To the editor:

CMV infection following nonmyeloablative allogeneic stem cell transplantation using Campath

We would like to comment on the recent report by Chakrabarti et al[1] on the risk of cytomegalovirus (CMV) infection following nonmyeloablative allogeneic transplantation. The conditioning regimen utilized by the authors consisted of fludarabine, melphalan, and a total dose of 100 mg of alemtuzumab (Campath-1H) given over 5 days. They found an 84.3% probability of CMV infection in patients at high (seropositive recipient) or intermediate (seronegative recipient, seropositive donor) risk. The authors suggested that the use of alemtuzumab in the conditioning regimen was responsible for the high rate of CMV infection observed and that attenuation of the alemtuzumab dose might reduce this risk. We would like to report on our experience of CMV infection following reduced intensity transplantations using a lower dose of Campath (50 mg) that suggests that this might not be the case.

Between January 1997 and June 2002, 2 reduced intensity conditioning regimens containing Campath were used concurrently. BEAM-Campath (Carmustine [BCNU] 300 mg/m^2 day −6, cytosine arabinoside 200 mg/m^2 days −5 to −2, etoposide 200 mg/m^2 days −5 to −2, melphalan 140 mg/m^2 day −1) was used for lymphoproliferative disorders.[2] Fludarabine (30 mg/m^2 days −9 to −7) was added to this regimen for unrelated donor transplantations (Flu BEAM-Campath). A second conditioning regimen consisting of fludarabine 30 mg/m^2 days −7 to −3, melphalan 140 mg/m^2 day −2, and Campath (FMC) was used primarily for other hematologic malignancies. In both regimens Campath was given on days −5 to −1 at a dose of 10 mg/day to a total dose of 50 mg. Initially, Campath-1G antibodies were used but were replaced by alemtuzumab given in the same dose and schedule from May 2000.

A total of 69 patients underwent transplantation, of which 36 were at risk of CMV infection (CMV seropositive recipient or donor). Patients received unmanipulated bone marrow or granulocyte colony-stimulating factor (G-CSF)–mobilized peripheral blood stem cells from a sibling (n = 25) or matched unrelated donor (n = 11). Detailed patient characteristics are shown in Table 1. In brief, the median age was 50.1 years (range, 23.6-59.9 years), 18 patients received fludarabine as part of the conditioning regimen (Flu BEAM-Campath or FMC), and 18 received BEAM-Campath. CMV screening was undertaken weekly by polymerase chain reaction (PCR) from day +14 to day +120. CMV infection was defined as PCR positivity on one assay confirmed on repeat testing.

Table 1. Patient characteristics

	BEAM-Campath, n = 18	Fludarabine-based conditioning,* n = 18
Male/Female	15/3	12/6
Median age, y (range)	48.7 (23.6-59.5)	51.8 (31.8-59.9)
Diagnosis		
AML	0	3
MM	0	3
Lymphoma/CLL	18	7
CML/MPD	0	4
MDS	0	1
HLA compatibility		
HLA-matched relative	14	5
1 antigen mismatch sibling	4	2
Matched unrelated donor	0	11

AML indicates acute myeloid leukemia; MM, multiple myeloma; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; MPD, myeloproliferative disease; and MDS, myelodysplastic syndrome.

*Flu BEAM-Campath or FMC.

Overall, 28 (77.8%) of 36 patients developed CMV infection. We analyzed a number of risk factors for the development of CMV infection in this cohort including type of transplantation, use of fludarabine in the conditioning, and the type of Campath used. As reported by Chakrabarti et al, there was no significant difference in the risk of CMV infection between recipients of sibling and unrelated transplantations. However, there was a significantly higher rate of CMV infection in those patients receiving fludarabine (17 of 18) and those not receiving fludarabine (11 of 18; Fisher exact test, $P = .041$; Figure 1). There was no significant difference in the incidence of CMV infection between patients receiving alemtuzumab (15 of 16) and those receiving Campath-1G antibodies (13 of 20).

The median time to CMV infection was 7.3 weeks (range, 2.3-15.1 weeks). Patients receiving fludarabine-containing regimens had significantly earlier infection at a median of 4.3 weeks (range, 2.3- 15.1 weeks) compared to a median of 7.8 weeks (range, 5.3-12.3 weeks) after transplantation in the BEAM-Campath group (Figure 1; log-rank χ^2, $P < .001$).

Our overall incidence of CMV infection is similar to that reported by Chakrabarti et al.[1] We had been concerned that a change to alemtuzumab would be associated with an increased risk of CMV infection as the humanized antibody has a longer half-life in vivo than Campath-1G antibodies[2,3] and potentially may cause more prolonged immune suppression. However, we did not find an

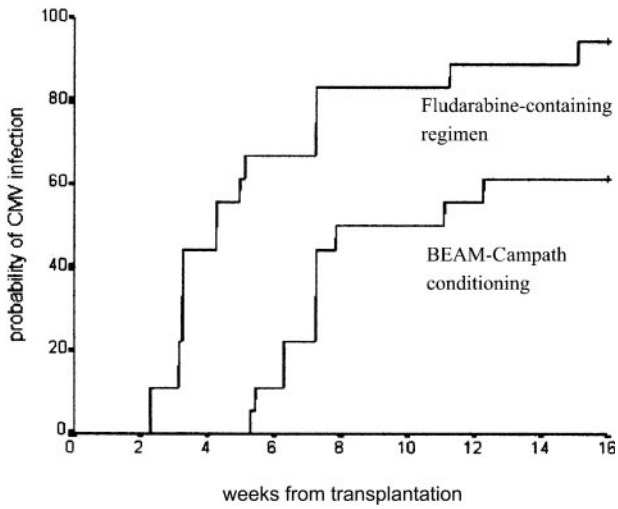

Figure 1. CMV infection after nonmyeloablative transplantation. A Kaplan-Meier graph shows the probability of developing CMV infection in patients receiving fludarabine-based conditioning (n = 18, events = 17) and patients receiving BEAM-Campath conditioning (n = 18, events = 11; $P < .001$).

increased incidence of CMV infection in the alemtuzumab group. Chakrabarti et al suggested that a reduction in the dose of alemtuzumab might reduce the risk of CMV infection. Our data, which uses half the dose of alemtuzumab, suggest that this may not be the case. Rather, we found that the inclusion of fludarabine in the conditioning regimen was associated with both a higher incidence of CMV infection and infection at an earlier time after transplantation. Fludarabine is highly immunosuppressive and even as a single agent can result in CMV reactivation.[4,5] We suggest that the combination of fludarabine and Campath is permissive to a higher risk of CMV infection and earlier CMV infection following reduced intensity allogeneic transplantations compared with patients who receive non–fludarabine-containing regimens such as BEAM-Campath. This may reflect the additional suppression by fludarabine of host CMV-specific T cells prior to the transplantation that might otherwise survive reduced intensity conditioning and thus offer some protection against CMV infection in the posttransplantation period.

Rowena D. Bainton, Jennifer L. Byrne, Barbara J. Davy, and Nigel H. Russell

Correspondence: Rowena D. Bainton, Haematology, Nottingham City Hospital, Hucknall Road, Nottingham, United Kingdom; e-mail: rowena.bainton@nottingham.ac.uk

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