measurement and to define relevant threshold values for high ERG and BAALC expression.

Anna Staffas
Department of Clinical Chemistry and Transfusion Medicine, University of Gothenburg, Gothenburg, Sweden

Meena Kanduri
Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden

Randi Hovland
Center of Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway

Richard Rosenquist
Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden

Hans Beier Ommen
Laboratory of Immunohematology, Department of Hematology, Aarhus University Hospital, Aarhus, Denmark

Jonas Abrahamsson
Department of Pediatrics, Sahlgrenska University Hospital, Gothenburg, Sweden

Erik Forestier
Department of Medical Biosciences, Umeå University, Umeå, Sweden

KirsI Jahnukainen
Department of Pediatrics, University Central Hospital of Helsinki, Helsinki, Finland

Ólafur G. Jónsson
Department of Pediatrics, University Hospital, Reykjavik, Iceland

Bernward Zeller
Department of Pediatrics, Oslo University Hospital, Oslo, Norway

Josefine Palie
Department of Women’s and Children’s Health, University Children’s Hospital, Uppsala, Sweden

Gudmar Lönnnerholm
Department of Women’s and Children’s Health, University Children’s Hospital, Uppsala, Sweden

Henrik Hasle
Department of Pediatrics, Aarhus University Hospital Skejby, Aarhus, Denmark

Hans Ehrencreona
Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden

Lars Palmqvist
Department of Clinical Chemistry and Transfusion Medicine, University of Gothenburg, Gothenburg, Sweden

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Correspondence: Lars Palmqvist, Institute of Biomedicine, Departmentof Clinical Chemistry and Transfusion Medicine, University of Gothenburg, SE-413 45 Gothenburg, Sweden; e-mail: lars.palmqvist@clinchem.gu.se.

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To the editor:

CMV-specific cellular therapy for acute myeloid leukemia?

We read with interest the recent paper by Elmaagacli et al documenting a striking association between early CMV replication after allogeneic transplantation and a subsequent reduction in relapse risk in patients with acute myeloid leukemia (AML).1 While the precise mechanism(s) underpinning the correlation remain obscure, the authors hypothesize that CMV-specific T cells with cross-reactive T-cell receptors, which were stimulated to expand by viral antigenemia, might be responsible. They further suggest that “controlled” induction of viral replication might be a future strategy to reduce relapse rates in these patients.

We use T cell–depleted conditioning regimens in patients with AML: an ablative regimen (120mg/kg cyclophosphamide, 14.4Gy TBI, plus 90mg/m² fludarabine with unrelated donors) along with in vitro alemtuzumab (20 mg mixed with the graft) in younger patients without significant comorbidities; a reduced intensity regimen (RIC; 150mg/m² fludarabine, 140mg/m² melphalan) with in vivo alemtuzumab in older patients or those with significant comorbidities. While alemtuzumab-containing regimens are associated with very high levels of CMV replication, the delayed T-cell reconstitution that characterizes their use would potentially eliminate the beneficial effects predicted by Elmaagacli et al, in much the same way as they suggest after CD34-selected grafts.1 However, during this period we have also performed a series of cellular immunotherapy studies, infusing CMV-specific T cell lines or directly-selected CMV-specific T cells.2-4 These have generally been infused early after transplantation, at which time the profound lymphopenia combines with viral antigen exposure to reproducibly induce massive expansions of CMV-specific T cells. This setting would therefore provide perhaps an ideal one in which to test their hypothesis on the protective effect of CMV-specific T cells. One hundred patients received transplants between January 2001 and January 2011, and survived more than 50 days after transplant
without relapse. None had refractory disease. All gave written informed consent for the transplant and for collection of the data presented here.

The cumulative incidence of relapse did not differ significantly according to donor source or conditioning intensity (Figure 1A-B). Disease status had the greatest impact (probably explaining the lack of positive impact of unrelated donors because transplants performed in CR1 more commonly used sibling donors), although not reaching statistical significance (Figure 1C). CMV replication was detected by quantitative PCR in 4/7 intermediate-risk patients (seronegative recipient/seropositive donor), 49/51 high-risk patients (seropositive recipient) and 0/42 low-risk patients (seronegative recipient/donor). The group with viral replication (PCR+) were well matched with those without (PCR-); no statistically significant differences in terms of age (median 45 [17-67] years versus 38 [15-66] years), conditioning (18/53 versus 15/47 RIC), donor source (27/53 versus 30/47 unrelated), or status at transplant (33/53 versus 29/47 CR1). The 5-year cumulative incidence of relapse was 22% in PCR- versus 28% in PCR+ patients (P = .4658, Figure 1D).

Nineteen patients received CMV-specific adoptive cellular therapy a median of 32 days after transplant. There were no significant differences in age, conditioning, or number in CR1 (12/19 versus 50/81), although this group included a higher number with related donors because of the inclusion criteria of the cellular immunotherapy studies (12/19 versus 31/81, P = .0707). We previously demonstrated the rapid kinetics of recovery of durable CMV-specific immunity in these patients. The 5-year cumulative incidence of relapse was 25%, versus 25% in those not receiving cellular immunotherapy (P = .7827, Figure 1E). While we appreciate that this is a retrospective study and that the number of patients receiving cellular immunotherapy is relatively low, we find no evidence for a protective effect of CMV-specific T cells. It is perhaps unlikely that a trial will be initiated to address this question directly, although 2 prospective national randomized studies of CMV cellular immunotherapy in the United Kingdom may provide further insights if sufficient patients with AML are enrolled.

Kirsty J. Thomson
Department of Haematology, UCL Cancer Institute, London, United Kingdom

Stephen Mackinnon
Department of Haematology, Royal Free Hospital, London, United Kingdom

Karl S. Peggs
Department of Haematology, UCL Cancer Institute, London, United Kingdom

Figure 1. Cumulative incidence of relapse. Comparative curves are shown according to (A) donor source, (B) intensity of conditioning, (C) disease status, (D) CMV replication detected by PCR, and (E) whether CMV-specific adoptive cellular therapy was given or not.
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Correspondence: Karl S. Peggs, Department of Haematology, UCL Cancer Institute 72 Huntley Street, London WC1E6BT, United Kingdom; e-mail: k.peggs@cancer.ucl.ac.uk.

References


Response:

T cells are required for the CMV-induced antileukemia effect after transplant

With great interest we read the letter by Thomson and coworkers who reported the results of their retrospective study evaluating the antileukemic effect of a CMV-replication after T cell–depleted transplantation using Campath in 100 patients with AML. Further, they evaluated the effect of a CMV-specific cellular therapy on the relapse incidence in 19 patients with AML after T cell–depleted transplantation. They found a 5-year cumulative incidence of relapse (CIR) of 22% in CMV PCR-positive patients versus 28% in PCR-negative patients, which was not statistically significant (P = .4658), whereas no difference in the 5-year CIR was found in 19 patients receiving a CMV-specific cellular therapy compared with 81 patients receiving no CMV-specific cellular therapy. Because of the small number of patients and the heterogeneity of donors and disease stages of patients in their study, they also found no statistical significant differences in the CIR with regard to disease stage in their patients (1.CR versus > 1.CR), or donor type (unrelated versus sibling donor), which might have influenced the incidence of relapse in AML after transplant, too. Furthermore, the time interval between the application of cellular therapy at a median of 32 days after transplant and time for inclusion of patients surviving 50 days in the study was too short to observe possible antileukemic effects from a CMV reactivation after transplant. In our study we addressed this issue by including only patients surviving 100 days after transplant.

However, we could confirm in a further retrospective study that patients with AML (n = 60) after myeloablative T cell–depleted transplantation using Campath (50 mg or 100 mg total dosage) did not benefit from a CMV-reactivation. The 5-year CIR for patients with CMV replication after transplant was 52.5% versus 50% in patients without detection of CMV replication (n.s.). These data as well as the study by Thomson and coworkers indicate clearly that T cells are required for the CMV-induced antileukemic effect after transplant. This is further supported indirectly by a multicentre study published recently by Craddock and coworkers who evaluated factors predicting outcome after unrelated donor stem cell transplantation without T-cell depletion in primary refractory AML. By performing a multivariate analysis they found that besides fewer than 3 courses of induction chemotherapy and a lower percentage of bone marrow blasts at transplant, patient CMV seropositivity was associated with an improved 5-year survival.

Thomson and coworkers have questioned the role of CMV-specific T cells with regard to relapse. The limited data provided by the authors are not sufficient enough to rule out an involvement of CMV-specific T cells in the antileukemic effect on AML of CMV-reactivation after transplant, since the number of applied CMV-specific T cells is comparably small with usually 1 × 10^6 T cells per kg/body weight of recipients in relation to the higher number of T cells of a non-T cell–depleted graft. However, how the complex mechanisms of CMV replication after transplant influence the relapse incidence remain unclear.

We appreciate this single-center analysis by Thomson et al and are eagerly awaiting results from other centers.

Ahmet H. Elmaagacli
Department of Bone Marrow Transplantation, West German Cancer Center, University of Duisburg-Essen, Essen, Germany

Michael Koldehoff
Department of Bone Marrow Transplantation, West German Cancer Center, University of Duisburg-Essen, Essen, Germany

Monika Lindemann
Institute of Transfusion Medicine, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

Marlene Sonius
Department of Bone Marrow Transplantation, West German Cancer Center, University of Duisburg-Essen, Essen, Germany

Markus Ditschkowski
Department of Bone Marrow Transplantation, West German Cancer Center, University of Duisburg-Essen, Essen, Germany

Nina Steckel
Department of Bone Marrow Transplantation, West German Cancer Center, University of Duisburg-Essen, Essen, Germany

Dietrich W. Beelen
Department of Bone Marrow Transplantation, West German Cancer Center, University of Duisburg-Essen, Essen, Germany

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Correspondence: Ahmet H. Elmaagacli, MD, Department of Bone Marrow Transplantation University Hospital of Essen, Hufelandstr 55, 45122 Essen, Germany; e-mail: ahmet.elmaagacli@uni-duisburg-essen.de.

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Kirsty J. Thomson, Stephen Mackinnon and Karl S. Peggs