Risks of Developing Epstein-Barr Virus–Related Lymphoproliferative Disorders After T-Cell–Depleted Marrow Transplants

By Geoff Hale and Herman Waldmann for CAMPATH Users

T-cell depletion of bone marrow for allogeneic transplantation is known to increase the risks of Epstein-Barr virus–driven lymphoproliferative disorders that may result in fatal lymphoma, especially with transplants from unrelated or mismatched donors. Over the past 15 years, we have monitored the outcome of 2,582 transplants using CAMPATH-1 (CD52) antibodies to deplete lymphocytes from donor and/or recipient to prevent graft-versus-host disease or rejection. Unlike many other methods of T-cell depletion, CAMPATH-1 antibodies also deplete B lymphocytes. The actuarial risk of lymphoproliferative disease using CAMPATH-1 for depletion of donor lymphocytes was up to 1.3%, hardly different from reported figures for conventional nondepleted transplants. In contrast, the risk in a small group of patients transplanted from unrelated donors using E-rosette depletion was as high as 29%, comparable to other reports of specific T-cell depletion. We conclude that the additional depletion of B cells is beneficial, possibly because it reduces either the virus load or the virus target until the time when T cells begin to regenerate.

B-CELL LYMPHOPROLIFERATIVE disorders (BLPD) related to infection with Epstein-Barr virus (EBV) are a well-recognized complication of intensive immunosuppression for organ transplantation[1-3] and a comparatively infrequent complication of allogeneic bone marrow transplantation (BMT).[4-8] Latent EBV is present in the majority of patients and donors and causes uncontrolled proliferation of B cells under conditions of intense immunosuppression. This can rapidly lead to a progressive and highly lethal lymphoma. Risk factors include severe graft-versus-host disease (GVHD), HLA incompatibility between donor and recipient, T-cell depletion of the donor bone marrow, and especially the use of certain anti–T-cell monoclonal antibodies.[5,9-12] Treatments such as discontinuance of immunosuppression or administration of antivirals (eg, acyclovir), interferon, or monoclonal antibodies have had only limited success,[4,5,11,13,14] but in recent years it has been shown that infusions of modest numbers of donor T cells can be extremely effective in bringing the B-cell proliferation under control.[15,16]

A recent report[12] described 65 children who received non–HLA-identical BMT at one institution. Nine of them (14%) suffered from BLPD, in contrast with none of 77 children who received HLA-identical BMT. BLPD was associated with a particular regimen that included monoclonal antibodies (CAMPATH-1G and anti-LFA1) for conditioning the recipients, together with T depletion by E-rosetting. These results are consistent with other reports of a particularly high incidence of BLPD after transplantation of T-depleted bone marrow from non–HLA-identical donors.[5,10]

The majority of EBV lymphomas occur in donor B cells.[9,17] Latently infected donor B cells may be a significant source of infection,[18] but there are cases of lymphoma in B cells from a seronegative donor, indicating that virus already present in the recipient may cause proliferation of donor B cells.[5] It is also possible that EBV may come from an exogenous third-party source (eg, blood transfusion). Whatever the origin of virus, we wondered whether removal of donor B cells would diminish the risk of BLPD after T-cell–depleted BMT. The CD52 monoclonal antibodies CAMPATH-1M (IgM) and CAMPATH-1G (IgG) have been widely used for T-cell depletion,[19-21] but they also recognize and deplete B cells equally as well.[22] We have reviewed the records of transplants performed by CAMPATH users to identify possible cases of BLPD.

MATERIALS AND METHODS

CD52 antibodies. CAMPATH-1M (rat IgM) and CAMPATH-1G (rat IgG2b) monoclonal antibodies were produced by the Therapeutic Antibody Centre and supplied to BMT centers for a variety of physician-initiated trials to prevent GVHD and/or transplant rejection.[20] CAMPATH-1M was used with human complement in vitro for depletion of T cells to prevent GVHD. CAMPATH-1G was used in three different ways: (1) in vitro (without complement) to opsonize donor T cells, marking them for destruction in vivo; (2) in vivo before the transplant to deplete recipient T cells to prevent rejection; and (3) in vivo at or just after the transplant to deplete donor cells and prevent GVHD. Combinations of these modes of antibody treatment were used in different trials as described more fully in Hale et al.[20]

Informed consent was obtained for participation in study protocols and submission of data to the CAMPATH registry according to the normal procedure at each center.

Statistical analysis. A database is maintained with details and outcome of all BMTs using these antibodies. We believe it is comprehensive, because it correlates with the antibody distribution records. Between July 1982 and May 1996, a total of 2,578 transplants were recorded, and all of them were reviewed to identify any suspect cases of BLPD. The collaborating transplant centers were contacted with a written questionnaire to obtain confirmation of the suspect cases and to discover whether there were any others that had not been reported. Replies were received from 46 of 54 centers, representing 97% of the patients in the database. Eight new cases were identified from the survey, but 4 of them occurred since May 1996 and were therefore not included in this analysis because we do not yet have details of all patients transplanted in this period (approximately 3 to 400 patients). The results were analyzed by the method of T-cell depletion and the match between donor and recipient. Statistical comparisons were performed using the χ^2 test, log rank survival analysis, or Mann-Whitney U test, as appropriate.

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Table 1. Patients With Confirmed or Suspect BLPD

Case No.	Sex/ Age	Disease	Donor	Transplant Date	Rejection Prophylaxis	T-Cell Depletion Method	GVHD Prophy-laxis	Graft Failure	Acute GVHD	Chronic GVHD	Day of Diag-nosis	Survival (d)	Comments
1	F/30	AML	HLA-id sib	Nov 02, 84	None	CP-1M in vitro	None	No	No	No	270	D 270	
2	M/36	CML	HLA-id sib	Jun 11, 86	None	CP-1M in vitro	None	No	No	No	522	D 522	Possibly relapse, not BLPD
3	M/29	CML	HLA-id sib	Mar 5, 87	None	CP-1G in vitro	CyA	No	Yes	No	118	D 139	
4	M/48	CML	Unrelated	July 20, 87	CP-1G	CP-1M in vitro	None	No	Yes	Yes	122	D 122	
5	M/1	Thal	Non-id family	July 13, 88	None	CP-1M in vitro	None	No	No	No	120	D 122	
6	F/39	CML	Unrelated	Apr 19, 90	CP-1G	CP-1G in vitro	CyA	No	Yes	NA	85	D 87	
7	F/17	AML	HLA-id sib	Jul 16, 90	CP-1G	CP-1M in vitro	None	No	No	No	205	A 300	Lost to follow-up
8	M/3	WA	Parent	Dec 22, 90	CP-1G, LFA-1	E-rosette	CyA	No	No	NA	32	D 40	
9	M/41	CML	Unrelated	Feb 22, 91	CP-1G	CP-1M in vitro	CyA	No	Yes	NA	108	D 108	
10	F/6	AML	Unrelated	Mar 7, 91	CP-1G, LFA-1	E-rosette	CyA	No	No	NA	81	D 87	
11	F/7	AML	Unrelated	Feb 13, 92	CP-1G, LFA-1	E-rosette	Mtx/CyA	No	Yes	Yes	55	D 124	
12	M/8	CML	Unrelated	Aug 13, 92	CP-1G, LFA-1	E-rosette	Mtx/CyA	No	Yes	No	80	D 125	
13	F/15	ALL	Unrelated	Sep 17, 92	CP-1G, LFA-1	E-rosette	Mtx/CyA	No	No	NA	59	D 82	
14	M/26	CML	Unrelated	Oct 14, 92	CP-1G	CP-1G in vivo	Mtx/CyA	No	Yes	NA	116	D 116	
15	F/43	CML	HLA-id sib	Oct 29, 92	CP-1G	CP-1G in vitro	None	No	No	No	177	D 245	
16	M/13	ALD	Unrelated	Jul 5, 93	CP-1G, LFA-1	CP-1M in vitro	Mtx/CyA	Yes	NA	NA	59	D 71	
17	M/61	MDS	HLA-id sib	May 9, 94	CP-1G	CP-1M in vitro	None	Yes	NA	NA	231	D 236	
18	F/40	CML	HLA-id sib	Jul 5, 95	None	CP-1G in vitro	None	No	Yes		347	D 370	
19	F/31	CML	Unrelated	Sep 15, 95	CP-1G	CP-1G in vivo	Mtx/CyA	No	Yes	Yes	162	D 180	
20	M/48	CML	HLA-id sib	Oct 6, 95	None	CP-1M in vitro	CyA	No	No	No	244	A 540	Responded to donor T cells

Abbreviations: AML, acute myeloid leukemia; CML, chronic myeloid leukemia; Thal, thalassemia; WA, Wiskott-Aldrich syndrome; ALL, acute lymphocytic leukemia; ALD, adrenoleukodystropy; MDS, myelodysplastic syndrome; NA, not applicable.

RESULTS

Cases of EBV-associated lymphoproliferative disease. A total of 20 possible cases of BLPD were identified (Table 1). The distribution with respect to patient's original disease, age, year of transplant, donor or recipient gender, and occurrence of graft rejection or graft failure was unremarkable. All cases occurred within the first year posttransplant (which is typical), with the exception of case no. 2, a patient who died at 17 months posttransplant of secondary lymphoma. In this case, there was no positive diagnosis of EBV, and it was considered possible that the lymphoma represented progression of the original malignancy (chronic myeloid leukemia [CML]). However, it has been included as a case of possible BLPD for the purpose of this analysis. Most of the cases occurred before the era of therapy with donor lymphocyte infusions and progression was generally very rapid. Sometimes the diagnosis was only made postmortem. However, case no. 20 has been successfully treated with donor T-cell infusions.

Analysis according to transplant protocol. The frequency of BLPD was analyzed according to the relationship between donor and recipient and according to the method of T-cell depletion (Table 2). Transplants from HLA-identical siblings were considered in one group and all other transplants (mismatched family donors and unrelated donors) in another. Most patients received marrow depleted of T and B cells with CAMPATH-1 antibodies either in vitro (marrow was treated with CAMPATH-M or CAMPATH-1G before infusion) or in vivo (the patient was treated with CAMPATH-1G on and/or after the day of transplant). Many patients also received CAMPATH-1G and occasionally other monoclonal antibodies as part of the conditioning regime to prevent rejection. The number of patients who received antibody therapy for rejection prophylaxis is shown in Table 2. Some of the patients who received lymphocyte-depleted bone marrow also received infusions of small numbers of donor lymphocytes (T-cell addback), sometimes at the time of transplantation[23] and sometimes

Table 2. Analysis of Lymphoma and Lymphoproliferative Disease According to Type of Match and Method of T-Cell Depletion

	HLA-Identical Sibling Donors			Other Donors		
Method of Lymphocyte Depletion of Donor	Total No. of Patients	Rejection Prophylaxis With CAMPATH-1G	Cases of Lymphoma	Total No. of Patients	Rejection Prophylaxis With CAMPATH-1G	Cases of Lymphoma
None	62	62	0	82	82	0
CAMPATH-1 in vitro (complete depletion)	1,019	332	8 (1.3%)*	622	479	5 (1.3%)
CAMPATH-1 in vitro (with T-cell addback)	258	31	0	45	30	0
CAMPATH-1 in vivo	84	84	0	374	374	2 (0.9%)
E-rosette	0	NA	NA	20	20	5 (29.0%)†
Other methods	6	6	0	10	10	0

Abbreviation: NA, not applicable.

*The actuarial risk at 2 years posttransplant of developing lymphoma or BLPD was calculated by life table analysis.

†The result for E-rosette depletion is significantly different from CAMPATH-1 depletion ($P < .0001$).

during the following 3 months.[24] The dose was typically in the range of 10^4 to 10^6 per kilogram. These patients have been analyzed separately.

Smaller groups of patients had no T-cell depletion or received bone marrow depleted of T cells by E-rosetting[25] or by an alternative methodology (12 with T-cell–specific antibodies plus rabbit complement, 2 with elutriation, and 2 with CD34 selection). In all these cases, CAMPATH-1G was used as part of the conditioning regimen.

There was no case of BLPD in the 144 nondepleted transplants. Among 20 patients transplanted from mismatched or unrelated donors with E-rosette depletion, there were 5 cases of BLPD (actuarial risk, 29% ± 16% at 2 years). In 2,401 transplants in which donor T cells were depleted with CAMPATH-1M or CAMPATH-1G, there were 15 patients who suffered from BLPD and/or secondary lymphoma (actuarial risk, 1.1% ± 0.4% at 2 years). There was no significant difference between sibling and nonsibling donors, and we could not detect an association with the use of antibody for rejection prophylaxis or any particular antibody protocol. There were no cases of BLPD in the subset of 303 patients who received T-cell addback, but this is still not a large enough number to be significantly different from the patients with complete T-cell depletion.

The median age of the E-rosette cases (7 years) was less than that of the CAMPATH cases (36 years), but this simply reflects the difference in the populations treated by the two methods.

Time to onset of BLPD. Diagnosis of BLPD was earlier among patients transplanted from unrelated donors or mismatched family donors (median, day 85) compared with HLA-identical sibling donors (median, day 238; $P < .001$, Mann-Whitney test). This difference is still significant if we exclude the doubtful case no. 2 ($P < .005$) or analyze days of survival rather than days to diagnosis ($P < .001$) or exclude the E-rosette patients ($P < .005$). Among the nonsibling donors, diagnosis was also earlier in the patients who received E-rosette–treated marrow (median, day 59) compared with CAMPATH-1–treated marrow (median, day 116; $P < .003$). However, this difference is no longer significant if we compare survival times. Because all the E-rosette patients were children treated at a single center, we surmise that BLPD might have been diagnosed sooner than in the disparate group of CAMPATH-1 patients observed at many different centers.

Measurement of residual T cells. The percentage of residual T cells in bone marrow treated by CAMPATH-1M and complement was estimated by E-rosette analysis or flow cytometry and reported for a large proportion of the patients (828/1,267). For HLA-matched siblings, the median total nucleated cell dose was 2.1×10^8/kg and the median proportion of residual T cells was 0.4%, giving a dose of approximately 8×10^5 T cells/kg infused. For other donors, the median total nucleated cell dose was 3.6×10^8/kg and the median proportion of residual T cells was 0.2%, giving a dose of approximately 7×10^5 T cells/kg infused. It is very likely that these figures are an overestimate of the number of functional donor T cells, because lymphocytes coated with CAMPATH-1M antibody that escaped lysis in vitro may still be lysed when they encounter additional complement in vivo. By the same token, it is not possible to measure the extent of cell lysis with CAMPATH-1G, because complement was not added in vitro and much of the cell lysis would occur after infusion of the marrow. Residual numbers of T cells were not reported for the bone marrow depleted by the E-rosette method.

DISCUSSION

The risks of BLPD after lymphocyte depletion with CAMPATH-1 are not substantially different from those reported for conventional BMTs in which there was no T-cell depletion. For example, Zutter et al[5] report 5 cases among 1,868 HLA-identical sibling transplants (0.45%) and 3 among 386 HLA-mismatched transplants (1.4%). However, the frequency of BLPD seen by CAMPATH users is substantially lower than that described in many other protocols of more specific T-cell depletion, whether using E-rosettes or other monoclonal antibodies where actuarial risks up to and exceeding 20% have been reported.[4,10,12,15,26]

A group of 20 patients who received marrow depleted by albumin gradient and E-rosette treatment were reported by one center to the CAMPATH users registry. These patients all received CAMPATH-1G as part of the conditioning regimen and were included in the 65 patients previously reported in Gerritsen et al.[12] We observed that they suffered an exceptionally high incidence of BLPD (29%). This group was not directly comparable with the rest of the CAMPATH-1–depleted patients for several reasons: (1) the average age was significantly lower (all were children), (2) all were transplanted from unrelated donors (18) or parents (2), and (3) a unique conditioning regime was used including a CD11a (LFA-1) antibody as well as CAMPATH-1G.[12] It is not possible to directly compare the levels of T-cell or B-cell depletion achieved by the different methods in the clinical cases, because data were not reported for the E-rosette–depleted marrow and a significant amount of cell lysis may occur in vivo with the CAMPATH-1 antibodies, especially CAMPATH-1G. However, there are numerous published data that show that both methods can give a profound degree of T-cell depletion when measured by functional analysis such as limiting dilution. For example, Frame et al[27] found 99.4% depletion of T cells by CAMPATH-1M plus complement, compared with 99.8% by soybean agglutinin plus E-rosettes. Jabado et al[26] compared the depletion measured by immunophenotyping with limiting dilution analysis. By staining with anti-CD3, they found a mean of 3.1×10^5 T cells/kg infused after CAMPATH-1M depletion and 1.6×10^5 after E-rosette depletion. However, the number of viable T cells estimated by limiting dilution analysis was more than 10-fold lower for the CAMPATH-1M–depleted samples.

The most conclusive evidence for the extent of T-cell depletion achieved with CAMPATH-1M or CAMPATH-1G is the effective prevention of GVHD that is achieved in the absence of posttransplant immunosuppression in both HLA-matched and mismatched transplants.[19-21] It is conceivable that a few T cells are spared, particularly if they are $CD52^-$,[28] and perhaps these are sufficient to control any emerging B cells. More likely, we think that the CAMPATH-1 will have depleted the donor B cells and thus removed both a potential reservoir of latent virus and its immediate target.

If donor B cells are preserved (eg, by E-rosette depletion), but CAMPATH-1G was administered to the recipient (to prevent

rejection), we anticipate the highest risk; indeed, this is borne out by other reports.[12,26]

It has often been remarked that the risk of BLPD is higher for mismatched transplants than for transplants from HLA-identical donors.[4,10,12] It would not be surprising if mismatched patients were at greater risk due to higher levels of immunosuppression and relatively impaired recovery of T-cell immunity. However, this effect was not seen in the CAMPATH-1–depleted transplants. Possibly the depletion of donor B cells by CAMPATH-1 is sufficient to overcome the other risk factors (eg, see Gerritsen et al[12]). Most of the patients also received CAMPATH-1G in vivo for prevention of rejection. This would have depleted any residual recipient B cells as well, and we cannot exclude a beneficial effect by this mechanism. However, it seems less likely, because we saw no association between the incidence of BLPD and the use (or not) of CAMPATH-1G in vivo.

T-cell depletion is currently enjoying a renaissance of interest after the success of transplants with peripheral blood stem cells. The ability to infuse large numbers of stem cells may overcome any problems of graft rejection or delayed engraftment that were previously seen with T-cell–depleted bone marrow. The possibilities of storing cryopreserved donor T cells or harvesting fresh ones may enable effective treatment of relapse and of viral infections including cytomegalovirus and EBV.[29] We suggest that the recipient EBV status should be checked before transplantation and that a negative result should be taken into account in deciding future management. However, if donor B cells can be removed from the transplant along with the T cells, the risks of developing lymphoproliferative disease would appear to be substantially reduced.

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