remission (CR) rate, including applying stringent polyclonal CR before and after administering HDM. Additional benefit for the patient may come from postintensification or consolidation therapy or maintenance treatment with nontoxic regimens.

Achieving sustained CR is a major goal for future investigations. Results from recent trials indicate that thalidomide during maintenance may prolong progression-free survival, although as yet not overall survival.[5,8] It may well be that subgroup analyses of large prospective trials may provide insight to which patients benefit from the use of novel agents in specific settings.[9] The trial performed by the Italian group may provide the background for omitting the paradigm of HDM200 as the absolute standard and opening up new ways to investigate combinations of novel agents with standard-dose cytostatics as an alternative postremission induction treatment in transplantation for myeloma.

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

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● ● ● CLINICAL TRIALS

Comment on Saussele et al, page 1880

Transplantation for CML: 2010

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In this issue of *Blood*, Saussele and colleagues from the German CML study group present data obtained from an interim safety analysis of a prospective multiarm trial in which allogeneic stem cell transplantation was used up front in selected low-risk CML patients, up front in patients presenting with advanced disease, or as planned second-line therapy after imatinib failure.[1]

Strict criteria for whom transplantation would be offered were developed, with most patients receiving pretransplantation imatinib. In this setting, excellent outcomes were achieved with a 3-year projected overall survival of 91% after allogeneic transplantation in chronic phase. In advanced disease, the projected overall survival was 59%. Remarkably, 88% achieved complete molecular remission and, when a matched-pair analysis was performed of transplanted CML patients in first chronic phase versus matched nontransplantation patients derived from the imatinib-responsive group, 3-year survivals were equivalent. The authors' conclusions are that allogeneic transplantation could become the preferred second-line option after imatinib failure for suitable patients with appropriate matched donors.

Despite this well-designed prospective study, the reality remains that second-generation tyrosine kinase inhibitors (TKI) have become standard therapy in the CML world. These agents may replace imatinib as first-line therapy,[2] as recent data presented at the American Society of Hematology meetings demonstrated superiority of nilotinib over imatinib in newly diagnosed patients. An updated set of management recommendations from the European LeukemiaNet for patients with chronic-phase CML defined a more standard and acceptable treatment pathway that would allow patients who fail imatinib to proceed to second-generation TKI for treatment purposes. Transplantation was third line. Allogeneic stem cell transplantation is reserved for patients who do not respond to second-generation TKI, develop the T315I-resistant mutation, or experience progression to accelerated or blast phase of their malignancy.[3] It was still recommended that patients with primary presentation of accelerated phase or blast crisis proceed to early transplantation, after appropriate disease reduction with TKI therapy. This approach is consistent with many current institutional algorithms trying to balance the potential of the drug therapy with the proven efficacy and mortality risk of allogeneic transplantation.[4]

What is most exciting about the data presented is that the treatment-related mortality had fallen to less than 10%, compared with previous results of 26% obtained in prospective transplantation trials performed by the same study group.[5] This same observation of a reduction in treatment-related mortality has also been reported in the Center for International Blood and Marrow Transplant Research analysis of the impact of pretransplantation imatinib mesylate on the outcome of stem cell transplantation for CML. In patients with chronic-phase CML, there was a 30% reduction in treatment-related mortality for patients exposed to imatinib compared with a historical control group of CML patients who underwent stem cell transplantation, prior to the availability of imatinib.[6] If the risk of treatment-related mortality can be successfully reduced for patients with CML undergoing transplantation with low tumor burden after TKI exposure and prior to further disease progression, then we again will find strong collaborations between the cell therapists and the drug therapists in defining optimal management pathways for all CML patients.

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

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HEMATOPOIESIS & STEM CELLS

Comment on Krueger et al, page 1906, and Zlotoff et al, page 1897

CCR7/CCR9: knockin' on the thymus door

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In this issue of *Blood*, independent reports by Zlotoff and colleagues and Krueger and colleagues show that the settling of hematopoietic progenitors in the thymus is severely reduced in the absence of the CCR9 and CCR7 chemokine receptors.

The periodic colonization of the thymus by hematopoietic progenitors is essential for the sustained differentiation of T lymphocytes. Although the myriad signals regulating the migration of these progenitors have begun to be untangled in recent years, many questions remain. The most direct means of assessing the specific roles of various chemoattractants in regulating the seeding of the thymus is to track the journey of individual hematopoietic progenitors. Although not yet feasible in mammals, this feat has been achieved in zebrafish. $CD41^+$ hematopoietic precursors have been traced traveling through the mesenchyme for more than 12 hours. They have been shown to traverse the mesenchyme and undergo directional migration to the nascent thymus from as far as 350 μm[1]! Thus, chemoattractants clearly regulate progenitor entry into the thymus.

In mammals, studies from multiple groups using various knockout mice have demonstrated the roles of signals mediated by CCL19-CCL21/CCR7, CCL25/CCR9, and P-selectin/PSGL-1 interactions. However, there appears to be a high level of redundancy as the abrogation of any one of these receptor-ligand interactions only modestly affects thymus colonization. Notably, a recent elegant study from Takahama et al identified a coordinated action between CCR7- and CCR9-mediated chemokine signals as being critical for colonization of progenitors in the fetal thymus; the concomitant absence of CCR7 and CCR9 on progenitor cells severely impaired fetal thymus colonization.[2] However, the finding that thymic cellularity was normal in CCR7/CCR9 double knockout (DKO) mice by postnatal day 1[2] raised questions as to what other mechanisms may regulate the seeding of the thymus after thymus vascularization.

The 2 articles by Zlotoff et al and Krueger et al in this issue of *Blood* shed new light on this topic. Using CCR7/CCR9 DKO mice, both groups show that during the adult period the absence of CCR7 and CCR9 severely impacts thymic settling capacity but compensatory expansion results in the recovery of thymic cellularity.[3,4] While hematopoietic stem cells (HSC) and multipotent progenitors (MPPs) do not appear to migrate from the bone marrow (BM) to the thymus,[5] thymic settling progenitors give rise to early thymic progenitors (ETPs) characterized as $c\text{-}kit^+CD25^-$. This ETP population was found to be reduced by more than 100-fold in CCR7/CCR9 DKO mice despite normal levels of hematopoietic precursors and differentiation in the bone marrow (BM).[3,4] Under conditions of competitive BM progenitor transfer, both wild-type (WT) and CCR7/CCR9 DKO mice were able to reconstitute blood progenitor populations, but DKO cells were virtually absent from the thymus. This was due to a specific defect in thymic settling as DKO progenitors were equivalent to their WT counterparts in generating ETPs and double-positive (DP) thymocytes when directly injected into the thymus.[3,4] Whereas the vast majority of ETP have been shown to express CCR9,[6] the CCR7/CCR9 status of the BM progenitors that seed the thymus is not known. Intriguingly, Zlotoff et al have detected a rare population of BM progenitors within the Lin-Flt3hi pool that express both CCR7 and CCR9.[3]

In the context of a 2-log reduction in ETP, the near-normal cellularity of the thymus in CCR7/CCR9 DKO mice strongly suggested that there was a compensatory expansion or reduced apoptosis at later stages of differentiation. Indeed, the reduction in thymocyte numbers in CCR7/CCR9 DKO mice was less than 3-fold at the DN3 stage and was virtually normal by the DP stage of differentiation. This raises the following possibilities: (1) CCR7/CCR9 DKO progenitors are more "fit" for proliferation; (2) CCR7/CCR9 DKO progenitors undergo less cell death; or (3) the environment of the DKO thymus is more conducive to thymocyte expansion. A significant number of impressive experiments performed by the groups of Zlotoff and Krueger point to the last explanation. Upon intrathymic injection of WT progenitors into WT and DKO thymi, Zlotoff et al found 100-fold more donor DP cells in the latter after 15 days,[3] while Krueger et al found a significantly higher level of DN3 proliferation in DKO compared with WT mice.[4]

Elucidating the signals resulting in the increased expansion/proliferation of progenitors in the CCR7/CCR9 DKO thymus will be an exciting challenge. At the DN3 stage, a central event is VDJ rearrangement at the TCR β chain locus. Those cells harboring a pre-TCR, composed of the rearranged TCRβ and the pre-Tα, undergo proliferative expansion. Notch signaling, independent of the pre-TCR, has been shown to be at least one of the elements that is required for proliferation after β-selection.[7,8] Most recently, CXCR4 signaling has been shown to play a key role in promoting the expansion of DN3 thymocytes, facilitating pre-TCR signals.[9,10] It is therefore of interest to assess whether the absence of CCR7/CCR9 impacts on thymic levels of notch ligands, CCL12, and cytokines such as IL-7 that are critical for thymocyte expansion. Irrespective of the mechanism, the alluring data presented in the papers by Zoloft et al and Krueger et al point to a level of robustness in thymocyte differentiation that was not previously appreciated.