Original Article
Infectious complications in cord blood and T-cell depleted haploidentical stem cell transplantation

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Abstract: Infections due to post transplant immune deficiency is a major problem following allogeneic stem cell transplantation, particularly in patients receiving cord blood or T-cell depleted haploidentical transplants. We evaluated the incidence and type of infectious complications that occurred in these two types of transplant for 65 patients, 37 cord blood and 28 haploidentical, who received the same conditioning regimen: fludarabine, melphalan and thiotepa. While incidence of infections appeared similar in both types of transplant, viral infections were more frequent than bacterial or fungal infections and were the most common cause of death in both groups. Patients in the haploidentical group were 1.7 times (95% CI: 1.1 to 2.5) more likely to have a viral infection (p=0.013). Bacterial, fungal and CMV infections still quite frequent but contributed less to mortality. Pneumonia was the most common clinical syndrome and the number one cause of death in both groups. Both pneumonia and bacteremia occurred within the first 100 days in the majority of HSCT patients while CBT patients had a bimodal distribution, with more than one third of episodes after 6 months post transplant.

Keywords: Infectious complications, cord blood transplantation, T-cell depleted haploidentical stem cell transplantation

Introduction

Mismatched related donors and umbilical cord blood are alternative donor sources for stem cell transplantation for patients who lack a histocompatible donor. Haploidentical stem cell transplantation (HSCT) has been limited by high rates of graft rejection and acute graft versus host disease (GVHD) [1]. T-cell depletion (TCD) decreased the rate of GVHD while increased the risk of severe infections [2]; however, higher doses of CD34+ cells have been shown to overcome HLA incompatibility, promote engraftment [3, 4] and lead to higher rates of immunological reconstitution in children [5]. Cord blood transplantation (CBT) is associated with delayed reconstitution of antigen-specific cellular immunity that predisposes patients to an increased risk of opportunistic infections [6, 7].

The relative risk of infection in adult SCT recipients from these 2 sources has not been compared. Here we evaluated the rate of infectious complications and mortality in 2 groups of adult patients with advanced hematological malignancies who received the same myeloablative conditioning regimen with fludarabine, melphalan and thiotepa followed by either TCD haploidentical or cord blood transplantation at a single institution.

Materials and methods

Patients

We identified 65 consecutive patients who had received a TCD haploidentical (n=28) or cord blood (n=37) stem cell transplant at The University of Texas MD Anderson Cancer Center between 10/2001 and 5/2008. Patients were treated during the same time period on separate protocols, based on stem cell source. Patients who received a CBT could have up to 10%

bone marrow blasts at the time of transplant, whereas no cutoff existed for HSCT recipients. All were treated on clinical trials approved by the Institutional Review Board (IRB) of MD Anderson Cancer Center, and provided written informed consent. An IRB-approved protocol and a waiver of informed consent were obtained for this retrospective study. Patient characteristics and treatment outcomes were previously published [8].

Conditioning regimen

All patients were treated with a preparative regimen consisting of melphalan at 140 mg/m² on day −8, thiotepa at 10 mg/kg on day −7, fludarabine at 160 mg/m² in divided doses given on days −6, −5, −4, and −3. CBT patients also received rabbit antithymocyte globulin (ATG) at 1.5 mg/kg/day on days −6, −5, −4, and −3 [9]. GVHD prophylaxis was a tacrolimus-based regimen plus either methotrexate or mycophenolate mofetil for the CBT patients, whereas the recipients of the T-cell depleted haploidentical allografts received no additional GVHD prophylaxis. Patients developing GVHD greater than grade 2 were routinely treated with steroids (methylprednisolone 2 mg/kg in divided doses). All treated patients received standard antimicrobial prophylaxis with voriconazole, valacyclovir, trimethoprim-sulfamethoxazole, or pentamidine. Patients received foscarnet prophylaxis for cytomegalovirus (CMV) infection and ganciclovir only for treatment of CMV antigenemia or disease.

Definitions

Infectious episodes were clinically documented if fever or other signs and symptoms of infection were present, along with laboratory and/or radiographic features consistent with pulmonary, sinus, brain, gastrointestinal, skin and soft tissue or other organ infection, but no pathogen was identified. An infection was considered microbiologically documented if, in addition to the above findings, a disease-causing organism was identified from a body fluid or tissue sample by microbiologic or molecular testing or pathology. Polymicrobial infection was defined as more than one microorganism detected in the same body fluid or tissue sample. Fever with or without neutropenia without clinical or microbiological documentation was excluded from reporting. Mild infections, those not causing significant

symptoms, not requiring therapy or hospitalization, were excluded.

All temporally-related positive blood cultures for the same organism were considered a single episode of bacteremia. For coagulase-negative *Staphylococcus*, more than one positive culture was needed to diagnose bacteremia in a symptomatic patient [6].

CMV infection and disease were diagnosed using standard guidelines [10]. The presence of an invasive fungal infection (IFI) was determined based on the revised definitions of the EORTC/MSG consensus group [11]. Death associated with a documented infection was defined as death of a patient with findings consistent with infection, or as detection of the pathogen at autopsy [12]. Patients were censored for graft failure, death or relapse.

Statistical analysis

Descriptive statistics were performed on infection and mortality data. The effects of transplant source on infections were investigated by survival analysis. Patients were followed up for 1 year after SCT to observe infections. Since some patients had multiple infection episodes during follow-up time period, survival analysis of recurrent events data was performed. All statistical analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC).

Results

Thirty-seven patients who had CBT and 28 who had HSCT were followed for 9495 and 4091 patient-days respectively (**Table 1**). The CBT group had 191 episodes of infection (20 infection episodes per 1,000 patient-days) versus 128 of the HSCT patients (31 per 1,000 patient-days). Survival analysis showed that transplant source (CBT versus HSCT) (*p*=0.23) did not have a significant effect on the probability to have an infection episode.

Causative agents

Viral infections were most common in both groups. During the first year after stem cell transplant, there were 18.3 episodes per 1,000 patient-days in HSCT and 9.8 episodes per 1,000 patient-days in CBT recipients. Patients in the HSCT group were 1.7 times (95% CI: 1.1 to

Table 1. Infections in the first 365 days post-transplant by causative agent in cord blood and T-cell depleted haploidentical transplant groups

Type of Transplant	Cord blood SCT (n=37)			T-cell depleted haploidentical SCT (n=28)		
	# of episodes	# of infected patients	# of episodes/total pt-days	# of episodes	# of infected patients	# of episodes/ total pt-days
Viral infection	93	29	9.8/1,000 pt-days	75	22	18.3/1,000 pt-days
Bacterial Infection	60	27	6.3 /1,000 pt-days	38	19	9.3/1,000 pt-days
Fungal infection	14	11	1.5 per 1,000 pt-days	9	8	2.2 per 1,000 pt-days
Total infection episodes*	191	36	20.1 per 1,000 pt-days	128	27	31.3 per 1,000 pt-days

SCT indicates stem cell transplant.
*Includes viral, bacterial, fungal infections, and all others such as clinically documented and parasitic infections.

Table 2. Types of viral infections in cord blood and T-cell depleted haploidentical stem cell transplant in the first year post transplant

Type of Transplant	Cord blood SCT		T-cell depleted haploidentical SCT		p-value*
Virus	# of episodes	# of infected pts	# of episodes	# of infected pts	
Cytomegalovirus	51	18	30	14	NS
Epstein-Barr virus	2	2	4	4	NS
Herpes simplex virus	5	5	8	6	NS
Varicella-zoster virus	3	3	2	2	NS
Human herpesvirus 6	0	0	1	1	NS
BK virus	11	11	15	15	0.02
Adenovirus	6	5	5	2	NS
Influenza virus	1	1	4	2	0.04
Parainfluenza virus	9	9	7	4	NS
RSV	6	6	0	0	NS
Molluscum contagiosum	1	1	0	0	NS
Total viral infections	93	29	75	22	0.001

SCT indicates stem cell transplant; NS, non significant; RSV, respiratory syncytial virus
* p-value is from survival analysis of recurrent events data on each infection.

2.5) more likely to have a viral infection (p=0.013). Table 2 shows the episodes of viral infection by frequency for each group, during the first 365 days post-transplant. CMV affected the most patients and recurred 1 to 2 times on average in affected patients in both groups. BK virus cystitis was second and, along with influenza, was more common in the HSCT group. Respiratory viruses included influenza, parainfluenza and respiratory syncytial virus (RSV) and, taken together, were third in frequency, followed by herpes simplex and varicella zoster virus reactivations.

Bacterial infections included 38 episodes in HSCT and 60 in CBT patients. On average, 9.3 and 6.3 episodes occurred per 1,000 patient-days for HSCT and CBT patients, respectively. Survival analysis showed no significant difference between the two groups in bacterial infection (p=0.69). The most common presentation was bacteremia. Pneumonia was second in frequency, with 10 episodes in 9 CBT and 13 episodes in 12 HSCT patients, eight of the later, and none of the former were polymicrobial, including molds and/or viruses. There were 7 episodes of *Clostridium difficile* colitis (5 episodes in 4 CBT patients) and 6 of microbiologically documented bacterial cellulitis in 3 CBT patients. Other sites of bacterial infection included the urinary tract, eye and gastrointestinal tract.

Invasive fungal infections were third in frequency, with 14 episodes in 11/37 (30%) CBT

Table 3. Number of episodes of the most frequent clinical syndromes by transplant type

Clinical Syndrome	Cord blood SCT (n=37)	T-cell depleted SCT (n=28)
Pneumonia	38	29
Bacteremia	35	19
Viral cystitis	11	17
Gastrointestinal infection	10	3
Disseminated infection	5	4
Sinusitis	6	2
Cellulitis	8	0

patients and 10 episodes in 9/28 (32%) HSCT patients. No significant difference in IFI was found between CBT and HSCT patients (*p*=0.67). In the CBT group, 6 infections were proven (2 candidemias, 3 *Candida* esophagitis and 1 *Rhizopus* sinusitis), in addition, one case of proven *Pneumocystis jirovecii* infection was included and 7 were probable pulmonary infections (4 with positive cultures for *Aspergillus* and 3 with positive galactomannan). HSCT patients had 5 proven (3 pneumonias caused by Zygomycosis, *Chaetomium sp* and *Aspergillus flavus*, 1 *Rhodotorula* fungemia and 1 *Rhyzopus* sinusitis), 3 probable pneumonias (1 with positive culture for *Aspergillus* and 2 galactomannan-positive) and 2 possible pneumonias. One proven IFI in an HSCT patient occurred after one year and is not counted in the table. All but 2 patients were receiving mold-active antifungal prophylaxis at the time of diagnosis, most with voriconazole or caspofungin. One had voriconazole held and one had no documentation of prophylaxis.

Clinical syndromes

Table 3 shows the most frequent clinical syndromes:

Pneumonia: The lung was the most common site of infection, eighteen of 28 (64%) HSCT and 22/37 (59%) CBT patients had at least one episode. Pneumonia occurred early in HSCT patients, with 79% of episodes in the first 100 days, and had a bimodal distribution in CBT patients, with 16 episodes (42%) in the first 60 days and 12(32%) after day 270.

Viral pneumonia was caused by CMV [5], parainfluenza [9], adenovirus [4], influenza [2] and RSV [4] in 24 episodes in 20 patients (9 HSCT and 11 CBT). Bacterial pneumonia was caused by gram-positives in 10 patients (6 were caused by *Staphylococcus aureus*) and gram-negatives in 12 episodes in 9 patients (6 were caused by *Stenotrophomonas maltophilia*). There were 15 episodes of fungal pneumonia in 14 patients, three were proven, 10 probable and 2 possible. *Aspergillus* was identified in 11 patients. There were 12 episodes of clinically documented pneumonia, 4 (14%) in HSCT and 8 (21%) in CBT patients. Polymicrobial pneumonias were more frequent in the former [9] than the later group [3]. *Toxoplasma*, *Nocardia*, *Pneumocystis* and *Mycobacterium avium* caused one episode of pneumonia each.

Bacteremia: Fourteen HSCT patients had 19 episodes of bacteremia, of which 13 were caused by gram-positives and 6 by gram-negatives. Twelve of 19 (63%) occurred in the first month post-transplant. Fourteen CBT patients had 35 episodes of bacteremia of which 30 were gram-positives and only 5 gram-negatives. Bacteremias followed a bimodal distribution in CBT patients, with 15 (43%) in the first month and 11 (31%) after 180 days post transplant. There was no predominant organism, gram-positives included *Enterococcus*, *Streptococcus viridans*, *Stomatococcus* and Staphylococci. Gram-negatives included *E. coli*, *Stenotrophomonas* and *Pseudomonas.*

Viral cystitis: occurred in 28 patients, 17 of them HSCT. Most were caused by BK virus, with a median time from transplant to diagnosis of 28 days (0 to 92 days) for HSCT and 29 (0 to 239 days) for CBT patients. Two episodes in the HSCT group were caused by adenovirus.

Gastrointestinal infections: There were 13 episodes of gastrointestinal infections, 10 in CBT patients, including 7 episodes of *C. difficile* colitis (2 in HSCT) and 3 episodes of neutropenic

Table 4. Causes of death by causative agent

Causative agent	Cord (n=14)	Haploidentical (n=8)
Viral		
Adenovirus	4	2
Influenza/parainfluenza	2	3
Epstein-Barr virus	0	1
Cytomegalovirus	1	0
Bacterial gram(+)/gram(-)	6	3
Fungal	1	2
Toxoplasmosis	0	2
Miliary tuberculosis	1	0
Sepsis (clinical)	1	1
Noninfectious/unknown	3	0

N indicates number of patients who died without relapse. Most patients had more than one infection contributing to death.

Table 5. Causes of death by clinical syndrome

Clinical syndrome	Cord (n=14)	Haploidentical (n=8)
Pneumonia	5	5
Disseminated infection		
Adenovirus	3	2
Toxoplasmosis	0	2
Tuberculosis	1	0
Sepsis	4	2
Encephalitis	1	1
Noninfectious/unknown	3	0

N indicates number of patients who died without relapse. Most patients had more than one infection contributing to death.

enterocolitis (1 HSCT), and one episode each of colitis and diverticulitis.

Disseminated infections: Adenovirus caused disseminated infection culminating in death in 2 HSCT and 4 CBT, one CBT patient had disseminated tuberculosis, one HSCT patient had disseminated toxoplasmosis and one had septic shock and multisystem organ failure of unknown etiology.

Other clinical syndromes: Eight episodes of sinusitis were clinically documented and there were 8 episodes of cellulitis in 4 patients, six of them caused by gram-positive bacteria. Other less frequent infections included pyelonephritis, otitis, endophtalmitis and encephalitis.

Outcomes

Non-relapse mortality was 28% (8/28) in HSCT and 38% (14/37) in CBT patients. An autopsy was performed in 4 patients of each group and all 8 died of one or more infections. Except for 2 HSCT and 6 CBT patients, the rest had more than one infection identified as contributing to his/her death. Viral infections were the most common cause of death in both groups, and adenovirus was the most common virus, followed by bacterial infections. IFI was a rare cause of death (**Table 4**).

Pneumonia was the most common clinical syndrome leading to death in both groups followed by disseminated opportunistic infections (adenovirus, toxoplasmosis and tuberculosis), sepsis and encephalitis (**Table 5**).

Discussion

Infections remain a significant cause of morbidity and mortality after alternative donor transplantation regardless of stem cell source. It is difficult to compare the impact of different stem

cell sources on infection risk since there are no randomized studies. We found one study comparing infectious complications between adult recipients of unrelated donor transplants and CBT [13] or TCD HSCT [14] and one comparing pediatric recipients of CBT versus TCD and unmanipulated bone marrow transplants [15].

Adult recipients of CBT after myeloablative conditioning have delayed neutrophil and lymphocyte recovery and an increased incidence of early bacterial infections, predominantly involving gram-positive organisms, with similar overall rates of infection at later time points compared to unmanipulated HLA-matched unrelated donor transplant recipients [16]. Parody et al. described a higher incidence of severe infections, especially bacterial, in the first 100 days post transplant and a higher risk of severe infections but no difference in overall survival or infection-related deaths by 3 years when comparing 48 CBT to 144 unrelated peripheral blood and bone marrow transplant recipients [13]. More recently, Cahu et al. reported on 31 adult CBT patients, 23 of whom received reduced-intensity conditioning and 27 received double CBT. A higher incidence of viral infection was documented. Infection-related mortality was only 8% and caused exclusively by viral agents. Higher total nucleated cell doses than previous studies, different infection monitoring and supportive treatment may account for the difference. Bacterial infections occurred early but were not the primary cause of death [17]. Conditioning regimens containing ATG and development of severe GVHD were risk factors for CMV infection [18].

TCD HSCT recipients (adults and children) had similar rates of serious and fatal infections when compared to unmodified marrow recipients but had significantly higher incidence of severe viral infections (especially CMV) and IFIs in a large randomized multicenter trial, in spite of reduction in GVHD, a major risk factor for infection [14]. Marks et al. reported that infection caused one half of deaths, with disseminated adenovirus causing one half of NRM. CMV reactivation was also important. Delayed immune reconstitution was the main culprit [19]. Aversa et al. noted that infection caused the death of 27/38 patients who died without relapse. CMV was the primary cause of death in 14 patients [20]. IFI followed viral infection in causing death in both studies. Later studies

showed that, since improvements were made in diagnosis and therapy of CMV, adenovirus has become the most lethal viral infection in HSCT patients during the first 6 months post transplant [19, 21].

There are few comparisons of CBT and HSCT recipients. A single institution small pediatric study found comparable survival between CBT, unmanipulated and TCD transplant recipients [22]. A retrospective study in children showed no difference in the cumulative incidence of serious infections in patients receiving CBT, unmanipulated or TCD unrelated bone marrow transplants at the University of Minnesota after myeloablative conditioning regimens. TCD patients had significantly more infections, with viral infections accounting for the difference, but mortality was similar [15]. An European registry-based analysis compared 262 unmanipulated (180 TCD and 99 CBT) pediatric patients with acute leukemia reported infection caused 30% of TCD and 40% of CBT mortality before day 100 and 12% versus 10% respectively after 100 days [23].

Our study is unique in comparing adult patients with advanced hematologic malignancies who received the same reduced-intensity conditioning regimen at a single institution, which offers a common base for comparing the infections in these two types of transplant. We found that the incidence of infection by source of transplant was not different; however, HSCT recipients were more likely to have viral infections than CBT patients, similar to what Barker et al. reported for pediatric patients [15]. Except for this finding, infections in both groups were remarkably similar (**Table 1**). Viral infections were more frequent than bacterial or fungal infections and were the most common cause of death in both groups. CMV, BK virus and respiratory viruses, in this order, were the most frequent in both groups. Of these, BK virus and influenza occurred more commonly in HSCT than CBT patients during the first year (**Table 2**).

Bacterial infections were not as common as in previously reported studies, especially in CBT recipients [6, 15, 16], and presented as bacteremia, with gram-positives as predominant organisms, followed by pneumonias. One fourth of patients in both groups had proven or probable IFIs, in spite of mold-active prophylaxis with voriconazole or caspofungin, however, fungal

infection was a cause of death in only 2 HSCT and 1 CBT patients. This may be due to heightened suspicion, early diagnosis and improved treatment of fungal infections.

Pneumonia was the most common clinical presentation of infection, with 59% of HSCT and 64% of CBT patients having at least one episode. Pneumonia was also the number one cause of mortality in both groups. Importantly, only 14% and 21% of episodes in HSCT and CBT patients respectively were not microbiologically documented. Polymicrobial pneumonias were relatively uncommon, but 7/18 (39%) HSCT and 10/22 (45%) CBT patients who had pneumonia had at least a second episode with a different organism, often separated by only a few weeks.

Both pneumonia and bacteremia occurred early, within the first 100 days, in the majority of HSCT patients while in CBT patients had a bimodal distribution, with more than one third of cases after 6 months post transplant. HSCT patients have a lower incidence of GVHD and immunosuppression is greatest in the first 6 months [21]. One recent single center study reported a similar finding in CBT adult recipients [24]. Adult CBT patients may have increased predisposition to late infections due to delayed immune recovery and immunosuppression from treatment of GVHD [7]. In spite of its frequency, bacteremia was not an important contributor to death, presumably due to early diagnosis, effective and timely treatment.

While CMV was the most frequent infection, it was implicated directly in the death of only one CBT patient. Improved detection, prophylaxis, pre-emption and management are to be credited [25]. Conversely, adenovirus killed 6 of the 7 patients infected and was the single most common cause of death in both groups. New strategies may decrease mortality in the near future including adoptive transfer of donor-derived virus-specific T-cells in patients with systemic adenovirus infection [26].

Our findings are limited by the small number of patients and its retrospective nature; however the study is enhanced by comparing groups treated in the same institution with the same reduced-intensity conditioning regimen and supportive care during the same period of time.

In summary, HSCT and CBT adult patients receiving the same reduced-intensity conditioning

regimen had a similar incidence of infection in the first year post transplant, but TCD HSCT patients had a higher frequency of viral infections. Viral infections were more frequent than bacterial or fungal infections and caused death more often in both groups. Pneumonia was the most common clinical syndrome and the number one cause of death in both groups. Bacterial, fungal and CMV infections are still quite prevalent but contributed less to mortality, most likely due to improvements in diagnosis and treatment. Similar improvements are desirable for viral infections, such as adenovirus, Epstein-Barr virus and respiratory viruses, while better screening, prophylaxis and detection for well known infrequent but deadly diseases such as toxoplasmosis and tuberculosis is needed.

Conflict of interest

The authors have no potential conflict of interest to declare.

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