Late Infections After Allogeneic Bone Marrow Transplantation: Comparison of Incidence in Related and Unrelated Donor Transplant Recipients

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Infectious complications are a major cause of morbidity and mortality after allogeneic bone marrow transplantation (BMT). We have evaluated the incidence of late infections (beyond day +50) in recipients of related (RD) and unrelated donor (URD) allogeneic BMT, factors associated with increased risks of infection, and the impact of the late infections on survival. Between 1989 and 1991, 249 patients received an RD (n = 151) or URD (n = 98) allogeneic BMT at the University of Minnesota and all late infections were investigated. Three hundred sixty-seven late infectious events developed in 162 patients between 50 days and 2 years after BMT. The incidence of any late infection was greater in URD versus RD recipients (84.7% *v* 68.2%, respectively; *P* = .009). In multivariate analysis, advanced graft-versus-host disease (GVHD) was significantly associated with late infections. The effect of GVHD was apparent only in RD recipients (relative risk [RR], 2.29; *P* = .003), whereas URD recipients, with or without GVHD, had more late infections compared with RD recipients without GVHD. Multivariate analysis showed that late posttransplantation infections were the dominant independent factor associated with increased nonrelapse mortality (RR, 5.5; *P* = .0001), resulting in improved 3-year survival for RD versus URD recipients (49.9% ± 8% *v* 34.4% ± 10%; *P* = .004). In this study, we observed that late infections are more frequent in URD recipients, resulting in substantially higher nonrelapse mortality. This prolonged period of increased infectious risk in URD recipients suggests the need for aggressive surveillance and therapy of late infections and perhaps prolonged antibiotic prophylaxis for all URD BMT recipients.

INFECTIONS ARE THE most frequent serious complication of bone marrow transplantation (BMT). Early infections can be attributed to several factors, including neutropenia and the breakdown of mucosal barriers to microbial invasion. After engraftment, infections may result from incomplete immune reconstitution or from the immunosuppression associated with graft-versus-host disease (GVHD) and its treatment.[1-5]

Clinical experience suggests that recipients of unrelated donor BMT remain at risk for infections longer than do recipients of related donor BMT. Therefore, we have examined in detail the comparative incidence of late infections after related (RD) and unrelated donor (URD) allogeneic BMT, factors associated with ongoing risk of infection, and the impact of these infections on survival.

MATERIALS AND METHODS

We performed a comprehensive review of infectious complications occurring later than 50 days after BMT in 315 consecutive patients receiving an allogeneic BMT at the University of Minnesota between 1989 and 1991. Data were obtained from prospectively collected records within the University of Minnesota BMT Database and review of all available hospital and outpatient medical records. Infections occurring between 50 days and 2 years after BMT were evaluated. All patients were observed for a minimum of 1 year after transplantation; all but 43 patients had at least 20 months of follow-up. Infection was identified if there were positive microbial culture results and a clinical syndrome in which specific antimicrobial treatment was initiated. For example, the following were not considered to be infections: asymptomatic colonization detected in surveillance cultures; viral upper respiratory infections; thrush; and positive blood cultures due to contamination. For bacteria and fungi, infections with the same organism occurring ≥30 days apart were considered to be two separate events. For viruses, successive infections with the same organism ≥60 days apart were recorded as two separate infectious events.

Of these 315 patients, 66 were excluded from this analysis of late infections because of either death before day 51 (n = 50), relapse or persistent malignant disease before day 51 (n = 14), or retransplantation before day 51 (n = 2).

Antibiotic prophylaxis consisted of clotrimazole or nystatin to 100 days after BMT and trimethoprim/sulfamethoxazole for 1 year after transplantation. Patients receiving therapy for GVHD also received oral penicillin. Patients who were cytomegalovirus (CMV)-seropositive before BMT or who received marrow from a CMV-seropositive donor received either high-dose acyclovir or intravenous Ig from days 30 to 150 after BMT. When both the patient and donor were CMV-seronegative, no specific CMV prophylaxis was administered beyond the use of CMV-seronegative or leukocyte-depleted blood products.

Acute GVHD was identified clinically and graded according to modified Seattle criteria. Histologically confirmed upper gastrointestinal acute GVHD was considered overall grade II, as reported previously.[6,7] Chronic GVHD was diagnosed and graded according to the Seattle criteria.[8,9] For this analysis, advanced GVHD is defined as grade II-IV acute GVHD and/or extensive chronic GVHD.

Acute GVHD developed in 171 of the patients at a median of 29 days (range, 8 to 85 days) after BMT. The incidence of acute GVHD was significantly greater in URD than in RD recipients (73.6% ± 8.8% [±95% confidence limits] *v* 66.0% ± 7.6%, respectively; *P* = .04). However, by 2 years after BMT, the incidence of chronic GVHD was not significantly different in the two groups (61.0% ± 13.4% URD and 49.6% ± 9.4% RD recipients: *P* = .19).

During the first year after BMT, patients are evaluated in the outpatient clinics at the University of Minnesota every 1 to 3 months and generally more frequently for patients with active GVHD. After the first year, follow-up visits are less frequent. In addition to clinic visits, written and verbal contact is maintained with the patient's local physicians. However, infections occurring remote from our

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transplant center might be underreported. Therefore, the comparative frequency of follow-up visits over eight time periods between 50 days and 2 years after BMT was evaluated in related and unrelated donor transplant recipients. Overall, there were no significant differences in follow-up contact rates (the number of visits per 1,000 patient days) between the two groups. Follow-up rates were slightly, but not significantly, higher in URD than in RD recipients between 50 and 100 days after BMT (48 *v* 33 visits/1,000 patient days, respectively) and between 9 and 12 months after BMT (18 *v* 14 visits/1,000 days, respectively). During the other time intervals, follow-up rates were similar among RD and URD recipients. In all time periods, follow-up contacts were more frequent for both RD and URD transplant recipients with advanced GVHD.

Between 50 and 100 days after BMT, RD and URD patients with advanced GVHD had 39 and 54 visits/1,000 days, respectively, whereas RD and URD patients without advanced GVHD had 26 and 37 visits/1,000 days. Between 9 and 12 months after BMT, there were 19 and 20 follow-up visits/1,000 days in RD and URD recipients with advanced GVHD. During the same time period, follow-up rates in RD and URD recipients without advanced GVHD were 7 and 12 visits/1,000 days, respectively.

Standard statistical methods and survival analysis were used in the data analysis.[10] Incidence of any late infection was estimated using the Kaplan-Meier product limit method[11] by treating the first infection as events and censoring patients at death or last follow-up. Ninety-five percent confidence intervals calculated from the standard errors are presented to reflect the precision of the estimates.

To account for multiple events, density incidence (total number of infections per 1,000 patient days) was used to describe the total rate of late infections. Density incidence for URD recipients was compared with that of RD recipients using Mantel-Haenszel methods[10] for four exclusive follow-up time windows (50 to 100 days, 3 to 6 months, 6 to 9 months, and 9 to 12 months after BMT) that were chosen before the analysis. All patients alive on the first day of a time window were included in the evaluation for that interval.

Multivariate analysis was conducted using a Cox proportional hazard model[12] to examine the difference in incidence of first infection between URD and RD recipients, adjusting for related confounders. Relative risk (RR) was used to measure the strength of association between donor type or other factors and risk of late infection. Nonbaseline variables (eg, the development of GVHD) were treated as time-dependent variables in the Cox regression model. Multiplicative interaction was tested in the model by entering the products of two variables of interest. Similar analyses were performed to evaluate the RR for second, third, and fourth infections among the patients who experienced the preceding infection.

RESULTS

Among the 249 evaluable patients, there were 397 infectious events between day 50 and 2 years after BMT. The clinical characteristics of these patients are shown in Table 1. Thirty events were censored (18 events after malignant relapse and 12 events after retransplantation), leaving 367 evaluable infectious events. Overall, 162 patients (74.2% ± 6.1%) had at least one late posttransplant infectious event. Ninety-four RD (68.2% ± 8.0%) and 68 URD (84.7% ± 8.8%) transplant recipients experienced one or more late infections (P = .009). Of the 367 infectious events, 307 involved a single site and 60 events involved infections at multiple sites. Sites of single-site infection included blood (40.1%), gastrointestinal tract (12.7%), skin (12.7%), upper respiratory tract (11.7%), lung (10.7%), urinary tract (6.8%), hepatobiliary system (1.6%), central nervous system (1.6%), and eye (0.7%).

Table 1. Patient Charactersitics

	RD		URD	
	n	%	n	%
Donor	151	60.6	98	39.4
Recipient age				
<18 yr	82	54.3	50	51.0
≥18 yr	69	45.7	48	49.0
Recipient sex				
Male	85	56.3	52	53.1
Female	66	43.7	46	46.9
HLA compatibility*				
Match	138	91.4	43	43.9
Mismatch	13	8.6	55	56.1
Diagnosis				
CML	35	23.2	40	40.8
Acute leukemia†	62	41.1	20	20.4
Other malignancy‡	18	11.9	6	6.1
Other nonmalignant§	36	23.8	32	32.7
Preparative regimen				
Chemotherapy + radiation‖	115	76.2	77	78.6
Chemotherapy alone¶	35	23.2	20	20.4
None	1	0.7	1	1.0
GVHD prophylaxis				
CSA containing#	17	11.3	63	64.3
Ex vivo T-cell depletion	23	15.2	0	0.0
Other**	111	73.5	35	35.7
CMV serologic status				
Both negative	53	35.6	21	21.4
Recipient or donor positive	96	64.4	77	78.6

* Match = 6 of 6 HLA-A, B, DR antigen compatibility. Mismatch = 5 of 6 antigen match.

† Includes acute lymphoblastic leukemia (n = 20 RD, 9 URD), acute nonlymphocytic leukemia (n = 41 RD, 11 URD), and other leukemia (n = 1 RD, 0 URD).

‡ Includes myelodysplastic syndrome (n = 8 RD, 6 URD), non-Hodgkin's lymphoma (n = 3 RD, 0 URD), Hodgkin's disease (n = 1 RD, 0 URD), neuroblastoma (n = 5 RD, 0 URD), and other solid tumor malignancy (n = 1 RD, 0 URD).

§ Includes aplastic anemia (n = 10 RD, 5 URD), immune deficiencies (n = 9 RD, 16 URD), and metabolic disorders (n = 17 RD, 11 URD).

‖ Includes cyclophosphamide (Cy)/total body irradiation (TBI); Ara-C/TBI; Cy/total lymphoid irradiation (TLI); multidrug regimens/TBI.

¶ Includes busulfan (Bu)/Cy; Cy alone; Bu/Cy/antithymocyte globulin (ATG); multidrug regimens.

Includes methotrexate (MTX)/cyclosporine (CSA)/prednisone; MTX/CSA; CSA/prednisone.

** Includes MTX/ATG/prednisone; MTX alone; anti-CD5 immunotoxin; none.

In the majority of infectious events, one organism was isolated, with more than one organism being involved in 43 events. Bacterial infections were most common, causing 52% of infectious events. Of these, 51.5% were gram-positive bacteria, most often coagulase-negative *Staphylococcus*, *Enterococcus*, or *Staphylococcus aureus*, and 48.5% were gram-negative bacteria, usually enteric bacilli. Viruses and fungi were involved in 37% and 11% of events, respectively. CMV caused 34% of late viral infections; other common viruses included Varicella zoster virus (VZV) and Herpes

simplex virus (HSV). In RD recipients, 35% of viral infections were caused by CMV, whereas VZV and HSV were involved in 26.2% and 15.0% of late viral infectious events, respectively. Similarly, in URD recipients, 33.3% of late viral infections were caused by CMV, whereas 11.8% were caused by VZV and 17.6% by HSV. Half of the fungal infections were caused by yeasts and the remainder were caused by molds, most commonly Aspergillus. Candida species caused 33.3% of late fungal infections in RDs and 50% in URDs, whereas Aspergillus was responsible for late fungal infections in 37.5% of RDs and 25.0% of URDs. The proportion of infections caused by bacteria, viruses, and fungi did not change significantly over time. Within related and unrelated donor subgroups, the relative frequency of bacterial, viral, and fungal infections was similar in all time periods (data not shown).

The majority of all late infections (65.7%) occurred between day 50 and 6 months after BMT, with 43.9% occurring between 50 and 100 days, 21.8% between 3 and 6 months, and 25.8% between 6 and 12 months. Few infections (8.5% of the total) occurred beyond 1 year after transplantation. The median number of infectious events in RD and URD transplant recipients was 2, with some patients having as many as 9 separate late infectious episodes. The range was 0 to 9 events in RD and 0 to 7 in URD transplant recipients. Fifty-seven patients (46.0%) had 3 or more late infections.

Of the 367 late infectious events, 103 were life-threatening. Infections were considered life-threatening if the patient was hypotensive, intravenous pressor agents were required, central venous pressure monitoring was needed, or mechanical ventilation was instituted. These late life-threatening events occurred at a median of 146 days after BMT (range, 52 to 625 days). In 54 events, infection was a primary cause of death, representing 52.4% of life-threatening infections and 14.7% of all infectious events.

Among life-threatening infections, 79 involved a single site and 24 involved two or more sites. The blood and lung were the most common sites of infection, accounting for 60.8% and 22.8% of the single site life-threatening events, respectively. Bacteria caused more than half (62.2%) of the late life-threatening infectious events (81.2% of these were gram-negative bacteria and 18.8% were gram-positive bacteria). Of the late life-threatening bacterial infections, 33% were lethal. Viruses and fungi were involved in 13.6% and 24.3% of late life-threatening infectious events, respectively. CMV caused 57.1% of late life-threatening viral infections; other viruses included respiratory syncytial virus, influenza virus, and parainfluenza virus. Forty percent of late life-threatening fungal infections were caused by Aspergillus; the others were caused by Candida species, Fusarium, Mucor, and Cunninghamella. Seventy-eight percent of the late life-threatening viral infections and 80% of the fungal infections were fatal. CMV caused 64% of lethal viral infections.

Infection rates over time after BMT. Rates of infection per 1,000 patient days were examined in the RD and URD patient groups over four time strata during the first year after BMT (Fig 1). Despite variation of some specific infections over time, URD recipients generally had a higher incidence of late infections ($P = .001$) and late life-threatening infections ($P = .02$) than RD recipients did over the four time periods. In the first time period (day 50 to 100), infections were 1.6 times more frequent in URD recipients ($P < .05$). Additionally, during the last interval (9 to 12 months after BMT) late infection rates were nearly 2.7-fold higher among URD recipients compared with RD recipients ($P = .001$). Most notable was a threefold increased rate of viral infections and a 2.5-fold increased rate of life-threatening infections during this latter period.

Risk factors for late infections: univariate analysis. We examined the following clinical features in univariate analysis for their association with the development of late infections: recipient age, recipient sex, CMV status, donor type (RD or URD), HLA compatibility, GVHD prophylaxis, and disease category. The results of these analyses are shown in Table 2.

Transplantation from an URD was associated with a statistically significant increased risk of late infection. By 1 year after BMT, 81% ± 9% of URD recipients had developed at least one late infection, compared with 67% ± 8% of RD recipients ($P = .015$). More frequent late infections were seen in patients ≥18 years of age, when either donor or recipient were CMV-seropositive before BMT, in patients receiving transplantation from an HLA-mismatched donor, and in patients undergoing transplantation for chronic myelogenous leukemia.

An additional univariate analysis was performed to evaluate the same clinical factors for their association with the development of late life-threatening infections. During the first year after BMT, 48% ± 6% of URD recipients had developed at least one late life-threatening infection, compared with 31% ± 8% of RD recipients ($P = .012$). A significantly increased incidence of late life-threatening infections was also seen in patients ≥18 years of age (48% ± 10% *v* 27% ± 9% in patients <18 years of age; $P = .0003$). In addition, HLA-mismatch and recipient or donor CMV seropositivity before BMT were associated with a higher frequency of late life-threatening infections (data not shown).

GVHD and its treatment can both result in immunosuppression and potentially in heightened risks of infection. To evaluate the effect of GVHD on the risk of late infections, we performed a series of Cox model regression analyses in RD and URD subgroups, with the development of advanced GVHD entered as a time-dependent covariate. As shown in Fig 2, among recipients of related donor BMT, the development of advanced GVHD was associated with a statistically significant increased incidence of infection ($P < .0001$). In contrast, for URD recipients the incidence of infection was similar with or without advanced GVHD and approximated that seen in RD recipients with GVHD.

The incidence of late life-threatening infections was also increased in both RD and URD recipients with advanced GVHD. Among RD recipients, 9% ± 7.6% without GVHD and 42% ± 10.8% with advanced GVHD developed a late life-threatening infection. In URD recipients, the incidence of late life-threatening infection was 27% ± 18.8% in those without GVHD and 48% ± 14.7% in those with advanced GVHD, respectively.

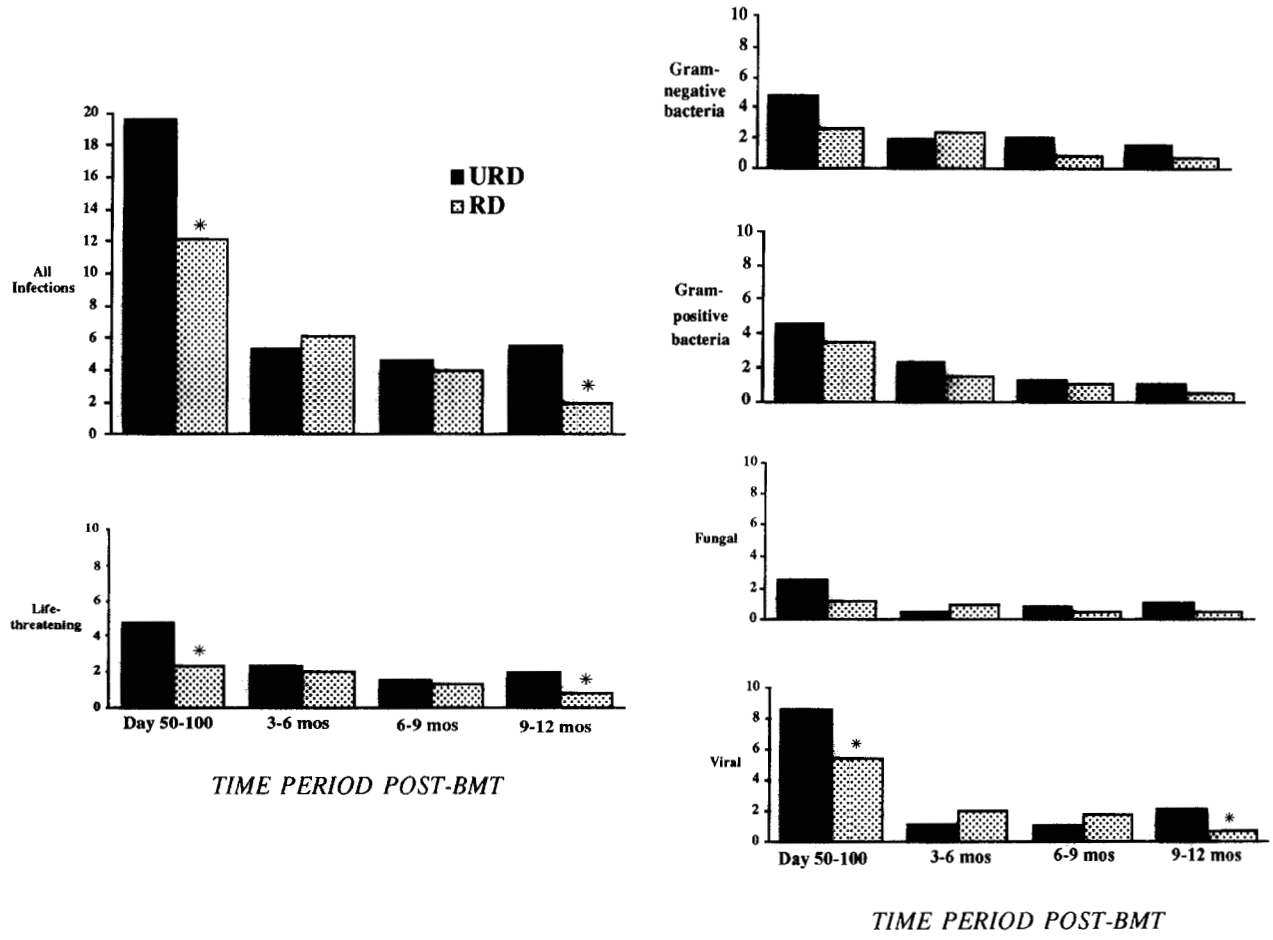

Fig 1. Infection rates per 1,000 patient days in RD and URD donor recipients during the first year after BMT. *$P < .05$.

Risk factors for late infection: multivariate analysis. Using the Cox regression model, we further evaluated the independent effect on late infection of the risk factors that were identified in the univariate analysis. As in the univariate analysis, a significant interaction between advanced GVHD and donor type was observed ($P < .01$). As shown in Table 3, advanced GVHD was associated with a significantly increased risk of late infection among RD recipients (RR, 2.29), but did not augment the risk among URD recipients (RR, 2.34/2.73 = 0.86). URD transplantation was associated with a 2.73-fold significantly increased risk of late infection among patients who did not develop advanced GVHD. However, transplantation from an URD was not associated with a further increased risk of late infection in patients with advanced GVHD (RR, 2.34/2.29 = 1.02). Older patient age was also independently associated with an increased risk of late infections (RR, 1.12 per decade of age; $P = .05$).

As an additional measure of continuing immunoincompetence over time, a series of multivariate regression analyses was performed to identify factors associated with the development of subsequent (second, third, and fourth) infections among patients who had the preceding infection. In each of these regression analyses, advanced GVHD remained as the most significant independent predictor of infection (ie, RR of 2.66, 2.55, and 2.44 for second, third, and fourth infections, respectively; all $P < .05$). As found for the initial late infection, transplantation from an URD and greater patient age were also associated with more frequent development of these subsequent late infections. For these later infections, we did not observe an interaction between GVHD and donor type, probably because of the small sample size (data not shown).

A multivariate analysis was performed to identify the predictors of late life-threatening infection. Advanced GVHD and donor type were again found to interactively affect the risk of a late life-threatening infection (Table 3). Similarly, older recipient age (RR, 1.18 per decade of age; $P = .03$) was significantly associated with late life-threatening infections. Although overall infection risk among URD recipients was unchanged with or without advanced GVHD (RR, 2.34 *v* 2.73, respectively), the risk of late life-threatening infections was greater in URD recipients with advanced GVHD (URD with GVHD: RR, 4.27; URD without GVHD: RR, 3.17).

Survival and nonrelapse mortality. After 3 years, 43.8% ± 6.4% of patients are alive. Nearly half (48%) of the nonrelapse deaths were caused by infections (Fig 3). At 3 years after BMT, 49.9% ± 8.4% of RD recipients are alive, com-

Table 2. Risk Factors for Late Infection: Univariate Analysis

	n*	Incidence (%) of Late Infection†	P
Donor type			
RD	151	67.3 ± 8.0	.015
URD	98	81.0 ± 9.3	
Recipient age			
<18 yr	132	65.9 ± 8.8	.015
≥18 yr	117	80.0 ± 8.2	
Recipient sex			
Male	137	70.4 ± 8.4	.36
Female	112	75.0 ± 8.9	
CMV serology pre-BMT			
Both negative	74	63.3 ± 11.7	.01
Recipient or donor positive	173	76.9 ± 7.1	
Donor:recipient histocompatibility			
Match	181	69.0 ± 7.3	.004
Mismatch	68	81.9 ± 11.2	
GVHD prophylaxis			
CSA containing	80	78.7 ± 5.2	.19
Ex vivo T-cell depletion	23	85.4 ± 9.1	
Other	146	67.5 ± 4.2	
Disease category			
CML	75	82.1 ± 9.4	.03
Other malignancy	106	64.6 ± 10.2	
Other nonmalignant	68	72.6 ± 11.6	

* Of 249 evaluable patients.

† Kaplan-Meier projected estimates ±95% confidence limits of the incidence of ≥1 late infection within the first year after BMT.

pared with 34.4% ± 9.7% of URD recipients (P = .004). Nonrelapse mortality (NRM; observation censored at time of malignant relapse) was significantly worse in URD recipients (Fig 3). In RD BMT recipients, NRM at 3 years after BMT was 38.4% ± 8.7%, compared with 62.4% ± 10.2% for patients undergoing URD BMT (P = .0001).

Table 3. Risk Factors for Late Infection: Multivariate Analysis

	RR	95% CI	P Value
A. Risk factors for any late infection			
RD without advanced GVHD	1.00	—	—
RD with advanced GVHD	2.29	1.45-3.59	.0003
URD without advanced GVHD	2.73	1.55-4.80	.0005
URD with advanced GVHD	2.34	1.45-3.76	.0005
Older recipient age (per decade)	1.12	1.00-1.25	.05
B. Risk factors for late life-threatening infection			
RD without advanced GVHD	1.00	—	—
RD with advanced GVHD	3.06	1.39-6.74	.005
URD without advanced GVHD	3.17	1.19-8.47	.02
URD with advanced GVHD	4.27	1.83-8.44	.0003
Older recipient age (per decade)	1.18	1.01-1.36	.03

To evaluate the contribution of late infections to this observed nonrelapse mortality, we performed a multivariate regression analysis considering the occurrence of any late infection as a time-dependent covariate, along with the factors previously identified as independent predictors of infection. As shown in Table 4, the development of any late posttransplantation infection was the predominant factor that was independently and significantly associated with higher nonrelapse mortality (RR, 5.46; P = .0001). Transplantation from an URD, advanced GVHD, and older patient age were also independent predictors of increased nonrelapse mortality. There was no interaction between advanced GVHD and donor type in this analysis.

DISCUSSION

In this analysis we observed that recipients of unrelated donor BMT experience a prolonged period of increased susceptibility to infection, well beyond that seen in recipients

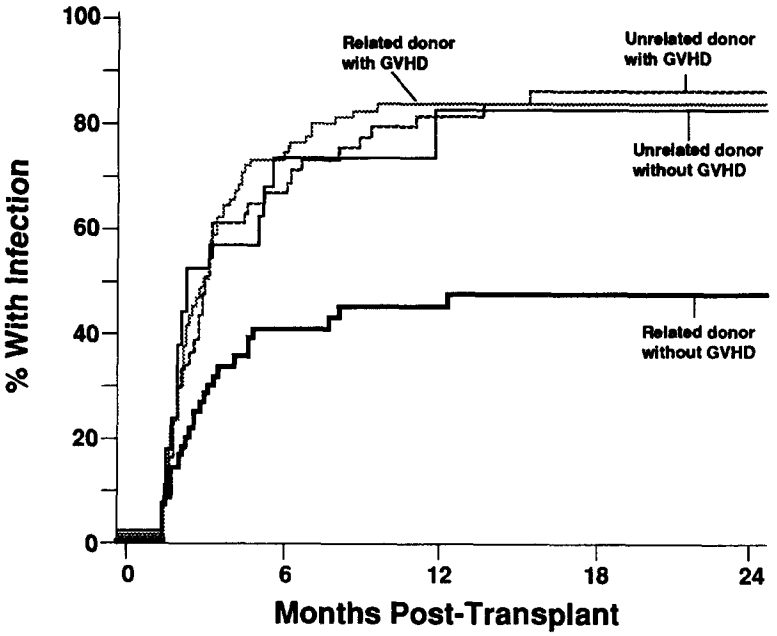

Fig 2. Incidence of late infections. The effect of donor source and GVHD on the incidence of late infection in RD and URD BMT recipients with advanced GVHD considered as a time-dependent covariate. In recipients of RD BMT, there was a statistically significant increased incidence of infection among those who developed advanced GVHD (P < .0001). The incidence of infection was not different in URD recipients with or without advanced GVHD and was similar to that seen in RD recipients with advanced GVHD.

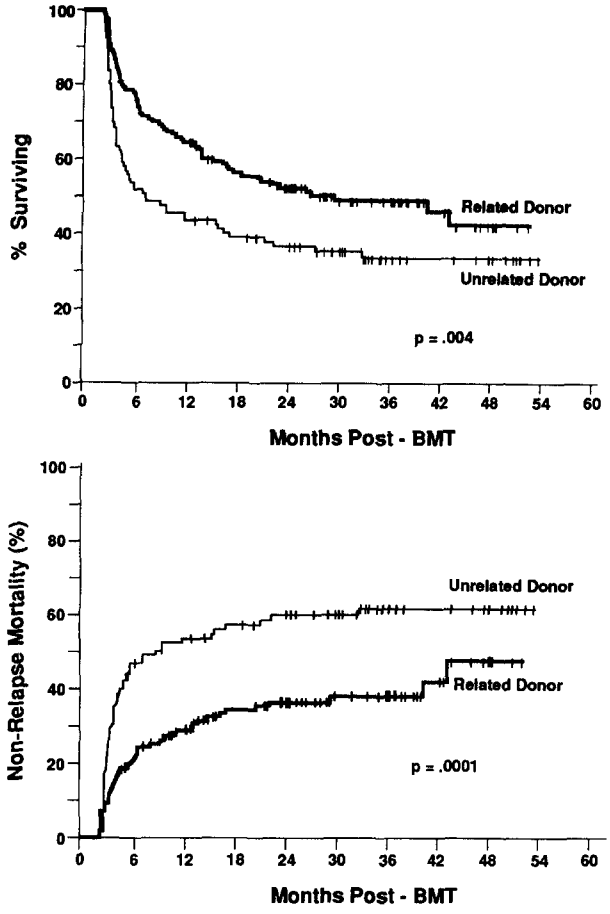

Fig 3. Overall survival (top) and nonrelapse mortality in RD and URD donor recipients. At 3 years after BMT, 34.4% of URD recipients are alive, compared with 49.9% of RD recipients (P = .004). Nonrelapse mortality at 3 years after BMT was significantly worse in URD recipients than in RD recipients (62.4% *v* 38.4%, respectively; P = .0001).

of related donor BMT. Furthermore, late infections were equally frequent regardless of whether URD recipients developed advanced GVHD. Kaplan-Meier analysis shows an increased incidence of any late infection in URD compared with RD recipients. However, Kaplan-Meier analysis does not account for multiple events in the same patient. To address this issue we evaluated infection densities in RD and URD recipients and again observed an increase in URD recipients. Most notable was an increase in late viral infections and an increase in late life-threatening infections of all types. Few investigations of late post-BMT infections have been reported. One study described life-threatening infections occurring beyond 3 months after BMT in 818 autologous and 1,007 allogeneic BMT recipients. In that study, 113 patients (6.2%) developed a late life-threatening infection; these infections were strongly associated with GVHD and/or ongoing immunosuppressive therapy.[13] Atkinson et al[14] evaluated the incidence of and risk factors for late infections in recipients of syngeneic or matched sibling donor allogeneic BMT. In that analysis, chronic GVHD was the only factor significantly associated with late viral infections other than Varicella zoster.[14] An additional report described an increased risk of viral infections in patients with active chronic GVHD and in patients receiving marrow from HLA-mismatched donors, whereas fewer infections were observed in children less than 10 years of age. The presence of circulating nonspecific suppressor cells further increased the risk of Varicella zoster infections, but not other viral infections.[15] A recent report that included URD recipients evaluated early infections in 103 patients (46 URD and 57 sibling donors) undergoing BMT for chronic myelogenous leukemia. They described an increase in serious viral infections in the URD marrow recipients, but bacterial and fungal infection rates were similar in the two groups.[16]

We have also shown that nonrelapse mortality was significantly greater in URD marrow recipients. URD recipients, including those without advanced GVHD, had markedly increased risks of late and life-threatening infection. These late infections were overwhelmingly the most important factor associated with increased nonrelapse mortality.

Infections occurring remote from our transplant center might be underreported, and differences in frequency of follow-up visits at our transplant center between RD and URD recipients might therefore result in surveillance bias. Therefore, we formally evaluated the adequacy of follow-up contact in RD and URD recipients and found similar follow-up rates (visits per 1,000 patient days) in the two groups. In addition, an analysis of late late-threatening infectious events showed a pattern similar to that for all infectious events. Because life-threatening events are unlikely to be unreported in our prospective BMT patient follow-up, this further suggests that surveillance bias does not substantially confound our study.

Abnormalities of both cellular and humoral immunity have been documented after BMT and may contribute to infectious risk after transplantation.[17-22] Several manifestations of immunodeficiency have been shown in vivo. Although total lymphocyte counts reach the normal range within months after transplantation, the relative and absolute number of $CD8^+$ T cells is elevated and of $CD4^+$ cells is depressed, resulting in an abnormal CD4:CD8 T-cell ratio.[23] Complement levels (CH50, C3, and C4) are normal after BMT and IgG and IgM levels increase towards normal soon after transplant. However, IgA levels along with IgG2 and IgG4 subclass levels often remain subnormal for months.[24] Other manifestations of immunodeficiency include decreased primary antibody response to antigen, impaired IgM to IgG switch after secondary antigen exposure, decreased antibody response to pneumococcal polysaccharide antigen,

Table 4. Risk Factors for Nonrelapse Mortality: Multivariate Analysis

	RR	95% CI	*P* Value
Any late infection	5.46	3.31-9.01	.0001
Unrelated donor	1.90	1.29-2.80	.001
Advanced GVHD	1.66	1.03-2.67	.04
Older recipient age (per decade)	1.13	1.00-1.28	.05

abnormal delayed type hypersensitivity skin testing,[25] and functional asplenia in patients with chronic GVHD.[26] Post-transplantation abnormalities of immune function that have been shown in vitro include failure of patient lymphocytes to secrete Ig when cultured with normal T lymphocytes and to provide helper function to normal lymphocytes,[27] inhibition of Ig production by nonspecific T cells,[28] and abnormal granulocyte chemotaxis.[29]

In most patients, these abnormalities of immune function are largely resolved by 1 year after transplantation. However, in patients with ongoing chronic GVHD, these abnormalities persist. Some defects, such as response to recall antigens, may be sustained up to 4 years after transplant.[30-33] Patients with chronic GVHD experience more infectious complications than comparable posttransplantation patients without chronic GVHD.[30] The persistent immunodeficiency observed in chronic GVHD patients undoubtedly contributes to their increased incidence of infections. Other factors associated with chronic GVHD may also predispose to infection. Oral or gastrointestinal mucosal involvement may compromise mucosal barriers to infection, whereas gastrointestinal chronic GVHD may produce malabsorption and malnutrition that may further impair host defenses.

In the majority of cases, URD BMT is complicated by acute and chronic GVHD.[34] Thus, a greater proportion of URD recipients compared with RD recipients are liable to exhibit GVHD-associated delayed immune reconstitution and resultant enhanced risks of late infections. URD recipients may also receive more aggressive and prolonged immunosuppression for prophylaxis of GVHD or may have ongoing immunodeficiency due to donor-recipient histoincompatibility—all of which may add to their risk of late infections. However, transplantation from an URD was associated with an increased risk of late infection, even in the absence of advanced GVHD. Our previous analysis identified similar response rates for treatment of acute GVHD in RD and URD recipients, but inferior survival in URD recipients.[35] This poorer survival is a consequence of the ongoing immunodeficiency and late infections reported herein. This suggests that URD BMT may lead to more profound and prolonged immunodeficiency compared with related donor BMT, even in the absence of clinical GVHD.

The increased rate of late infections observed in this series, especially in URD recipients, was the dominant factor associated with increased nonrelapse mortality. In RD recipients without advanced GVHD, the risk of late infections decreases significantly by 6 months after BMT. However, URD recipients, including those without advanced GVHD, remain at increased risk for infection well beyond 1 year after BMT. This extended period of vulnerability to infection identifies a need for prolonged antibiotic prophylaxis, especially directed toward viral and perhaps fungal infections. If effective, extended prophylaxis could diminish the risks of late infection after URD BMT and thereby improve survival.

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