that cytogenetic and molecular subgroups be carefully characterized in current and future trials using CXCR4 antagonists.

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Response

Sensitization initiated

In their letter to the editor, Heuser et al showed that acute myelogenous leukemia (AML) cells are mobilized into the peripheral blood using the CXCR4 inhibitor AMD3100 (Plerixafor; Genzyme Inc).\(^1\) Interestingly, they further studied the effect of this agent on the mobilization of leukemia stem cells (LSCs) in their model system. Their results showed no significant difference in the number of LSCs present in the bone marrow or peripheral blood using granulocyte colony-stimulating factor (G-CSF), AMD3100, or the VLA-4 inhibitor MOL27575. The authors also investigated the activity of AMD3100 in combination with low- or high-dose cytarabine and showed there was no additive effect of cytarabine. Although there are several possible explanations for the results, the investigators indicated that AMD3100 is nothing but a “reload” of G-CSF, and that the 20 years of experience using G-CSF to prime leukemia cells has failed to show improvement in the mortality of patients with AML. They also indicated that the activity of G-CSF and AMD3100 is similar through their effects on the CXCR4/SDF-1 axis.\(^2\)

Several years ago, studies demonstrated that G-CSF induced a gradual decrease in SDF-1 in the bone marrow through degradation by neutrophil elastase,\(^3,4\) thereby leading to stem cell mobilization through the CXCR4/SDF-1 axis. More recent studies have shown that AMD3100 leads to mobilization of hematopoietic stem cells (HSC), even after failure of mobilization by G-CSF, indicating a different level of activity of AMD3100 and G-CSF.\(^2,5\) In addition, AMD3100 enhanced the activity of G-CSF when used in combination, which led to the approval of this agent in the mobilization of HSCs in patients with multiple myeloma (MM) and lymphoma.\(^6\) Therefore, the notion that AMD3100 is just another G-CSF is not supported by many elegant scientific studies, which have shown that the inhibition of CXCR4 activity is biologically different from the neutralization of SDF-1 activity in the bone marrow. However, further studies are required to examine in depth the mechanistic differences in stem cell mobilization between G-CSF and AMD3100.

The interaction of cancer cells with their microenvironment in the bone marrow (BM) provides a protective environment and resistance to therapeutic agents.\(^7,8\) We have recently demonstrated that interrupting the CXCR4/SDF-1 axis through inhibition of CXCR4 by AMD3100 leads to mobilization of malignant cells from the BM and increases their sensitization to therapeutic agents.\(^9,10\) Contrasting with the nonadditive effect of AMD3100 and cytarabine in AML that was shown by the authors, we found in our study a significant enhancement of the effect of bortezomib, dexamethasone, doxorubicin and melphalan in vitro and the effect of bortezomib in vivo in MM.\(^9\) These differences may be explained by the timing and dosing of bortezomib and AMD3100, as well as the biologic differences between MM and AML cells. In our study,
MM cells mobilization peaked at 2 hours after injection with AMD3100 and we administered bortezomib at that time. At 24 hours after injection the numbers of mobilized MM cells returned to baseline. Therefore, knowing that the half-life of AMD3100 is short and that its effect is reversible, an accurate timing of the chemotherapy dosing compared with the peak of mobilization of the malignant cells is crucial. In addition, our study showed there was a difference in timing of the mobilization of MM and normal HSCs, again indicating that there are significant differences in CXCR4/SDF-1 signaling between different cell types and between normal and malignant cells.9

Similarly, Heuser et al showed that LSCs were not affected by the use of AMD3100. These results have to be taken in context with the duration of use and the timing of AMD3100. More studies are required to investigate differences in CXCR4 signaling in LSCs compared with other AML cells, which may indicate that AMD3100 should be used for a longer duration or at a higher dose to induce mobilization or sensitization of these cells to chemotherapy.

Therefore, we agree that cytogenetic and molecular subgroups of malignant cells, whether they are AML or MM cells, should be carefully characterized in current and future trials using CXCR4 antagonists. Further studies are also needed to examine mechanisms of sensitization to therapy by blocking CXCR4 signaling, and differences between inhibition of CXCR4 signaling and SDF-1 neutralization in inducing sensitization to therapy. In conclusion, “Is priming with GSF reloaded?” We believe the answer is “No.” But to the question “Is sensitization with AMD3100 initiated?” we believe the answer is “Yes,” and that more studies are required to define the role of CXCR4 inhibitors in the different subtypes of MM, AML, and other malignancies.

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References

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