To the editor:

Searching for factors to improve the antileukemic effect of donor lymphocyte infusion

The lymphopenic environment can induce T-cell expansion/activation, a phenomenon referred to as lymphopenia-induced proliferation that can be distinguished from (allogenic) antigen-induced proliferation.1 Dudley et al showed that a cyclophosphamide (Cy) and fludarabine (Flu) lymphodepleting regimen could improve the in vivo expansion/activation, and consequently the therapeutic effect, of infused autologous melanoma-specific cytotoxic T lymphocytes (CTLs), notably by eliminating regulatory T cells and modifying levels of homeostatic regulatory cytokines such as IL-7 or IL-15.2 Because Cy/Flu regimen was also associated with profound neutropenia, Dudley et al administered granulocyte colony-stimulating factor (G-CSF) in 25 of 35 patients after CTL injection, and observed a significantly improved neutrophil recovery.3

In the field of hematologic malignancies treatment, we read with interest the recent article by Miller et al who reported that Cy/Flu–induced lymphopenia of recipients amplified the clinical manifestations of allostereactivity following donor lymphocyte infusion (DLI) administered to patients who relapsed after allogeneic hematopoietic stem cell transplantation (HSCT).4 This was demonstrated in a series of 15 patients receiving a fixed dose of 10^9 CD3+ cells/kg immediately after the lymphodepleting treatment. In comparison to an historical cohort, lymphodepletion prior to DLI was associated with a significantly higher incidence of acute graft-versus-host disease (GVHD) than after DLI alone. This trial was interrupted due to an excess of GVHD-related mortality.4

These results are of prime importance for the design of improved DLI for treating post-HSCT relapse. However, we think that the potentially important role of G-CSF treatment further needs to be considered in these observations. On the one hand, G-CSF treatment has been described as polarizing T-cell subsets toward Th2 differentiation, reducing alloreactivity and favoring the generation of regulatory T cells (for reviews see Anderlini and Champlin5 and Morris et al6). Most of these observations have been made in healthy donors who had received G-CSF prior to peripheral blood stem cell mobilization or in patients who had received G-CSF–mobilized transplants. On the other hand, when G-CSF was administered after HSCT to improve neutrophil recovery, a very large comparative study of the European Blood and Marrow Transplantation group demonstrated that G-CSF treatment was associated with an increased risk of GVHD.7

Although the Cy/Flu doses were slightly lower in the study of Miller et al4 in comparison to what has been done in the autologous setting,3 this lymphodepleting regimen also led to profound neutropenia, with a white blood cell nadir of 0.61 × 10^9/L. However, there is no information regarding potential G-CSF treatment after Cy/Flu conditioning. If some of those patients have received G-CSF to reduce the neutropenia period after DLI, it may have influenced donor T-cell alloreactivity and likewise GVHD. Such information would be of importance to better understand the role of lymphodepletion in the amplification of alloreactivity. It may also help to better define the benefit/risk profile of G-CSF treatment for the design of future trials of autologous or allogeneic T-cell immunotherapy.

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References


Response

The role of G-CSF on the risk of graft-versus-host disease after donor lymphocyte infusions

The letter written by Maury et al raises an interesting question regarding the role of G-CSF on the increased incidence of acute graft-versus-host disease (aGVHD) we observed when giving donor lymphocyte infusions (DLIs) after lymphodepleting chemotherapy.1 To address their concern we reviewed the patient charts and pharmacy records for our cohort. Because of the known immunologic effects of G-CSF, including its potential to inhibit immune function, the protocol did not prohibit but did allow the use of G-CSF if necessary for patient safety. Of the 8 patients who developed grade III to IV aGVHD, G-CSF was either not given (1 patient) or was given 15 to 22 days after the onset of a definitive diagnosis of severe aGVHD (3 patients), excluding G-CSF as a causative agent in DLI-induced severe GVHD. The remaining 4 patients did receive G-CSF with the following timing after DLI in
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