Old wine in a new bottle: ready to drink?

Jan J. Cornelissen

In this issue of Blood, Walter et al describe the impact of minimal residual disease (MRD) as measured by multicolor flow cytometry (MCF) on relapse, progression-free survival (PFS), and overall survival (OS) in acute myeloid leukemia (AML) patients who received an allogeneic hematopoietic stem cell transplantation (alloHSCT). Since the concept of MRD was introduced in the early 1980s, it has only been gradually introduced into clinical practice. The most important examples are the current standard use of quantitative polymerase chain reaction (qPCR) in patients with chronic myeloid leukemia and the use of flow cytometry and qPCR in acute lymphoblastic leukemia. Apart from the use of PCR in acute promyelocytic leukemia, MRD is currently not routinely monitored in AML patients. Walter et al report that MRD strongly impacts on PFS and OS in alloHSCT recipients with AML, and in a similar degree in first and second remission. That effect became evident as from a cutoff level of 0.1%, without significantly changing in patients with increasing levels of MRD.

Although MRD as an innovative concept was first suggested in AML, it took almost 3 decades for MRD to mature in AML. An important question to be addressed today is whether recent studies, including the present study from Seattle, urge us to adapt our transplant policy. The choice of postremission treatment in AML is currently under intense debate (see figure). Although alloHSCT provides the strongest antileukemic treatment, the benefit can be compromised by nonrelapse mortality (NRM). Therefore, a careful assessment of the most important variables affecting relapse and NRM should be included in the workup of transplant recipients nowadays. A recent review by the European Leukemia Net (ELN) AML working group described that approach in detail for AML transplant recipients, taking into account on one hand the parameters predicting relapse and on the other hand parameters predicting NRM in a time-dependent fashion (see figure). The ELN recommended to aim for a disease-free survival (DFS) benefit by alloHSCT of at least 10% for the individual patient as compared with a non-alloHSCT approach. Such a DFS benefit may be achieved in AML intermediate- and poor-risk patients, provided that the risk of NRM does not exceed 25% and 35%, respectively. Good-risk AML patients, as defined by cytogenetic and molecular hallmarks, do not currently receive an alloHSCT as part of first-line treatment because the DFS benefit is limited and those patients may effectively be rescued upon relapse.

Should intermediate-risk patients without MRD after induction chemotherapy be considered as good-risk patients? The study by Walter et al and by other investigators may seem to suggest this, but more information is needed before adapting a transplant policy. First, prospective studies reporting outcome of AML intermediate-risk MRD-negative patients who do not proceed to alloHSCT because of MRD negativity would be needed. Prospective studies, addressing this particular issue have not been reported yet, and the question whether
Collectively, the present study¹ and other studies in AML⁸,⁹ strongly suggest that the net effect of the combination of an anthracycline and cytarabine in AML currently needs to be evaluated by both flow cytometry and microscopic evaluation to obtain optimal information regarding the risk of relapse. A change of transplant policy seems premature in intermediate-risk patients who become MRD-negative after induction chemotherapy and further prospective studies would be needed. Finally, despite the adverse prognostic impact of MRD-positivity, these patients do benefit from alloHSCT, which, therefore, should be pursued, even with alternative donors, and preferably be optimized by exploiting GVL more effectively. Therefore, after 30 years of MRD maturation in AML, we may now begin to sip of this extraordinary wine.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES

© 2013 by The American Society of Hematology

***TRANSPLANTATION***

Comment on Dong et al, page 1802

Tregs, HSCT, and acute GVHD: up close and personal

John Koreth¹ and Jerome Ritz¹
DANA-FARBER CANCER INSTITUTE

In this issue of Blood, Dong et al present a unique detailed view of human regulatory T-cell (Treg) diversity in homeostatic and pathological states after allogeneic hematopoietic stem cell transplantation (alloHSCT).¹

AlloHSCT provides curative graft-versus-tumor potential for patients with hematologic malignancies. However, donor effector immune responses to allogeneic (donor/recipient polymorphic) and autologous (donor/recipient nonpolymorphic) antigens also underlie acute and chronic graft-versus-host disease (GVHD), the major toxicities of this therapeutic approach. CD4⁺CD25⁺Foxp3⁺ regulatory T lymphocytes comprise ~5% to 10% of circulating CD4⁺ T cells and migrate to inflammatory sites to control innate and adaptive immune responses, especially those due to effector lymphocytes of helper T (Th) subsets: Th1, Th2, Th17, and follicular Th cells (reviewed by Ohkura et al).² Tregs play a critical role in the prevention of autoimmunity and several studies have suggested that Tregs also play a central role in the establishment and maintenance of immune tolerance after alloHSCT.
Old wine in a new bottle: ready to drink?

Jan J. Cornelissen