SPECIAL REPORT

Mechanisms of graft-versus-leukemia effects after allogeneic stem cell transplantation: effects on the leukemia stem cell?

H-J Kolb^{1,2}, H Schmetzer^{1,2}, C Schmid^{1,2}, I Bigalke^{1,2}, R Buhmann^{1,2}, A Moosmann^{1,2}, C Falk^{1,2}, S Reuther^{1,2}, F Schuster^{1,2} and A Borkhardt^{1,2}*Leukemia Supplements* (2014) 3, S16–S17; doi:10.1038/leusup.2014.9**Keywords:** TBI; graft-versus-leukemia; allogeneic stem cell transplantation with T cell depletion; Transfusion of Donor Lymphocytes

Total body irradiation (TBI) was originally thought to be capable of eradicating leukemia, but with time it became apparent that we cannot eradicate this disease with TBI.¹ Today we know that graft-versus-leukemia effects are more important than previously thought. Strong evidence came from the depletion of T cells from the graft for the prevention of graft-versus-host disease (GVHD): the rate of relapses increased particularly in chronic myelogenous leukemia (CML),² and in some patients the graft was even rejected. However, some patients with refractory acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) were treated with intensive chemotherapy and a single dose of TBI and are alive and in remission today more than 30 years later. Therefore, the question arises whether immune therapy with lymphocytes from the stem cell donor can eradicate leukemia stem cells without the help of high-dose TBI or stem-cell toxic chemotherapy. The best clinical evidence for leukemia stem cells is provided by the occurrence of late relapses presumably arising from radio- and chemo-resistant, quiescent stem cells. Late relapses after allogeneic stem cell transplantation were observed in patients treated for CML³ and less frequently in those treated for AML and ALL.⁴ In these patients stem cells of leukemia may have been recruited from a quiescent state and may have given rise to open relapse.

It is known that hematopoiesis is the first target of the GVH reaction, leukemia cells of the host may be eliminated by donor T cells without severe sequelae, as the hematopoiesis of the host is replaced by donor hematopoiesis. To determine the optimal conditions for eliminating residual hematopoiesis of the host, we performed studies on dogs. In dogs, transplantation of anti-thymocyte globulin-treated (T-lymphocyte depleted) bone marrow from dog leukocyte antigen-identical littermates showed mixed chimerism and development of GVHD was prevented. Transfusion of donor lymphocytes (DLTs) produced fatal GVHD, if given within 60 days of marrow transplantation.⁵ After this time, DLT could be given without GVHD. Nevertheless, the degree of chimerism increased to complete chimerism in dogs given DLT, whereas those not given DLT remained mixed chimeras until the end of the observation period 8 years after transplantation. It is well established that after bone marrow transplantation complete chimerism is required to avoid recurrence of leukemia. This form of treatment, which was proven successful in dogs, was also thought to be applicable to humans. The treatment strategy included (i) allogeneic stem cell transplantation with T-cell

depletion, (ii) establishment of chimerism and tolerance, (iii) adoptive immunotherapy with donor lymphocytes. Prior to preemptive DLT we studied the treatment of leukemia relapse after transplantation with DLT. Two of three patients treated for recurrent CML⁶ are still in molecular remission more than 20 years later, one patient relapsed 20 years after treatment of relapse with DLT. In an EBMT study,⁷ it was shown that CML in hematological relapse and cytogenetic relapse showed the best response toward DLT; 70–80% of patients experienced cytogenetic remission. Relapse in transformed phase was less responsive and responses were not durable. In patients with progressive and relapsing MMY response rates were around 50%, but responses were also not durable. Response rates were less in AML and least in ALL patients.

Importantly, remissions in CML patients improved from clinical and cytogenetic remission toward molecular remission in 50% of patients after 6 months and in another 30–40% of patients after a year. We have speculated that the continued response in CML is due to the sustained production of dendritic cells by leukemic stem cell (Figure 1). The genetic marker of the Philadelphia chromosome was found in dendritic cells. Therefore, the GVL reaction continues as long as there are leukemia cells of the host differentiating. Moreover, we think that CD4 T cells are necessary to activate dendritic cells and to help CD8 T cells that recognize peptides of minor histocompatibility antigens presented by human leukocyte class I antigens. In ALL and AML, leukemic stem cells do not differentiate spontaneously into dendritic cells, hence the differences in responsiveness to the treatment.

There are multiple possible mechanisms of immune escape for leukemia cells, one of these may be the quiescence of the leukemia stem cell that does not proliferate and does not produce dendritic cells. CML cells from freshly diagnosed patients are to a large proportion human leukocyte antigen class II negative, and T cells of these patients are downregulated with downregulated ϵ -chain and ζ -chain of their T-cell receptor.⁸ However, T cells can be rescued by the treatment with interferon- α .⁹ According to these results, we have treated patients with low-dose interferon- α and escalating doses of DLT without the occurrence of GVHD or myelosuppression until BCR-ABL1 PCR has become negative; they experience a durable remission. In addition to the stimulation of dendritic cells and

¹Clinical Cooperative Group Haematopoietic Cell Transplantation, Department of Medicine III, University of Munich, Munich, Germany and ²Helmholtz Zentrum Muenchen—German Research Center for Environmental Health, Munich, Germany. Correspondence: Professor H-J Kolb, 3. Med. Klinikum rechts der Isar, Techn. Universitaet Muenchen, Ismaningerstr. 15, 81675 Muenchen, Germany.
E-mail: H-J.Kolb@lrz.tu-muenchen.de

Figure 1. Graft-versus-leukemia effect in CML.

rescue of T cells, interferon- α may have an activating effect on quiescent stem cells.¹⁰

CONFLICT OF INTEREST

H-JK and SH have received lecture fees from Neovii Fresenius Biotech EBMT and TEVA education. RB declares no conflict of interest.

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