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T cell depletion

Excessive T cell depletion of peripheral blood stem cells has an adverse effect upon outcome following allogeneic stem cell transplantation

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Summary:

We evaluated the outcome of two modes of T cell depletion for HLA-identical sibling stem cell transplants in 34 consecutive adult patients: group A ($n = 11$) received PBSC post CliniMACs immuno-magnetic enrichment of CD34$^+$ cells and group B ($n = 23$) received bone marrow following *in vitro* incubation with CAMPATH-1M and complement. All patients received an identical conditioning regimen which consisted of *in vivo* CAMPATH-1H 20 mg over 5 days, thiotepa 10 mg/kg, cyclophosphamide 120 mg/kg and 14.4 Gy TBI. No additional graft-versus-host disease prophylaxis was given. The mean T cell dose administered was $0.02 \pm 0.05 \times 10^6$/kg for group A and 2.8 ± 2.8 10^6/kg for group B ($P < 0.001$). With a median follow-up of 28 months overall survival was 36.4% for group A at 12 months compared to 78.3% for group B ($P = 0.001$). Transplant-related mortality in group A at 12 months was 63.6% as compared to 18.0% in group B ($P = 0.003$). Most of the procedure-related deaths in group A occurred secondary to infection. These results suggest that extensive *in vitro* T cell depletion of peripheral blood stem cells in combination with *in vivo* T cell depletion may have profound effects upon the incidence of infections following allogeneic stem cell transplantation and this may adversely effect transplant-related mortality. *Bone Marrow Transplantation* (2001) **28,** 827–834.

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T cell depletion (TCD) is an effective means of reducing the incidence and severity of acute or chronic graft-versus-host disease (GVHD) following allogeneic stem cell transplantation (SCT).[1–4] A number of different methods for TCD have been developed over the last two decades that include counter-flow elutriation,[2] lectin agglutination,[4] monoclonal antibodies directed at T cell antigens with narrow[5] or broad specificity[1] or depletion through positive selection of CD34$^+$ stem cells.[6,7] The clinical benefit of TCD allogeneic SCT is controversial since this approach may be compromised by increased rates of graft rejection[8] and a higher rate of relapse.[9] To overcome the risk of graft rejection additional approaches have been adopted that include increasing pre-transplant immunosuppression,[10] 'partial' TCD[11] or increasing the number of stem cells administered by using peripheral blood stem cells (PBSCs).[12,13] The optimal T cell content of a graft that maintains a significant graft-versus-leukaemia (GVL) effect has not yet been defined. Although TCD is used widely by many different transplant centres, few studies have assessed directly how different modes of TCD affect clinical outcome.

One area of potential concern is the significant delay in immune reconstitution that occurs following TCD allogeneic SCT. This is particularly the case in adults, where the initial T cell repertoire is dependent upon peripheral expansion of mature T cells in the graft.[14–16] Delayed recovery of CD4$^+$, CD4$^+$CD45RA$^+$ and TCR$\gamma\delta^+$ T cells with a concomitant reduction in TCR diversity are typical features of the early post-transplant period following TCD allogeneic SCT.[16–19] T cell purging may thus exacerbate post-transplant immunodeficiency and be complicated by an increased incidence of opportunistic infections, particularly CMV re-activation.[20]

In this report, we highlight the major impact on clinical outcome of two approaches to *in vitro* TCD, using either positive selection of CD34$^+$ cells from PBSC or CAMPATH 1M treatment of bone marrow, as part of a protocol that employed additional *in vivo* TCD. Patients who received donor PBSCs heavily depleted of T cells (5 log) by immuno-magnetic selection of CD34$^+$ cells had a substantially higher procedure-related mortality than recipients of CAMPATH 1M-treated bone marrow. The higher number of procedure-related deaths was caused by a marked increase in the number of opportunistic infections within the TCD PBSC group. This study suggests that following HLA-identical sibling SCT in adults, extensive *in vitro* TCD of PBSC in combination with *in vivo* TCD is compli-

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cated by a profound immunodeficiency that outweighs any benefit in terms of reduction of GVHD.

Patients and methods

A total of 34 consecutive adult patients who received a TCD HLA-identical sibling donor stem cell transplant at University College Hospital London, UK between January 1997 and October 1999, were included in the analysis. During this period, the method of *in vitro* TCD was changed due to an insufficient supply of CAMPATH 1M. The protocols were approved by the local institutional review committees and all patients gave informed consent. Two groups of patients were defined according to the mode of T cell depletion employed: 'group A' consisting of 11 patients who received PBSC following CliniMACs immuno-magnetic enrichment of $CD34^+$ cells and 'group B' comprising 23 who received bone marrow following *in vitro* incubation with CAMPATH 1M and complement.

Patient characteristics

The patient characteristics for each group are shown in Table 1. Patients were considered to be 'standard risk' in the case of acute myeloid leukaemia (AML) in first complete remission (CR) or chronic myeloid leukaemia (CML) in first chronic phase.[21] All other diagnoses were considered high risk. There were no significant differences between the groups in terms of age, sex, performance status at the time of transplant, time to transplant or those at risk of CMV disease (Table 1). However, only one patient in group A was considered to be high risk as compared to 11 of 23 patients in group B ($P = 0.05$). This reflected, in part, the lack of patients with lymphoproliferative disorders in group A. Three patients in group B had received a previous SCT and none in group A.

Table 1 Comparison of groups A and B

	Group A (n = 11)	*Group B (n = 25)*	*P value*
Sex, male/female (*n*)	5/6	4/19	
Median, age years (range)	41 (26–51)	41 (17–59)	
Diagnosis (*n*)			
AML CR1	8	7	
AML CR2	1	2	
MDS	0	3	
MM	0	2	
HD	0	2	
HG-NHL	0	1	
CML 1st cp	2	5	
CML ap	0	1	
Risk status, standard/high	10/1	12/11	0.05
Median time to transplant, months (range)	6.5 (2–17)	7.5 (4–57)	
Previous transplant	0	3	
CMV serology (*n*)			
P–/D–	5	4	
P+/D–	0	3	
P–/D+	4	8	
P+/D+	2	8	

MDS = myelodysplastic syndrome; MM = multiple myeloma; HD = Hodgkin's disease; HG-NHL = non-Hodgkin's lymphoma; 1st cp = first chronic phase; ap = accelerated phase; P = patient; D = donor.

Antibodies

CAMPATH-1H is a humanized IgG1 monoclonal antibody against the CD52 antigen.[22] It was prepared from the culture supernatant of Chinese hamster ovary cell transfectants cultured in a hollow fibre fermentor. It was purified by affinity chromatography on Protein A sepharose and size exclusion chromatography on Superdex 200 and formulated in phosphate-buffered saline. The half-life of CAMPATH-1H in humans is dependent on the amount of target CD52 antigen in the patient. Based on work in progress, there is persistence of CAMPATH-1H *in vivo* post day 0 sufficient to cause T cell lysis by ADCC. CAMPATH-1M is a rat IgM antibody that recognises the same antigen. It was prepared from hybrid myeloma cells using stirred fermentors, purified by fractionation with ammonium sulphate and reformulated in phosphate-buffered saline.

Conditioning regimen

All patients received the same conditioning regimen which consisted of *in vivo* CAMPATH-1H 20 mg on days −9 to day −5, thiotepa 5 mg/kg on days −8 and −7, cyclophosphamide 60 mg/kg on days −6 and −5 and 14.4 Gy total body irradiation, with partial lung shielding, in eight fractions over 4 days.

For stem cell collection for group A patients, sibling donors received G-CSF at 10 μg/kg subcutaneously once daily on day −4 to day 0. Leukaphereses were performed on day 0 ± day +1 using conventional techniques for PBSC. TCD was performed by positive immuno-magnetic selection of $CD34^+$ cells using a CliniMACs, (Miltenyi Biotec, Bergisch Gladbach, Germany) cell separation system.[23]

For group B patients, donor bone marrow was aspirated under general anaesthesia and TCD performed *in vitro* upon the derived buffy coats by incubation with 25 mg CAMPATH 1M at room temperature for 10 min followed by incubation with 10–30% autologous plasma at 37°C for 45 min.

For both protocols, the level of TCD was monitored by flow cytometric analysis of CD3 staining.

Supportive care

Patients were managed in reverse isolation in conventional or laminar air flow rooms. All patients received prophylaxis with cotrimoxazole or pentamadine against *Pneumocystis carinii* infection. Aciclovir and triazole prophylaxis were routinely used. Blood products were irradiated to 25 Gy. Red cell and platelet transfusions were given to maintain the Hb >9 g/dl and platelet count $>10 \times 10^9$/l. Patients who were CMV seronegative received only blood products from CMV seronegative donors; seropositive patients received blood products from donors unscreened for CMV. Febrile neutropenic patients received intravenous piptazobactam and gentamicin as first line antibiotic therapy. Patients received G-CSF at 5 μg/kg/day from day +6 until

the ANC was at least 1.0×10^9/l for 2 consecutive days. CMV seropositive patients were monitored weekly from transplantation until at least day 120 by qualitative PCR of CMV DNA from peripheral blood. Pre-emptive ganciclovir therapy (5 mg/kg twice daily intravenously or adjusted according to renal function) was given following two consecutive positive PCR results and discontinued after 2 weeks if a negative PCR was obtained.[24] In the event of continued PCR positivity, foscarnet was substituted for ganciclovir and the drugs alternated every 2 weeks according to the PCR results. A single patient (UPN5) received cidofovir as initial pre-emptive therapy for PCR detection of CMV re-activation.

GVHD prophylaxis and grading

No additional GVHD prophylaxis was given. Patients who survived 100 days or longer were evaluable for chronic GVHD. Both acute GVHD and chronic GVHD were graded according to the consensus criteria.[25,26]

Evaluation of infective complications

An infective complication was defined as any infection occurring post day 21 which required continued or new hospital admission/referral. CMV re-activation was defined as two consecutive peripheral blood PCR positive results. CMV disease was diagnosed on the basis of an inflammatory process due to CMV confirmed by the presence of typical cytopathic and immuno-fluorescent features in histological preparations or positive detection of early antigen fluorescent foci (DEAFF) and/or CMV culture from relevant material such as washings from broncho-alveolar lavage (BAL). Pulmonary fungal infection was diagnosed either by histological confirmation or characteristic high resolution CT appearances (halo sign) plus positive cultures from a BAL. Fungal infection at other sites was identified from post-mortem histological analysis of affected organs. RSV, parainfluenza I and III or influenza B infection were defined as pulmonary signs plus direct immunofluorescence and/or culture for the relevant viruses from naso-pharyngeal aspirate or BAL. Confirmation of Legionaire's disease was made by the presence of urinary *Legionella* antigen on two consecutive occasions and confirmed by post mortem histological examination of lung. Adenoviral, RSV and measles infection were confirmed by histological examination of the relevant organs postmortem. Pneumonia was defined as fever, associated with signs of lung consolidation and new infiltrates identified on chest X-ray or high resolution CT.

Statistical analysis

Overall survival (OS) was measured from transplantation until death from any cause. Patients still alive at the time of the analysis were censored at the last follow-up date. Transplant-related mortality (TRM) was determined from the date of transplantation until death related to transplantation. Patients who died from other causes were censored at the time of death. OS and TRM were estimated by the Kaplan–Meier method and the significance of differences between the curves was estimated by the log rank test. Patient characteristics in the two groups were compared by Fisher's exact test or the Mann–Whitney test, whichever was appropriate.

Results

T cell depletion

Patients in group A received approximately 2 log less T cells than group B patients (Table 2). The mean T cell dose was $0.02 \pm 0.05 \times 10^6$/kg for group A recipients and 2.8 ± 2.8 10^6/kg for group B patients ($P < 0.001$). Three patients in group A had 'add-back' of donor T cells following the transplant (Table 2). Two of these patients, UPN6 and UPN8, received 1×10^6/kg T cells at 4 and 5 months,

Table 2 Patient and graft characteristics

UPN	*Age*	*Sex*	*Diagnosis*	*CD34⁺ dose*[a]	*T cell dose*[a]
Group A					
1	51	F	AML CR1	4.6	0.0005
2	37	F	AML CR1	5.1	0.02
3	49	M	CML 1st cp	2.1	0.004[b]
4	26	M	AML CR1	3	0.0006
5	44	M	AML CR1	6.8	0.005
6	38	M	AML CR1	2.4	0.2[b]
7	44	F	AML CR1	4.5	0.0005
8	43	F	AML CR1	6.7	0.00007[b]
9	27	M	AML CR2	4.8	0.003
10	35	F	AML CR1	6.4	0.0007
11	41	F	CML 1st cp	2	0.0007
Group B					
12	44	M	MM PR	ND	ND
13	17	F	AML CR1	1.6	0.5
14	28	M	HD Rel 2	2	ND
15	41	F	HD Rel 2	3.1	6.6
16	41	M	AML CR1	1.2	1
17	40	F	AML CR1	4.2	3[b]
18	46	M	AML CR1	2.9	1.7
19	27	M	MDS RAEB	0.7	2.8
20	46	F	MM PR	0.7	0.6[b]
21	36	M	CML 1st cp	1.6	1.1
22	36	M	HG-NHL CR3	1	0.3
23	37	M	MDS RA	3.2	10.5
24	45	F	AML CR2	1.4	0.6
25	59	M	CML ap	1.87	2.4
26	26	F	AML CR1	1.4	2.1
27	57	M	CML 1st cp	ND	7.4
28	36	M	AML CR1	0.4	0.07
29	57	M	MDS RAEB	0.7	2.9
30	44	M	CML 1st cp	1	4.7
31	56	F	CML 1st cp	2	0.2
32	38	F	AML CR1	1	6.4
33	37	F	CML 1st cp	1.3	4.2
34	42	M	AML CR2	1.7	3.9

[a]$\times 10^6$ cells/kg recipient weight.
[b]Patients had donor lymphocyte infusions at following doses $\times 10^6$ CD3 cells/kg recipient weight (time post transplant in months): UPN3 (10+); UPN6, 1 (4+); UPN8, 1 (5+); UPN17, 3 (11+); and UPN20, 202 (12+).
MDS = myelodysplastic syndrome; RA = refractory anaemia; RAEB = refractory anaemia with excess blasts; MM = multiple myeloma; HD = Hodgkin's disease; HG-NHL = non-Hodgkin's lymphoma; 1st cp = first chronic phase; ap = accelerated phase; Rel = relapse; PR = partial response; ND = not done.

respectively, because of progressive pulmonary infections. UPN3 was given 3×10^6/kg T cells for cytogenetic relapse of CML at 10 months. Two patients in group B received donor T cells. UPN17 received 3×10^6/kg T cells at 11 months for relapsed AML and UPN20 received 2×10^8/kg T cells for treatment of relapsed multiple myeloma.

Engraftment

The mean $CD34^+$ cell dose per patient was $4.4 \pm 1.8 \times 10^6$/kg in group A and $1.7 \pm 1.0 \times 10^6$/kg in group B ($P < 0.001$). Neutrophil engraftment occurred more rapidly in group A, with neutrophils $>0.5 \times 10^9$/l on day 12.0 ± 2.1 compared to day 17.2 ± 4.0 for group B ($P < 0.001$). One patient in group B failed to engraft and died on day +74. All patients in group A engrafted. No cases of secondary graft failure occurred in either group. No differences were observed between the groups in terms of transfusional independence by day 100 (four of seven evaluable patients in group A as compared to 15 of 22 evaluable patients in group B were transfusion independent).

GVHD

The incidence of acute GVHD was low in both groups (Table 3). No patients in group A developed acute GVHD of greater than grade I as compared to two of 23 patients in group B. For patients who survived day 100 no difference in either the incidence or extent of chronic GVHD was observed. Thus, three of seven evaluable patients in group A developed chronic GVHD (extensive in all cases) as compared to 11 of 22 patients in group B (extensive in three patients and limited in the remaining eight patients).

In both groups, patients who received T cell add-back post SCT were at high risk for the development of extensive chronic GVHD. Thus, four of five patients who received a donor T cell infusion following the transplant subsequently developed extensive chronic GVHD. One patient (UPN3) died of progressive GVHD at 12 months following SCT and 2 months following infusion of 3×10^6/kg donor T cells for relapsed CML. The remaining patients have all required prolonged treatment with prednisolone and cyclosporine.

Infective complications

Most of the deaths in group A occurred secondary to infection (Table 3). Thus, at 12 months six of 11 patients in group A died secondary to infection (CMV disease $n = 2$, invasive pulmonary aspergillosis (IPA) $n = 1$, RSV/measles pneumonits $n = 1$, *Legionella* $n = 1$, *E. coli* sepsis $n = 1$) compared to only one of 23 patients (adenovirus) in group B ($P = 0.002$).

The propensity to infection in group A is also highlighted by the greater number of documented serious infections post day 21 in group A than in group B (Table 4). Thus, with a median follow-up of 28 months, four of 11 patients in group A had three or more significant infections as compared to one of 23 in group B ($P = 0.03$). Furthermore, patients in group A were more likely to have co-existent infections, with six of 11 patients in group A having two or more simultaneous infections as compared to only two of 23 patients in group B ($P = 0.005$). In a number of patients from group A, infection progressed despite the appropriate anti-microbial therapy. Patients UPN2 and UPN6 both developed IPA which failed to respond to conventional, and then liposomal amphotericin therapy. Patient UPN2 also developed a large, deep skin ulcer secondary to HSV II (proven on culture and biopsy), which failed to respond to aciclovir, foscarnet or cidofovir. Patient UPN5 developed CMV colitis and pneumonitis despite pre-emptive therapy with foscarnet and cidofovir and subsequent therapy with ganciclovir and intravenous immunoglobulin.

There were no significant differences between the two groups in terms of the frequency of CMV reactivation in that five of six CMV seropositive individuals in group A and 11 of 19 in group B met the criteria for pre-emptive treatment for CMV reactivation or CMV disease. The median total duration of anti-CMV therapy administered was 98 days (range 8–127 days) in group A and 33 days in group B (range 13–129 days). Two patients from group A died from CMV disease in group A and none from group B.

Immune reconstitution

Group A patients showed a significant delay in the recovery of the absolute lymphocyte count following transplant. Thus, at 2 months post transplant the absolute lymphocyte count was $>1.0 \times 10^9$/l in none of nine evaluable patients in group A but 10 of 21 patients in group B ($P = 0.01$). Absolute lymphocyte numbers for the first 5 months for both groups are shown in Figure 1. Analysis of T cell subsets at our centre is usually performed at 3 monthly intervals post transplant. The poor outcome of patients in group A meant that the majority were not evaluated and thus an evaluation of T cell subset reconstitution was not possible.

Overall survival and transplant-related mortality

With a median follow-up of 28 months the overall survival (OS) and TRM for all 36 patients at 12 months were 64.7% and 33.0%, respectively. However, there was a major difference in OS between the groups (Figure 2). Thus, at 12 months OS was 36.4% for group A and 78.8% for group B ($P = 0.001$). This difference was accounted for to a great extent by the high number of procedure-related deaths in group A (Figure 3). At 12 months the TRM was 63.6% in group A and 18.0% in group B ($P = 0.003$). The causes of procedure-related deaths for the whole group are shown in Table 3. The median time for procedure-related death in group A was 87 days (range 28–221 days) and in group B was 184.5 days (range 74–287 days). All but one of the procedure-related deaths in group A were secondary to infection.

Discussion

This report highlights important differences in the outcome of HLA-identical sibling SCT following two approaches to

Table 3 Patient outcome

UPN	*Neutrophils* $>0.5 \times 10^9/l$	*aGVHD*	*cGVHD*	*Infections*[a]	*Current status (months)*	*Cause of death*
Group A						
1	10	0	0	1	Alive in CR 19+	
2	10	I	E	4	Dead	IPA
3	17	I	E	1	Dead	Relapse
4	13	0	0	0	Alive in CR 13	
5	11	0	0	2	Dead	CMV Pn
6	11	I	E	5	Alive in CR 12+	
7	13	0	0	1	Dead	IP
8	10	0	0	4	Dead	Measles/RSV
9	11	0	NE	0	Dead	*E. coli* sepsis
10	14	0	NE	3	Dead	*Legionella* Pn
11	12	0	NE	2	Dead	CMV Pn
Group B						
12	21	0	0	1	Dead	Relapse
13	19	0	0	0	Alive in CR 37+	
14	14	0	0	1	Alive in CR 37+	
15	14	0	0	3	Dead	Adenovirus
16	16	0	0	0	Alive in CR 35+	
17	17	0	E	1	Alive-relapse 11+	
18	17	0	0	0	Alive in CR 35+	
19	23	0	0	1	Alive in CR 35+	
20	14	III	E	1	Dead	Relapse
21	30	0	0	2	Alive in CR 34+	
22	15	0	0	0	Alive in CR 34+	
23	19	0	0	1	Alive in CR 34+	
24	11	0	0	2	Dead	ARDS
25	16	0	L	2	Alive in CR 29+	
26	15	I	0	1	Alive in CR 27+	
27	13	0	L	2	Alive in CR 25+	
28	21	0	0	0	Alive in CR 24+	
29	16	0	0	2	Alive in CR 23+	
30	19	0	E	1	Alive in CR 19+	
31	17	0	L	0	Dead	EBV-LPD
32	NA	0	NE	1	Dead	Graft failure
33	17	II	E	1	Alive in CR 16+	
34	15	0	0	1	Alive in CR 11+	

[a]Infections post day 21.
L = limited; E = extensive; Pn = pneumonitis; IP = idiopathic pneumonitis; IPA = invasive pulmonary aspergillosis; CMV = cytomegalovirus; RSV = respiratory syncitial virus; ARDS = adult respiratory distress syndrome; EBV-LPD = Epstein–Barr virus-associated lymphoproliferative disorder; NE = not evaluable.

in vitro TCD, using either positive selection of $CD34^+$ cells from PBSC or CAMPATH 1M treatment of bone marrow. Patients in both treatment groups received additional *in vivo* TCD, identical conditioning and no post-transplant immunosuppression. We found that allogeneic SCT using PBSC heavily depleted of T cells by immuno-magnetic selection of $CD34^+$ cells, was associated with prolonged lymphocytopenia and an extremely high number of opportunistic infections leading to a high rate of procedure-related deaths. In contrast, allogeneic SCT using *in vitro* CAMPATH 1M treatment of bone marrow was associated with a lesser depletion of T cells, fewer infections and more rapid immune reconstitution. Both strategies were effective at preventing acute GVHD, and excluding those patients who received donor lymphocytes post transplant, at preventing extensive chronic GVHD. There was a low risk of graft rejection in both groups. Since the follow-up is relatively short and there are too few long-term survivors in group A, no conclusions can be made regarding the risk of relapse.

It seems likely that the overall determinant of clinical outcome in this report was degree of T cell depletion. There are five important qualifications to this statement. First, the type of graft differed in each group, such that patients in group A received PBSC and patients in group B received bone marrow. Thus, there may have been both quantitative (eg the number of $CD34^+$ cells or $CD34^+CD38^+$ lymphocyte progenitors)[27] and qualitative differences (eg the balance between Th1 or Th2 T cells)[28] that could have conceivably affected outcome. However, to our knowledge, there are no substantive clinical data to support the contention that these differences could account for such a poor outcome in the PBSC arm. Second, exact comparison of the degree of TCD for the two methods is difficult since following $CD34^+$ cell selection nearly all the remaining T cells will be viable whereas this may not be the case following *in vitro* treatment with CAMPATH 1M.[29] Indeed, antibody coated T cells may undergo further lysis when they encounter fresh complement following infusion. Furthermore, pre-transplant *in vivo* CAMPATH 1-H treatment could have resulted

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