IVYSPRING INTERNATIONAL PUBLISHER

Journal of Cancer

2011; 2:339-340

Short Report

Innovative Platforms for Haploidentical Stem Cell Transplantation: The Role of Unmanipulated Donor Graft

Fabio Ciceri, Marco Bregni, Jacopo Peccatori ✉

Hematology and BMT Unit, Department of Oncology, San Raffaele Scientific Institute, Milano, Italy

✉ Corresponding author: Fabio Ciceri MD, San Raffaele Scientific Institute, Via Olgettina 60, 20132, Milano, Italy. Phone +39 02 2643 3903; Fax +39 02 2643 4760; email: fabio.ciceri@hsr.it

Received: 2011.05.18; Accepted: 2011.06.01; Published: 2011.06.03

Abstract

We exploited the dual positive effects of rapamycin to prevent GvHD and control malignant cells upon infusion of unmanipulated grafts from family haploidentical donors to patients affected by advanced hematological malignancies. Preliminary results on 45 patients show the feasibility of this platform with an appreciable low rate of GvHD.

Key words: Stem Cell Transplantation, Haploidentical, Donor Graft

The great interest in transplantation from haploidentical donors arises from the immediate availability of a suitable one-haplotype mismatched donor for virtually all patients, particularly for those who urgently need a transplant. In the absence of a HLA full matched donor, alternative donors such as cord blood or haploidentical HSCT have been intensively investigated in the past decade[1]. The most experienced transplantation platform has been the T-cell depleted grafts with high cell dose of CD34+ cells coming from family haploidentical donors. Progress have been made in the optimization of conditioning regimens and graft selection to allow a stable hematopoietic engraftment across major HLA-barriers, with promising leukemia-free survivals in adults with acute leukemias. The largest series has been reported by the Acute Leukemia Working Party registry of EBMT; a CD34+ selected graft produced a high engraftment rate, minimal GvHD and relevant leukemia-free survival was reported for patients transplanted in complete remission[2]. Unfortunately, transplant-related deaths are observed in a significant proportion of recipients. Leading causes of deaths reported were infections and interstitial pneumonia: any further reduction in TRM will only be achieved by hastening post-transplant immune recovery. The group in Perugia has recently developed a strategy for transferring donor pathogen-specific immune responses safely across the HLA barrier[3]. Several additional strategies are currently exploring different cell therapy approaches aimed at improving post-transplant immune reconstitution while controlling GvHD: regulatory T cells[4] and the add-back infusions of donor lymphocytes genetically engineered with the herpes simplex virus-thymidine kinase (HSV-TK) suicide gene[5]. A partial T-cell depletion can be provided by alternative selections, such as CD3/CD19 negative selection or selective depletion of alloreactive T-cells[6]; T-cell content of $1x10^5$/kg in the graft requires a post-transplant immune prophylaxis and translates into a significant risk of acute GvHD.

Recently, new platforms for haploidentical transplantation from unmanipulated graft have been developed[7]. We designed a clinical study investigating the feasibility of haploidentical SCT in the absence of ex-vivo T-cell depletion, addressing patients with

leukemias in advanced diseases. To this purpose, we selected a calcineurin inhibitor-free GvHD prophylaxis based on rapamycin, mycophenolate mofetil (MMF) and anti-T lymphocytes globulin (ATG-Fresenius), in the attempt to promote a fast post-transplant immune recovery with a preferential accumulation of regulatory T cells (Tregs). Rapamycin is an immunosuppressive drug that, in contrast to calcineurin inhibitors, promotes the generation of natural Tregs in murine models. Natural Tregs are cells endowed with suppressive activity, that does not require previous antigen exposure and are thus attractive candidates for the clinical modulation of excessive immune responses, including autoimmunity and transplantation reactions. In mouse models of SCT, the adoptive transfer of purified natural Tregs has been shown to prevent GvHD while sparing a significant graft-versus-leukemia (GvL) effect. The infusion of Tregs after UCB[8] and haploidentical SCT to prevent GvHD has produced promising results in recent clinical trials[4]. Besides its effects on Tregs, rapamycin exerts a direct antineoplastic activity against different haematological malignancies. In our study, we exploited these dual positive effects of rapamycin to prevent GvHD and control malignant cells upon infusion of unmanipulated grafts from family haploidentical donors to patients affected by advanced hematological malignancies. Preliminary results on 45 patients show the feasibility of this platform with an appreciable low rate of GvHD.

Conflict of Interest

The authors have declared that no conflict of interest exists.

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