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Comment on Walter et al, page 1813

Old wine in a new bottle: ready to drink?

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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).¹

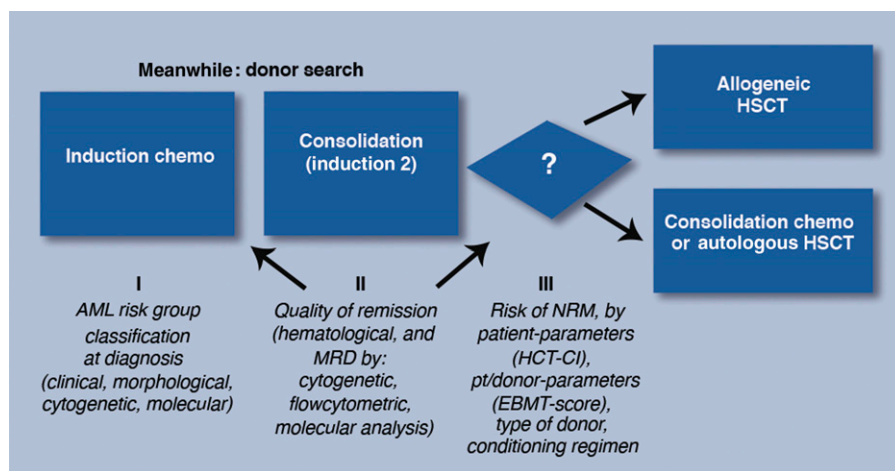
Since the concept of MRD was introduced in the early 1980s, it has only been gradually introduced into clinical practice.² The most important examples are the current standard use of quantitative polymerase chain reaction (qPCR) in patients with chronic myeloid leukemia³ and the use of flow cytometry and qPCR in acute lymphoblastic leukemia.⁴ 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.¹ 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.⁵ 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 group⁶ 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,⁶ 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.⁷

Should intermediate-risk patients without MRD after induction chemotherapy be considered as good-risk patients? The study by Walter et al¹ and by other investigators^{8,9} 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



Time frame and parameters for decision making prior to allogeneic hematopoietic stem cell transplantation (HSCT) in AML. HCT-CI, hematopoietic stem cell transplantation comorbidity index; EBMT, European Group for Blood and Marrow Transplantation. Professional illustration by Marie Dauenhimer.

alloHSCT can be withheld in that subgroup is still open but urgent. Especially because of a lower rescue rate with reinduction chemotherapy in intermediate-risk patients in general.¹⁰ Second, methods of MCF vary among different studies. Some of the methods apply MRD monitoring by first establishing a leukemia-associated phenotype (LAP) at diagnosis.^{8,9} The present study applied a different approach by defining MRD by any deviation of the normal pattern of regenerating or normal marrow, which circumvents the need for a LAP and also circumvents the problem of a phenotypic shift that may occur during chemotherapy. This approach may seem very attractive, but from a technical point of view, the method is challenging and so far is only being used by a very limited number of centers. Therefore, the MCF method applied in the present study would need validation in prospective studies on a broader scale. Moreover, such confirmation is also needed to be able to quantitatively weigh all relevant prognostic markers prior to alloHSCT within a single, large study, including parameters predicting for NRM.

MRD-positivity in the present study appeared to be associated with a 3-year OS of 32% and 44% in CR1 and CR2 patients, respectively. Although the relapse rate after alloHSCT was relatively high in those patients, the allogeneic graft-vs-leukemia (GVL) effect was suggested not to differ between MRD-negative and MRD-positive patients. Of interest, as a reflection of GVL activity, the present study showed a strong reduction of relapse (hazard ratio: 0.46 (0.24-0.88); $P = .02$) in patients with chronic graft-vs-host disease, which was similarly exerted in patients with or without MRD. Therefore, the higher relapse rate in MRD-positive patients does not indicate that GVL was absent, but rather suggests that the allogeneic GVL effect would need to be exploited more effectively. Several approaches may be developed into that direction, but monitoring of MRD at regular intervals after alloHSCT with subsequent adaptation of the immunosuppressive regimen and/or donor lymphocyte infusion may be one of them. In addition, intermediate-risk patients who are MRD-positive after induction and consolidation chemotherapy may be candidates for an alloHSCT using stem cells from alternative donors, which type of transplants is currently not routinely offered to those patients if MRD information is lacking.

Collectively, the present study¹ and other studies in AML^{8,9} 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. ■

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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).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 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.



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