Chapter 8

Influence of Cytomegalovirus-seropositivity on outcome after T cell depleted bone marrow transplantation: contrasting results between recipients of grafts from related and unrelated donors

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Abstract

Whether cytomegalovirus (CMV)-seropositivity still remains a serious adverse risk factor for overall survival (OS) and transplant-related mortality (TRM) in allogeneic bone marrow transplantation (BMT) is under debate. We therefore analysed the effect of CMV serostatus on OS and TRM in 253 consecutively treated patients receiving partial T cell depleted (TCD) bone marrow from either matched related donors (MRD, n=205) or matched unrelated donors (MUD, n=48). All patients were given leukocyte-depleted blood products. CMV monitoring was performed using the pp65 antigenemia assay. Pre-emptive therapy consisted of short-course (2 weeks) low-dose (2.5 mg/kg intravenously b.i.d.) ganciclovir treatment as soon as a positive antigenemia assay was obtained (≥ 1 positive staining granulocyte/150.000 cells). Ganciclovir prophylaxis, identical to pre-emptive therapy, was given to CMV-seropositive patients with acute graft-versus-host disease (aGVHD) grade II-IV who were treated with high-dose corticosteroids. After multivariate analyses, inferior OS and increased TRM were predicted by extensive chronic (c) GVHD ($p<0.001$) in MRD recipients. Furthermore, high-risk disease status and older age adversely influenced OS ($p=0.001$) and TRM ($p=0.002$), respectively, while older age resulted in a trend towards a decreased OS ($p=0.066$). After multivariate analyses in MUD recipients OS and TRM were strongly influenced by patient (but not donor) CMV-seropositivity ($p=0.013$ and 0.007, respectively), while aGVHD also predicted for increased TRM ($p=0.024$). These data show that CMV-seropositivity is not an adverse risk factor for OS and TRM in MRD recipients of partial TCD-BMT. However, in MUD recipients, patient CMV-seropositivity has a high impact on OS and TRM.

Introduction

Cytomegalovirus (CMV) infections in recipients of allogeneic bone marrow transplants (BMTs) historically have been an important cause of morbidity and mortality, primarily due to CMV pneumonia. It did occur mainly in CMV-seropositive recipients by CMV reactivation, but also in CMV-seronegative recipients who acquired primary CMV infection by transfusion of unfiltered blood components or unmanipulated bone marrow from CMV-seropositive donors[1]. In CMV-seronegative recipients of unmanipulated grafts from CMV-seronegative donors or T cell depleted (TCD) grafts from CMV-seropositive donors, primary CMV infection could be prevented by a transfusion policy making use of either CMV-seronegative donors or leukocyte-depleted blood products[2-5]. A major step in preventing the occurrence of CMV pneumonia in CMV-seropositive patients was accomplished by prophylactic long-term (3-4 months) therapy with antiviral drugs like ganciclovir[6-9]. However, in these trials overall mortality was hardly improved because of side effects of long-term ganciclovir prophylaxis such as neutropenia, resulting in bacterial and fungal infections, and more late-onset CMV disease[7-9]. We previously showed that short-course (2 weeks) low-dose (2.5 mg/kg intravenously b.i.d.) ganciclovir therapy initiated either prophylactically, when high-dose corticosteroids were given for acute graft-versus-host disease (aGVHD), or pre-emptively, when CMV-antigenemia was detected, almost completely prevented the occurrence of CMV pneumonia in CMV-seropositive recipients of partial TCD transplants from matched related donors[10]. Furthermore, short-course ganciclovir did not lead to granulocytopenia or late-onset CMV disease. Whether CMV-seropositivity still remains an important risk factor in allogeneic BMT, preventing CMV-disease as described above, is under debate. We therefore analysed the effect of CMV-serostatus on transplant related mortality (TRM) and overall survival (OS) in 253 recipients of partial TCD BMTs of HLA-identical sibling donors or matched unrelated donors.

Methods

Patients For this study data of 253 consecutively treated patients receiving either bone marrow from matched related donors (MRD) (n=205) or from matched unrelated donors (MUD) (n=48) were analysed. Patients with acute leukaemia's in first complete remissions (CR), chronic myeloid leukaemia (CML) in first chronic phase (CP) and untreated severe aplastic anaemia (SAA) were considered low-risk. All patients with other diseases were considered high-risk. TRM was defined as any mortality after transplantation, except relapse. Transplantations were performed between July 1990 and May 2000 at the Department of Haematology of the University Medical Centre Utrecht. Patients were treated according to clinical protocols approved by the local investigation review board after informed consent was obtained.

Transplantation procedure Conditioning regimens consisted of cyclophosphamide (60 mg/kg/day) on each of two successive days, followed by total body irradiation (TBI) (600 cGy/day) on each of 2 successive days, with partial shielding of the lungs (total lung dose 850 cGy). The graft was infused after the second TBI fraction (day 0). Antithymocyteglobulin (ATG) (Thymoglobulin™, Sangstat, Amstelveen, the Netherlands) was given to MUD patients before cyclophosphamide was infused, in a dose of 4 mg/kg/day intravenously for 5 days. Due to a change in national treatment protocols, ATG dose was lowered to 2 mg/kg/day for 4 days from April 1999. All patients received cyclosporin from day -2 in a dose of 3 mg/kg/day by continuous infusion for 3-4 weeks, thereafter it was given orally for 4-6 weeks in a dose that gave comparable through levels, followed by tapering. Cyclosporin was discontinued within 3 months after transplantation, when no active GVHD was present. Infection prevention for all patients consisted of ciprofloxacin, fluconazole and amphotericin B given orally until granulocyte counts exceeded 500 cells/μl. Cephalothin was given intravenously for 10 days from day +3. Furthermore co-trimoxazole and valacyclovir were given orally from day +1 until 12 months post-BMT or longer in case of active GVHD, in a dose of 480 mg b.i.d. and 500 mg b.i.d., respectively. GVHD was classified according to the Seattle criteria[11]. Acute GVHD grade I was treated with topical corticosteroids; grade II or higher was treated with high-dose systemic corticosteroids as described[12]. Limited chronic GVHD was not treated and extensive chronic GVHD was treated with systemic corticosteroids, sometimes combined with cyclosporin[12].

CMV monitoring During the first 4 months post-transplant, all CMV-seropositive patient/donor combinations (R+/D+, R+/D-, R-/D+) were monitored for CMV antigenemia. When patient serostatus was positive (R+/D+, R+/D-) the pp65 assay was performed thrice a week until day 60 after BMT, thereafter twice a week until day 120. In patients with active GVHD monitoring was continued. When patient serostatus was negative (R-/D+) antigenemia was tested twice a week until discharge, thereafter once a week until 5 consecutive negative tests. Seronegative patient/donor combinations were not monitored. In this patient group, CMV-seronegativity was readdressed 3 months after BMT.

CMV pp65 assay This assay was performed as described[13-14]. CMV reactivation was defined as CMV pp65 antigenemia of ≥ 1 positive staining granulocyte/150.000 cells.

CMV disease Patients with symptoms of pneumonia, gastritis or enteritis underwent bronchoscopy, gastroscopy or sigmoidoscopy, respectively. CMV pneumonia/gastritis/enteritis was defined histologically by typical cytopathic effects and immunohistochemically by immunofluorescence with use of monoclonal antibodies to immediate early CMV antigens in biopsy specimens. When cultures of BAL fluid, saliva, urine and buffy coat were performed in case of infectious complications, these included always CMV cultures, irrespective of CMV serostatus.

Ganciclovir therapy CMV-seropositive patients who demonstrated CMV reactivation or who were treated with high-dose corticosteroids for aGVHD grade II-IV received pre-emptive or prophylactic therapy, respectively, with ganciclovir in a dose of 2.5 mg/kg intravenously twice a day for 14 days[10]. When patients were symptomatic (unexplained fever or symptoms compatible with CMV disease), CMV antigenemia was rising or remained positive after 14 days of treatment, ganciclovir dose was doubled or foscarnet treatment was started instead of ganciclovir in a dose of 60 mg/kg twice a day for 14 days. When serum creatinine increased above 200 μmol/l, ganciclovir dose was reduced. When granulocyte count decreased below 500/μl ganciclovir was replaced by foscarnet. CMV disease was treated with ganciclovir 5 mg/kg twice a day for at least 14 days and continued until symptoms resolved and/or antigenemia became negative, whichever was latest. In case of disease progression or rising antigenemia foscarnet treatment was started instead of ganciclovir in a dose of 60 mg/kg twice a day. Furthermore, treatment with CMV specific immunoglobulins was added to antiviral therapy in patients with CMV pneumonia.

HLA-matching In all MRD patient-donor pairs, class I antigens (A, B and Cw) were analysed by serological typing, in case of doubt low resolution molecular typing was performed. Class II antigens (DRB1, DRB3, DRB4, DRB5 and DQB1) were analysed by serological typing until 1993 and since 1993 by low resolution molecular typing with sequence specific primers. In MUD patient-donor pairs HLA analysis was performed as in MRD recipients until 1993, thereafter class I antigens (A, B) were analysed by serological typing, in case of doubt low resolution molecular typing was performed. Class I Cw and class II antigens (DRB1, DRB3, DRB4, DRB5 and DQB1) were analysed by low resolution molecular typing with sequence specific primers. DRB1, B3, B4 and B5 antigens were as well defined by high resolution typing since January 1999.

BMT In vitro partial TCD of the marrow was performed using the Soy Bean Agglutinin/Sheep Red Blood Cell (SBA/SRBC) technique until 1997[15]. Thereafter, the immunorosette (IR) depletion technique was used[16]. After this maximal T cell depletion procedure the residual number of T cells was counted and nonmanipulated T cells (from a small BM fraction that was set apart) were added to obtain the desired fixed low number of T cells (1-5 x 10^5 T cells/kg recipient weight)[12]. Since May 1998 B cell depletion, for prevention of Epstein-Barr virus-associated lymphoma, was added to grafts from MUDs[17].

Statistical analysis OS was estimated by the Kaplan-Meier method. Probabilities of TRM and aGVHD were calculated by the cumulative incidence procedure. For TRM, death without TRM was the competing risk; for aGVHD death without aGVHD was the competing risk. Univariate analyses were performed using the log rank test. Variables which showed to influence OS/TRM at a level of $p<0.1$ were used in a multivariate Cox regression analysis. P values from regression models were calculated with the Wald test. The post-transplant variables 'CMV reactivation', 'aGVHD' and 'cGVHD' were as well analysed as time-dependent covariates. Calculations were performed using SPSS/PC+ 10.0 (SPSS Inc, Chicago Il, USA).

Results

Patient characteristics Characteristics of MRD and MUD recipients are described in Table 1. MRD recipients were significantly older compared to MUD recipients (40 vs 31 yr, respectively, $p<0.001$). In contrast to the MUD group, 35% of MRD recipients were multiple

myeloma or lymphoma patients. Most patients received bone marrow transplants, some MRD patients received peripheral blood stem cell transplants (PBSCT) (MRD: 89% BMT vs 11% PBSCT; MUD: 100% BMT). Only 40% of recipients of matched related donor grafts and 38% of recipients of matched unrelated donor grafts were considered low-risk. Acute GVHD developed in 83% and 70% of MRD and MUD recipients, respectively (p=0.086), and grade II-IV in 50% and 38%, respectively. Chronic GVHD occurred in 56% of evaluable MRD recipients and in 36% of evaluable MUD recipients (p=0.032). The disease was extensive in 27% and 24% of MRD and MUD recipients, respectively. CMV reactivation was observed in 13% of all MRD patients (26% of the CMV-seropositive recipients) and in 25% of all MUD recipients (50% of the CMV-seropositive recipients) (p=0.054). No primary infections were seen in the group with CMV-seronegative patients with seropositive or seronegative donors. Six patients developed CMV disease: pneumonia (n=4), gastritis (n=1) and encephalitis (n=1). All were CMV-seropositive. The disease developed despite pre-emptive treatment with ganciclovir in 3 patients. In the other 3 patients pre-emptive therapy was omitted because of protocol violation (MRD: n=2, MUD: n=1). Four of the 6 patients died from CMV pneumonia, including the 3 not receiving pre-emptive therapy. Two, while successfully treated for CMV disease, died from other causes: varicella-zoster pneumonia -one year after CMV disease- and aspergillus pneumonia -3 months after CMV disease-. Primary graft failure was observed in two patients (1 MRD, 1 MUD), as was secondary graft failure.
In Table 2 causes of mortality are described. “Other causes” of TRM consist of: acute respiratory distress syndrome (ARDS), acute liver failure, pancreatitis with multi-organ failure, cerebral bleeding or infarction, cardiac toxicity, thrombotic or idiopathic thrombocytopenic purpura (ITP or TTP) with bleeding and suicide. Mortality from infections was significantly higher in CMV-seropositive MUD recipients compared to seronegative recipients (38% vs 8%, p=0.016).

Analyses in MRD recipients

Overall survival Median and mean follow up was 20 and 34 (range 1-118) months, respectively. Median survival was 43 months (CI 95%: 14-72 months). Five year overall survival was 47% (CI 95%: 39-55%). From Table 3 and 4 it appears that after univariate and multivariate analyses, high-risk disease status (p<0.001 and 0.001, respectively) and extensive cGVHD (p<0.001) were adverse risk factors for overall survival. After univariate analysis older age significantly affected OS (p=0.003), however, after multivariate analysis a

Table 1 Patient characteristics

	MRD patients (n=205)	MUD patients (n=48)	P
Age, mean years (range)	40 (16-58)	31 (17-48)	<0.001
Diagnosis			
AML cr1	35 (17)	2 (4)	
AML>cr1	7 (3)	6 (13)	
ALL cr1	17 (8)	1 (2)	
ALL>cr1	4 (2)	6 (13)	
CML cp1	32 (16)	8 (17)	
CML>cp1	7 (3)	8 (17)	
SAA	4 (2)	8 (17)	
NHL	27 (13)	0	
MDS	10 (5)	4 (8)	
MM	46 (22)	0	
Other	16 (8)	5 (10)	
CMV serostatus R/D			
+/+	66 (32)	10 (21)	ns
+/-	35 (17)	14 (29)	
-/+	30 (15)	11 (23)	
-/-	74 (36)	13 (27)	
Source			
BM	183 (89)	48 (100)	
PB	22 (11)		
Risk status			
Low	82 (40)	18 (38)	ns
High	123 (60)	30 (62)	
aGVHD			
I	67 (33)	15 (32)	0.086
II-IV	103 (50)	18 (38)	
III-IV	8 (4)	7 (15)	
No	35 (17)	14 (30)	
cGVHD			
Lim	50 (29)	4 (12)	0.032
Ext	47 (27)	8 (24)	
No	78 (45)	22 (65)	
CMV reactivation			
Yes	26 (13)	12 (25)	0.054
No	179 (87)	36 (75)	
CMV disease			
Yes	3 (1.5)	3 (6)	
No	202 (98.5)	45 (94)	

Data are no. (%) of patients, unless otherwise indicated; AML = acute myeloid leukemia; ALL = acute lymphoid leukemia; CML = chronic myeloid leukemia; SAA = severe aplastic anaemia; NHL = non-hodgkin lymphoma; MDS = myelodysplastic syndrome; MM = multiple myeloma; R/D =recipient/donor; BM = bone marrow; PB = peripheral blood; aGVHD = acute graft-versus-host disease; cGVHD = chronic graft-versus-host disease; Lim = limited; Ext = extensive.

Table 2 Causes of Mortality

	CMV serostatus Recipient/Donor							
	+/+		+/-		-/+		-/-	
	MRD	MUD	MRD	MUD	MRD	MUD	MRD	MUD
No. of patients	35	9	23	11	16	6	31	5
Relapse	12	2	10	2	9	4	12	3
TRM	23	7	13	9	7	2	19	2
CMV disease	1	1	1	1	0	0	0	0
EBV-LPD	0	2	2	1	2	2	3	0
Infections (other)	10	1	3	3	3	0	6	0
GVHD	4	1	1	2	0	0	2	1
IP/toxicity	1	0	4	0	1	0	4	1
VOD	3	0	0	0	1	0	0	0
Other	4	2	2	2	0	0	4	0

EBV-LPD = Epstein-Barr virus associated lymphoproliferative disease; IP = interstitial pneumonia; VOD = veno-occlusive disease.

Table 3 Univariate analyses of OS and TRM in MRD recipients

	OS in MRD	TRM in MRD
	P	P
Recipient CMV serostatus (pos vs neg)	ns	ns
Donor CMV serostatus (pos vs neg)	ns	ns
Age (continuous)	0.003	0.002
Risk status (high vs low)	< 0.001	0.040
R/D sexe (male/female vs other)	ns	0.057
Source (pb vs bm)	ns	0.028
T cell (graft) (continuous)	ns	ns
aGVHD (II-IV vs other)	ns	ns
cGVHD (extensive vs other)	< 0.001	< 0.001
CMV reactivation (yes vs no)	ns	0.020

Abbreviations: see Table 1.

trend towards decreased survival was observed (p=0.066). The effect of CMV serostatus was analysed in two ways. First, the 4 groups with all possible patient/donor CMV serostatus combinations were analysed separately (patient/donor: R+/D+, R+/D-, R-/D+, R-/D-). In a second analysis, the group with CMV-seropositive patients (irrespective of donor serology) was compared to the group with CMV-seronegative patients. After both analyses no significant differences were observed. Adjusted probability of OS according to recipient CMV serostatus is displayed in Figure 1.

Furthermore, donor CMV serostatus did not affect outcome. In contrast to the MUD group, 35% of MRD recipients were multiple myeloma or lymphoma patients. Analyses without these patients gave fully comparable results.

Transplant related mortality TRM at one year was 23% (CI 95%: 17-29%). From Table 3 it appears that TRM was determined by extensive cGVHD (p<0.001), older age (p=0.002), CMV reactivation (p=0.020), source (PB) (p=0.028), high-risk disease status (p=0.040) and recipient/donor sexe (R^m/D^f) (p=0.057) after univariate analyses. After multivariate analysis (Table 4) only extensive cGVHD (p<0.001) and age (p=0.002) predicted increased TRM. Adjusted probability of TRM according to recipient CMV serostatus is displayed in Figure 1.

Analyses in MUD recipients

Overall survival Median and mean follow up was 8 and 20 (range 1-102) months, respectively. Median survival was 7 months (CI 95%: 4-10 months). Five year overall survival in MUD recipients was 30% (CI 95%: 14-46%). Overall survival in MUD recipients was

Table 4 Multivariate analyses of OS and TRM in MRD recipients

	Overall Survival			Transplant Related Mortality		
	RR	**95% CI**	**P value**	**RR**	**95% CI**	**P value**
cGVHD (ext. vs other)	2.70	1.68-4.36	< 0.001	3.71	2.01-6.86	< 0.001
Risk status (high vs low)	2.12	1.36-3.28	0.001			ns
Age (continuous)	1.02	1.00-1.04	0.066	1.04	1.02-1.07	0.002

Abbreviations: see Table 1.

Figure 1

Adjusted probability of overall survival and transplant related mortality in MRD recipients according to recipient CMV serostatus.

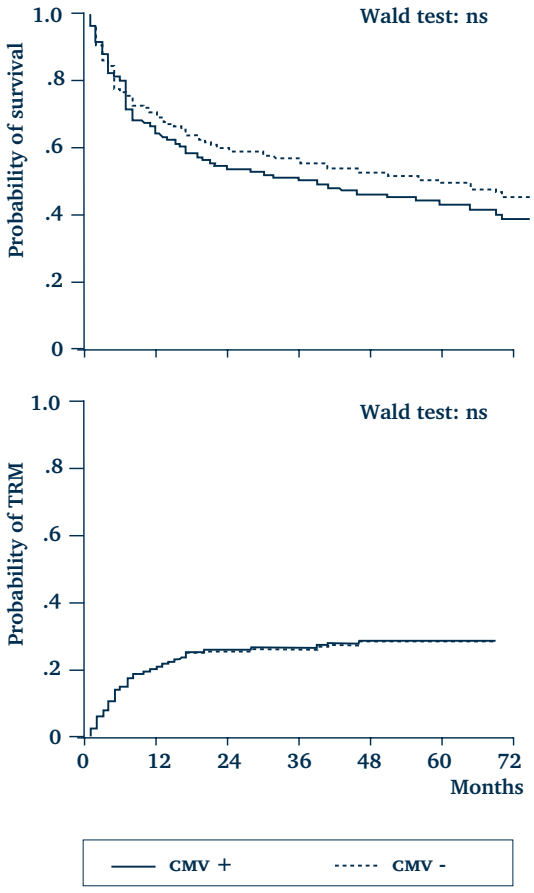


Table 5 Univariate analyses of OS and TRM in MUD recipients

	OS in MRD	TRM in MRD
	P	P
Recipient CMV serostatus (pos vs neg)	0.007	< 0.001
Donor CMV serostatus (pos vs neg)	ns	ns
Age (continuous)	0.051	ns
Risk status (high vs low)	ns	ns
p/d sexe (m/f vs other)	ns	ns
T cell (graft) (continuous)	ns	ns
aGVHD (II-IV vs other)	ns	0.002
cGVHD (extensive vs other)	ns	ns
CMV reactivation (yes vs no)	ns	0.066

Abbreviations: see Table 1.

strongly determined by CMV serostatus (p=0.007) after univariate analyses; age was a less important factor (p=0.051) (Table 5). Again the effect of CMV serostatus was analysed in two ways. First, the 4 groups with all possible patient/donor CMV serostatus combinations were analysed separately (patient/donor: R+/D+, R+/D-, R-/D+, R-/D-). Overall, the groups differed significantly (p=0.027), which could be ascribed to differences between group 1 (R+/D+) and 4 (R-/D-) (p=0.012), group 1 (R+/D+) and 3 (R-/D+) (p=0.062) and group 2 (R+/D-) and 4 (R-/D-) (p=0.068). In a second analysis, the group with CMV-

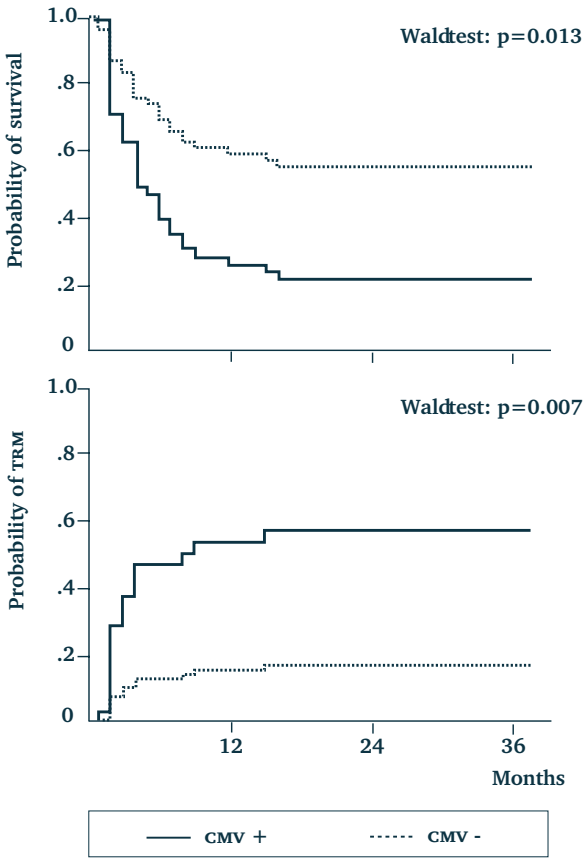
Table 6 Multivariate analyses of OS and TRM in MUD recipients

	Overall Survival			Transplant Related Mortality		
	RR	95% CI	P value	RR	95% CI	P value
Recipient CMV serostatus (pos vs neg)	2.77	1.22-5.40	0.013	4.60	1.51-14.00	0.007
aGVHD (II-IV vs other)			ns	2.94	1.15-7.51	0.024

Abbreviations: see Table 1.

Figure 2

Adjusted probability of overall survival and transplant related mortality in MUD recipients according to recipient CMV serostatus.



seropositive patients (irrespective of donor serology) was compared to the group with CMV-seronegative patients, which revealed a highly significant difference (p=0.007). After multivariate analysis (Table 6 and Figure 2) only a positive recipient CMV serostatus influenced OS (p=0.013), with no effect of donor serostatus.

Transplant related mortality After univariate analysis recipient CMV-seropositivity ($p<0.001$) and aGVHD ($p=0.002$) showed a strong adverse effect on TRM (Table 5), which was also observed after multivariate analysis (recipient CMV-seropositivity: $p=0.007$; aGVHD: $p=0.024$; Table 6 and Figure 2). Cumulative incidence curves for time to aGVHD showed no effect of recipient CMV serostatus on probability of developing aGVHD by day 100 post-transplant. After univariate analysis CMV reactivation also affected TRM. This effect disappeared after multivariate analysis, which is logical given the strong effect of a positive CMV serostatus. TRM at 1 year for all MUD recipients was 37% (CI 95%: 23-51%). In CMV-seropositive recipients one year TRM was 58% (CI 95%: 38-78%) and in CMV-seronegative recipients 17% (CI 95%: 2-32%).

Discussion

Our data show that recipient and/or donor CMV-seropositivity was not predictive for OS and TRM in patients treated with partial T cell depleted bone marrow transplantation from matched related donors, receiving low-dose short-term pre-emptive and prophylactic treatment with ganciclovir. In contrast, in MUD recipients, patient (but not donor) CMV-seropositivity had a great impact on overall survival. In our institution CMV reactivation was monitored by the CMV pp65 antigenemia assay and pre-emptive therapy with ganciclovir was given when antigenemia was demonstrated. Prophylactic therapy was given when CMV-seropositive patients had to be treated with high-dose steroids for aGVHD grade II-IV. A previous study of our group showed that none of the 41 CMV seropositive MRD patients, monitored and treated similar as described above, developed CMV disease[10]. Now we found that 3 of 205 MRD patients (1.5%) and 3 of 48 MUD recipients (6%) developed CMV disease.

Several studies have been published analysing the impact of CMV-seropositivity on OS and TRM in recipients of non-TCD grafts. In three of them outcome was not significantly influenced by patient and/or donor seropositivity[18-20], although in the study of Nichols et al[20] a borderline significant decreased survival was observed in the R-/D+ group compared to the R-/D- group. In MUD recipients only, patient CMV-seropositivity was an adverse risk factor for outcome[21,22], although this was not supported by a subgroup analysis by Nichols et al[20].

Two studies performed analyses among recipients of TCD grafts[23,24]. Broers et al[23] found patient and/or donor seropositivity to be associated with decreased survival and increased TRM in MRD recipients. They instituted pre-emptive treatment when 4 or more cells were positive in the antigenemia assay, used conventional dose ganciclovir, performed no T cell add back and gave no prophylactic therapy to seropositive patients with aGVHD grade II-IV. Results of a study among MUD recipients of TCD grafts[24] were comparable to studies performed among MUD patients receiving non-TCD grafts[21,22]. Overall, when TCD is performed or not, CMV serostatus seems not to influence outcome in MRD recipients in the era of pre-emptive treatment. However, CMV-seropositive MUD recipients were found to have a decreased survival in nearly all studies. In a large EBMT mega file analysis the effect of donor serostatus was analysed in CMV-seropositive recipients. In MRD recipients donor serostatus did not affect outcome. In MUD recipients of non-TCD transplants outcome was improved in those receiving seropositive grafts[25]. We did not observe a positive impact of donor seropositivity in CMV-seropositive recipients, neither in MRD recipients nor in MUD recipients. This is in concordance with the findings of the EBMT study[25], since all our patients received (partial) TCD grafts. In several reports the recovery of CMV-specific (CMVs) immune response was associated with the infusion of bone marrow from seropositive donors[26,27], probably by transfer of CMVs cytotoxic T cells. However, when TCD grafts are infused, CMVs immune recovery is probably not influenced by donor serostatus.

Recently it was demonstrated that CMV infection inhibited maturation and antigen-presenting function of dendritic cells, which can have severe and multiple consequences for T and B cell responses[28] and may contribute to the immunosuppressive effect of CMV infection[29]. It might be hypothesized that many CMV-seropositive transplant recipients suffer from sub clinical CMV infection, which is not detected by the antigenemia assay. Recovery of T cells after T cell depleted BMT is much more impaired in MUD recipients compared to MRD recipients, probably related to the use of ATG in MUD patients[30]. Therefore, considering the immunosuppressive effect of CMV infection, sub clinical CMV infection might be of more importance in MUD recipients compared to MRD recipients. Indeed, mortality from (viral and fungal) infections was higher in the CMV-seropositive MUD group compared to the CMV-seronegative group (38% vs 8%; $p=0.016$).

In conclusion, CMV-seropositivity should not be considered an adverse risk factor for OS and TRM in MRD recipients of partial T cell depleted grafts, when an appropriate prevention of CMV disease is applied. In patients receiving grafts from MUDs, patient (but not donor)

CMV-seropositivity has a high impact on overall survival, may be due to further impairment of immune reconstitution in this already heavily immune suppressed patient population. Approaches that will lead to a better T cell immune reconstitution after TCD stem cell transplantation from unrelated donors are probably necessary to improve outcome in CMV-seropositive MUD recipients.

References

1 Meyers JD, Flournoy N, Thomas ED. Risk factors for cytomegalovirus infection after human marrow transplantation. J Infect Dis 1986; 153: 478-488.

2 Bowden RA, Slichter SJ, Sayers MH et al. Use of leukocyte-depleted platelets and cytomegalovirus-seronegative red blood cells for prevention of primary cytomegalovirus infection after marrow transplant. Blood 1991; 78: 246-250.

3 Verdonck LF, de Graan-Hentzen YCE, Dekker AW et al. Cytomegalovirus seronegative platelets and leukocyte-poor red blood cells from random donors can prevent primary cytomegalovirus infection after bone marrow transplantation. Bone Marrow Transplant 1987; 2: 73-78.

4 van Prooyen HC, Visser JJ, van Oostendorp WR et al. Prevention of primary transfusion-associated cytomegalovirus infection in bone marrow transplant recipients by the removal of white cells from blood components with high-affinity filters. Br J Haematol 1994; 87: 144-147.

5 de Gast GC, Boland GJ, Vlieger AM et al. Abortive human cytomegalovirus infection in patients after allogeneic bone marrow transplantation. Bone Marrow Transplant 1992; 9: 221-225.

6 Schmidt GM, Horak DA, Niland JC et al. A randomized controlled trial of prophylactic ganciclovir for cytomegalovirus pulmonary infection in recipients of allogeneic bone marrow transplants. N Engl J Med 1991; 324: 1005-1011.

7 Goodrich JM, Bowden RA, Fisher L et al. Ganciclovir prophylaxis to prevent cytomegalovirus disease after allogeneic marrow transplant. Ann Intern Med 1993; 118: 173-178.

8 Winston DJ, Ho WG, Bartoni K et al. Ganciclovir prophylaxis of cytomegalovirus infection in allogeneic bone marrow transplant recipients. Ann Intern Med 1993; 118: 179-184.

9 Boeckh M, Gooley TA, Myerson D et al. Cytomegalovirus pp65 antigenemia-guided early treatment with ganciclovir at engraftment after allogeneic marrow transplantation: a randomized double-blind study. Blood 1996; 88: 4063-4071.

10 Verdonck LF, Dekker AW, Rozenberg-Arska M, van den Hoek MR. A risk adapted approach with a short course of ganciclovir to prevent cytomegalovirus (CMV) pneumonia in CMV-seropositive recipients of allogeneic bone marrow transplantation. Clin Infect Dis 1997; 24: 901-907.

11 Thomas ED, Storb R, Clift RA et al. Bone marrow transplantation. N Eng J Med 1975; 292: 832-843.

12 Verdonck LF, Dekker AW, de Gast GC et al. Allogeneic bone marrow transplantation with a fixed low number of T cells in the marrow graft. Blood 1994; 83: 3090-3096.

13 Schirm J, Timmerije W, van der Bij W et al. Rapid detection of infectious cytomegalovirus in blood with aid of monoclonal antibodies. J Med Virol 1987; 23: 31-40.

14 van der Bij W, Torensma R, van Son WJ et al. Rapid immunodiagnosis of active cytomegalovirus infection by monoclonal antibody staining of blood leukocytes. J Med Virol 1988; 25: 179-188.

15 Reisner Y, Kirkpatrick D, Dupont B et al. Transplantation for acute leukaemia with HLA-A and B nonidentical parental marrow cells fractionated with soybean agglutinin and sheep red blood cells. Lancet 1981; 15: 327-331.

16 Slaper-Cortenbach ICM, Wijngaarden-du Bois MJGJ, de Vries-van Rossen A et al. The depletion of T cells from haematopoietic stem cell transplants. Rheumatology 1999; 38: 751-754.

17 Meijer E, Slaper-Cortenbach ICM, Thijsen SFT, Dekker AW, Verdonck LF. Increased incidence of EBV-associated lymphoproliferative disorders after allogeneic stem cell transplantion from matched unrelated donors due to a change of T-cell depletion technique. Bone Marrow Transplant 2002; 29: 335-339.

18 Humar A, Wood S, Lipton J et al. Effect of cytomegalovirus infection on 1-year mortality rates among recipients of allogeneic bone marrow transplants. Clin Infect Dis 1998; 26: 606-610.

19 Peggs KS, Preiser W, Kottaridis PD et al. Extended routine polymerase chain reaction surveillance and pre-emptive antiviral therapy for cytomegalovirus after allogeneic transplantation. Br J Haematol 2000; 111: 782-790.

20 Nichols WG, Corey L, Gooley T et al. High risk of death due to bacterial and fungal infection among cytomegalovirus (CMV)-seronegative recipients of stem cell transplants from seropositive donors: evidence for indirect effects of primary CMV infection. J Infect Dis 2002; 185: 273-282.

21 Kröger N, Zabelina T, Krüger W et al. Patient cytomegalovirus seropositivity with or without reactivation is the most important prognostic factor for survival and treatment-related mortality in stem cell transplantation from unrelated donors using pretransplant in vivo T-cell depletion with antithymocyte globulin. Br J Haematol 2001; 113: 1060-1071.

22 Castro-Malaspina H, Harris RE, Gajewski J et al. Unrelated marrow transplantation for myelodysplastic syndromes: outcome analysis in 510 transplants facilitated by the national marrow donor program. Blood 2002; 99: 1943-1951.

23 Broers AEC, van der Holt R, van Esser JWJ et al. Increased transplant-related morbidity and mortality in CMV-seropositive patients despite highly effective prevention of CMV disease after allogeneic T-cell-depleted stem cell transplantation. Blood 2000; 95: 2240-2245.

24 Craddock C, Szydlo RM, Dazzi F et al. Cytomegalovirus seropositivity adversely influences outcome after T-depleted unrelated donor transplant in patients with chronic myeloid leukaemia: the case for tailored graft-versus-host disease prophylaxis. Br J Haematol 2001; 112: 228-236.

25 Ljungman PT, Brand R, Einsele H et al. Donor CMV serostatus influences outcome after unrelated donor stem cell transplantation; an EBMT megafile analysis. Blood 2001; 98: S480a. Abstract.

26 Cwynarski K, Ainsworth J, Cobbold M et al. Direct visualization of cytomegalovirus-specific T-cell reconstitution after allogeneic stem cell transplantation. Blood 2001; 97:1232-1240.

27 Li CR, Greenberg PD, Gilbert MJ et al. Recovery of HLA-restricted cytomegalovirus (CVM)-specific T-cell responses after allogeneic bone marrow transplant: correlation with CMV disease and effect of ganciclovir prophylaxis. Blood 1994; 83: 1971-1979.

28 Moutaftsi M, Mehl AM, Borysiewicz LK, Tabi Z. Human cytomegalovirus inhibits maturation and impairs function of monocyte-derived dendritic cells. Blood 2002; 99: 2913-2921.

29 Verdonck LF, de Gast GC. Is cytomegalovirus infection a major cause of T cell alterations after (autologous) bone-marrow transplantation? Lancet 1984; 8383: 932-935.

30 Meijer E, Bloem AC, Dekker AW, Verdonck LF. Effect of Antithymocyteglobulin on quantitative immune recovery and graft-versus-host disease after partially T cell depleted bone marrow transplantation: a comparison between recipients of matched related and matched unrelated donor grafts. Transplantation 2003; 75: 1910-1913.