to infection, 8 (50%) were caused by bacterial species alone: VRE ($n = 2$), *Staphylococcus aureus* ($n = 1$), *Stenotrophomonas maltophilia* ($n = 1$) coinfection with VRE and *Pseudomonas* spp. ($n = 2$), coinfection with MRSA and *Pseudomonas* spp. ($n = 1$), and coinfection with *Achromobacter xylosoxidans* and *Pseudomonas* spp. ($n = 1$). One patient each died of influenza A and disseminated herpes simplex infection. Four deaths were

Table 3. Organisms causing bacterial infection episodes by time of onset after receiving a second allo-HCT in 60 patients.

Organism	<30 days ($n = 35$)[a]	30–100 days ($n = 21$)[a]	>100 days ($n = 20$)[a]	Total ($n = 76$)[a]
CoNS	3	1	5	9
bacteremia	2	1	5	
conjunctivitis	1	0	0	
VRE	7	2	3	12
bacteremia	6	2	2	
UTI	1	0	1	
C. difficile	7	6	2	15
Pseudomonas	2	3	4	9
bacteremia	1	1	3	
UTI	0	1	0	
pneumonia	1	1	1	
MRSA	3	0	1	4
bacteremia	1	0	0	
pneumonia	1	0	1	
conjunctivitis	1	0	0	
MSSA pneumonia	1	0	0	1
VSE	5	2	1	8
bacteremia	3	1	1	
UTI	2	1	0	
Non-*Pseudomonas* Gram (-) bacilli[b]	3	4	3	10
bacteremia	3	1	2	
UTI	0	3	1	
Streptococci	3	2	0	5
bacteremia	3	1	0	
pneumonia	0	1	0	
Other bacteremia[c]	1	1	1	3

CoNS coagulase negative *Staphylococcus*, *VRE* vancomycin-resistant *Enterococcus*, *UTI* urinary tract infection, *MRSA* methicillin-resistant *Staphylococcus* aureus, *MSSA* methicillin-susceptible *Staphylococcus aureus*, *VSE* vancomycin-susceptible *Enterococcus*.
[a]Some patients had more than one site of infection and some had concomitant infection with several different bacteria.
[b]Includes E. coli, Citrobacter spp., Enterobacter spp., Klebsiella spp.
[c]Includes Achromobacter spp., Corynebacterium spp., and Stenotrophomonas spp.

attributed to fungal infections alone, all occurring in the late post-engraftment period; organisms included *Rhizopus* spp. ($n = 2$), *Aspergillus* spp. ($n = 1$), and *Pneumocystis jirovecii* ($n = 1$). Two patient deaths were related to concomitant bacterial and fungal infections; one patient had *C. glabrata* fungemia, VRE bacteremia, *and C. difficile* infection, and the other had a probable invasive aspergillosis of the lung and brain and VRE bacteremia.

Most of the 16 deaths from hematologic causes were related to disease relapse ($n = 11$) or graft failure ($n = 3$), with the remainder due to GVHD ($n = 1$) and VOD ($n = 1$) (Table 6).

DISCUSSION

This study emphasizes the occurrence of infectious complications in adults who received a second allo-HCT. All but 4 of our patients undergoing a second allo-HCT experienced an infection, in contrast to lower rates noted following a single allo-HCT [13–17]. Bacterial infections were more common than viral and fungal infections and among infectious etiologies, were the most frequent cause of death. In contrast to bacterial infections, which clustered in the pre-engraftment period, most CMV and BK virus infections occurred later in the early post-engraftment period. Fungal infections occurred equally across all post-transplant periods. These results are not dissimilar to those reported following single allo-HCT [18].

Among bacterial infections, the prominent pathogens were VRE and *C. difficile*. VRE has emerged as a leading cause of early bloodstream infections and has been associated with increased mortality among single allo-HCT recipients [19–21]. We noted a high incidence of VRE infection, and almost a third of deaths associated with an infectious episode were in patients who had an enterococcal bloodstream infection. Our experience with *C. difficile* infections following a second allo-HCT closely reflects that reported after single allo-HCT [22–24]. Most of the non-clostridial bacterial infections, especially bloodstream infections, occurred in the pre-engraftment period. Infections due to Gram positive cocci were more common than those due to Gram negative bacilli, a trend reported by others for single allo-HCT [14, 17, 25].

CMV infection was manifested in almost all patients as viremia and not tissue invasive disease. Close monitoring with early detection and treatment of viremia may explain the absence of end organ CMV disease in these patients [26]. Consistent with data reported for single allo-HCT, CMV infections were most common in the early post-engraftment period in our cohort. However, we also noticed high rates of CMV infection in the pre-engraftment period, which we suspect might be related to residual cell-mediated immune defects incurred with the first allo-HCT. Our findings are similar to those from other institutions reporting on viral infections following single allo-HCT in patients not receiving

Table 4. Organisms causing viral infection episodes by time of onset after receiving a second allo-HCT in 60 patients.

Organism	<30 days ($n = 18$)	30–100 days ($n = 24$)	>100 days ($n = 17$)	Total ($n = 59$)
Cytomegalovirus	7	11[a]	3	21
BK virus[b]	4	6	0	10
Herpes simplex[c]	4	0	0	4
Respiratory virus[d]	0	2	9	11
HHV-6 viremia	2	2	0	4
Epstein-Barr viremia	1	2	1	4
Varicella zoster virus	0	1	4	5

[a]Two patients had colitis as well as viremia.
[b]Hemorrhagic cystitis was present in 3 patients <30 days and in 4 patients 30–100 days.
[c]Disseminated disease (n = 1), mucocutaneous infection ($n = 3$).
[d]Parainfluenza (3), influenza A (2), rhinovirus (2), respiratory syncytial virus (2), coronavirus (1), human metapneumovirus (1); 7 were upper respiratory tract infections and 4 were lower respiratory tract infections.

Table 5. Proven or probable fungal infection episodes by time of onset after receiving a second allo-HCT in 60 patients.

Organism	Site of infection	<30 days $n = 6$	30–100 days $n = 4$	>100 days $n = 6$	Total $n = 16$
Aspergillus species	lung (3) lung & brain (2)	1	2	2	5
Alternaria species	skin (1) sinusitis (1)	2	0	0	2
Candida glabrata[a]	fungemia	1	2	1	4
Candida parapsilosis	fungemia	1	0	0	1
Fusarium species	sinusitis	1	0	0	1
Pneumocystis jirovecii	lung	0	0	1	1
Rhizopus species	disseminated (1) lung (1)	0	0	2	2

[a]One patient had 2 separate episodes of *C. glabrata* fungemia.

Table 6. Cause of death over 2 years by time of onset after receiving a second allo-HCT in 60 patients.

Deaths	<30 days	30–100 days	>100 days	2 years	Total deaths
Total deaths	7	9	11	12	39
Infection related	5	2	5	4	16
Bacterial	4	1	3	0	8
Viral	1	1	0	0	2
Fungal	0	0	4	0	4
Bacterial and Fungal	0	0	0	2	2
Hematology related	1	6	5	4	16
Relapse	0	3	5	3	11
Graft failure	1	2	0	0	3
GVHD	0	0	0	1	1
VOD	0	1	0	0	1
Other[a]	1	1	1	4	7

GVHD graft-versus host disease, *VOD* veno-occlusive disease.
[a]Includes acute myocardial infarction (1), subdural hematoma (1), alveolar hemorrhage (1), acute respiratory distress syndrome (1), and unknown causes (3).

CMV prophylaxis [17, 26, 27]. The recent approval of letermovir, which was not available at the time this study was performed, has markedly decreased the incidence of CMV infection/disease post allo-HCT [28, 29]. Letermovir is currently approved for prophylaxis of CMV infection and disease in adult allo-HCT recipients who are CMV-seropositive, and it is likely to reduce the overall incidence of CMV infection/disease and its associated morbidity in this patient population.

Proven and probable fungal diseases were seen throughout the post-transplant period and were responsible for more than a third of infection-related deaths. Invasive pulmonary aspergillosis was the most common mold infection, as noted in many transplant centers [30, 31]. More uncommon mold infections, such as fusariosis and mucormycosis, have been reported to be increasing in some transplant centers [32, 33], but in our cohort they were uncommon.

The 2-year mortality rate of 65% that we observed is significantly greater than that noted for adults undergoing a single allo-HCT for AML or MDS [34], but it is comparable to the 2-year mortality rate of 64% reported in adults ages 70 and above undergoing first allo-HCT [35]. Other reports of mortality rates following a second allo-HCT among children as well as adults are

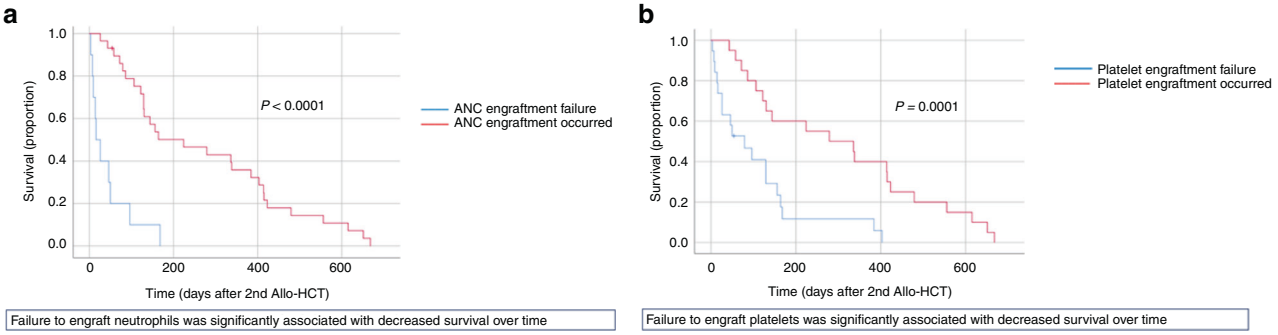

Fig. 1 Survival related to neutrophil and platelet engraftment after second Allogeneic Stem Cell Transplant. Kaplan-Meier curve shows survival was significally decreased among patients who failed neutrophil and platelete engraftment (figure **a** and **b**).

similar to the mortality rate we noted in our patient cohort [4, 8, 36]. Infection accounted for 41% of deaths in our study in comparison to rates as low as 24% noted by others [8].

Failure to engraft either platelets or neutrophils after a second allo-HCT was significantly associated with decreased survival over time. Persistent neutropenia likely contributed to the large number of infections in patients undergoing a second allo-HCT. The high mortality rate is likely a consequence of the cumulative immunosuppression secondary to intense exposure to chemotherapy, given that the most common indication for second allo-HCT in our study was relapse of leukemia.

The strengths of this study are that data from two different transplant centers were included, the number of patients is higher than in many other reports detailing outcomes of second allo-HCT in adults, and standard definitions of fungal and viral infections were used. However, there are several limitations. Patients receiving cord blood HCT and haploidentical HCT were excluded so these data cannot be generalized to those specific populations. The retrospective study design is a drawback. The data were collected from the years 2010–2017 and changes in practice have occurred since that time, perhaps making these data less generalizable.

In conclusion, we found that infections occur frequently throughout all post-transplant periods after a second allo-HCT. The mortality from infectious complications after a second allo-HCT is high and is primarily due to bacterial and fungal pathogens. Prevention of infection should be a high priority in patients in whom a second allo-HCT is undertaken.

DATA AVAILABILITY

There is no data bank or repository associated with this study

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AUTHOR CONTRIBUTIONS

SMM: data collection, manuscript writing. KAL: data collection, result interpretation, manuscript writing. CAK: result interpretation, manuscript writing. PM: data collection. JA: data collection. PC: study design, manuscript review. SR: data collection, manuscript review. MHM: study design, data analysis, result interpretation, manuscript review.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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