Azacitidine after allo-SCT: the good without the bad?

Mohamad Mohty and Patrice Chevallier
CHU DE NANTES

In this issue of Blood, Goodyear and colleagues show that azacitidine after allogeneic stem cell transplantation (allo-SCT) can increase the number of regulatory T cells (Tregs) while inducing a cytotoxic CD8+ T-cell response, suggesting a potential mechanism for augmenting the graft-versus-leukemia (GVL) effect without increase in graft-versus host disease (GVHD).

In allo-SCT, the potential benefit of the GVL effect has always been offset by the detrimental effect of GVHD. For more than 4 decades, separation between GVHD and GVL remained challenging and has been considered the Holy Grail in the field of allo-SCT. Several direct and indirect lines of evidence already suggested a close correlation between GVHD and the risk of relapse after allo-SCT. Donor lymphocyte infusions (DLIs) after allo-SCT provide direct evidence for the potency of the GVL effect. Nevertheless, the best responses to DLI are observed in patients with chronic myeloid leukemia. In other hematologic malignancies such as acute myeloid leukemia (AML), response rates do not usually exceed 15% to 20%. However, all of these approaches remain experimental and none of them has been adopted in routine practice for treatment or for prevention of relapse after allo-SCT.

At present, disease relapse is the main cause of treatment failure in a significant proportion of patients undergoing allo-SCT and the rate has remained relatively constant for decades. Therefore, there is an urgent need for developing efficient, standardized, safe, and easy-to-export approaches that can reduce the risk of relapse after allo-SCT without a concomitant increase of GVHD, such as the use of imatinib in Philadelphia-positive leukemias.

The hypomethylating agent azacitidine is currently approved for the treatment of myelodysplastic syndromes and for AML with 20% to 30% blasts and multilineage dysplasia, according to the World Health Organization classification. Azacitidine, an analog of cytidine, functions as a DNA methyltransferase inhibitor and has shown substantial potency in reactivating epigenetically silenced tumor suppressor genes. The antineoplastic activity of azacitidine is thought to be mainly due to incorporation into RNA with disruption of RNA metabolism, and inhibition of DNA methylation. However, the precise mechanism by which this agent exerts an antitumor effect remains unknown, and it appears that clinical responses are influenced both by epigenetic alterations and by apoptosis induction. In addition, recent evidence suggested that azacitidine can significantly impact some important immune functions via epigenetic modifications, making it an attractive candidate for pharmacologic manipulation of the immune system.

In the present study by Goodyear et al, the adjunctive administration of azacitidine after allo-SCT in a series of 27 AML patients was well tolerated despite the drug being started soon after allo-SCT. Of note, increased numbers of circulating Tregs were detected in patients who had received 3 courses of posttransplant azacitidine compared with a control group of patients studied at similar time points after transplantation. Moreover, azacitidine administration induced a CD8+ T-cell response to 1 or more tumor-specific peptides in more than half of the patients who had received 3 or more cycles of azacitidine. In patients who could receive at least 6 cycles of azacitidine, a CD8+ CTL response to a range of tumor antigens including MAGE-A1, MAGE-A2, MAGE-A3, BAGE-1, RAGE-1, and WT1 could be documented both in the peripheral blood and bone marrow. From the functional standpoint, the detectable tumor-specific responses were also active in response to peptide.

This is, to our knowledge, the first demonstration that azacitidine has the capacity to increase both circulating Tregs and CD8+ tumor-specific T-cell responses in humans in...
the context of allo-SCT, without increasing the incidence of acute and chronic GVHD compared to both control patients and previous studies using a similar conditioning regimen.

How does this study improve our strategies for GVL induction in patients undergoing allo-SCT? The strengths of this study are its prospective nature, inclusion of a fair number of homogenously treated allo-SCT AML patients, and use of state-of-the-art, modern immune monitoring tools. The combined beneficial effect of azacitidine on both Tregs and CD8+ T cells represents an ideal scenario after allo-SCT toward induction of tolerance and improving disease control. Obviously, the role and impact of Tregs in GVHD remains controversial. However, recent convincing evidence showed that sustained Treg expansion in vivo correlated with the amelioration of the manifestations of active chronic GVHD.9

Thus, administration of azacitidine after transplantation is an appealing and potentially interesting alternative strategy for Treg expansion. On the other hand, the true clinical relevance of CD8+ T-cell responses to tumor antigens after allo-SCT is yet to be established. However, it is an attractive mechanism by which the GVL effect might be augmented after allo-SCT. Furthermore, one could anticipate that the use of azacitidine in combination with DLI may further augment the safety and antitumor effect of DLI. Such trials are currently ongoing.

The exact mechanisms underlying the effects of azacitidine after allo-SCT are still to be deciphered. It is possible that azacitidine can regulate several genes and pathways that are involved in regulation of T-cell differentiation. For instance, epigenetic regulation of some cytokine genes is a key event in the initiation of immune responses.10

In conclusion, these far-reaching findings suggest that azacitidine administration after allo-SCT is feasible and can allow for Treg expansion, as well as an impressive induction of CD8+ T-cell responses to tumor antigens without GVHD. It raises the possibility of therapeutically separating GVHD and GVL. While the optimal dosing, schedule timing, and duration of azacitidine administration after allo-SCT are still to be established,11 and further refined understanding of molecular events associated with the immunomodulatory effects of novel epigenetic therapies is needed, this agent could eventually allow selective targeting of the GVHD and GVL pathways (see figure).

Conflict-of-interest disclosure: M.M. has received research support and honoraria from Celgene. P.C. declares no competing financial interests.

REFERENCES


Azacitidine after allo-SCT: the good without the bad?

Mohamad Mohty and Patrice Chevallier