Collectively, the present study and other studies in AML strongly suggest that the net effect of the combination of an anthracycline and cytarabine in AML currently needed to be evaluated by both flow cytometry and microscopic evaluation to obtain optimal information regarding the risk of recurrence. 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.

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Comment on Dong et al, page 1802

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

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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).

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 al²). 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.
Specifically, several studies have found that levels of circulating CD4+ CD25+ Foxp3+ Tregs are inversely correlated with acute or chronic GVHD.1,4 In acute GVHD, Tregs were found to express lower levels of granzyme A and chemokine receptors (eg, CCR5, CXCR3), suggesting that Treg-suppressive function and target tissue homing may also be impaired.7 In chronic GVHD, impaired thymic generation of naïve Tregs (CD45RA+CD25−) and increased apoptosis sensitivity of proliferating memory/effectort Tregs (CD45RA−) selectively alter Treg homeostasis and contribute to the inability to maintain adequate numbers of Tregs relative to conventional effector CD4+ T cells (Tcons).8,9

Using new methods to assess gene expression in single cells, Dong et al now present a close-up view of Tregs in human thymus, umbilical cord blood, normal adult blood, and during early reconstitution post-HSCT.1 Characterizing CD4+ CD25+ Tregs as naïve (CD45RA+HLADR−), activated (CD45RA−HLADR+), and memory (CD45RA−HLADR+) subpopulations, they define a “Treg core” gene expression signature that not only distinguishes CD4+ Tregs from CD4+ Tcons but also differentiates each Treg subset. Single cells within each Treg subpopulation show remarkable stability of Foxp3+ expression and lack of IL-2 expression, and also exhibit considerable heterogeneity in expression of various transcription factors, signaling molecules, and homing receptors. At the single-cell level, expression of interferon-γ or interleukin-17A (IL-17A) was very infrequent, suggesting little overlap with Th1 or Th17 lineages. In patients with acute GVHD, overall Treg frequencies and “Treg core” signature appeared to be preserved but there was a marked decrease in the naïve Treg subpopulation with preservation of the activated Treg pool. However, residual activated Tregs retained suppressive capacity in in vitro assays.

What are some of the implications? Diversity is a hallmark of the adaptive immune system. The heterogeneity described within circulating Treg subpopulations is reminiscent of that seen in CD4+ Tcons. While this report likely identifies only a fraction of the overall diversity in vivo that also includes T-cell receptor diversity, activation state, cytokine milieu, and target organ homing, etc, even this limited view is indicative of the extensive complexity and diversity of immune regulators that appear to match the diversity of immune effectors. Furthermore, the timing of naïve Treg deficiency, that may precede acute GVHD, suggests that impairment of Treg thymic neogenesis is an early event. This is not entirely unexpected because the thymus has been shown to be an acute GVHD target organ, resulting in a decline in T-cell receptor excision circle (TREC) T cells and an oligodochial T-cell repertoire that is observed even in grade 1 acute GVHD.

There may also be therapeutic implications. The observed stability of Foxp3+ expression and limited capacity for Th1 and Th17 cytokine secretion are potentially reassuring when considering adoptive Treg therapy, given the proinflammatory milieu in GVHD and its potential for inducing Treg lineage conversion to effector Tcons. However, adoptive Treg survival, activity, and lineage stability in the inflamed host receiving immunosuppressive agents for GVHD remain to be determined in the clinic. Additionally, low-dose IL-2 can induce clinical responses, augment Tregs in vivo, and restore Treg homeostasis in chronic GVHD due to enhancement of Treg thymic neogenesis, proliferation, survival, and function.9,10 A similar impact on acute GVHD may be possible and should be considered. More speculatively, a combination of adoptive Treg infusion plus low-dose IL-2 may offer synergy in GVHD control. Treg-based GVHD therapies may also offer therapeutic potential in other disorders of impaired peripheral tolerance (eg, autoimmunity, solid organ transplantation). More Treg close-ups posttransplantation are in order.

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