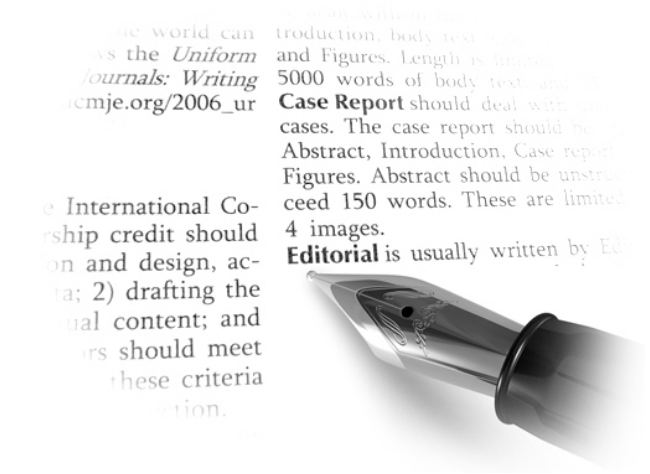

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Editorial

CXCR4 antagonists in hematologic malignancies: more than just mobilizers?

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Stromal cell-derived factor-1 (SDF-1) is a chemokine constitutively expressed and produced in bone marrow (BM) stromal cells. It plays a central role in the migration and homing of hematopoietic stem cells (HSCs) and hematopoietic progenitor cells (HPCs) through signaling via its receptor CXCR4. AMD3100 is a small bicyclam molecule, which was originally developed as a CXCR4 antagonist that could block the entry of the HIV into T cells. It inhibits the binding of SDF-1 to CXCR4 and induces peripheral mobilization of HSCs and HPCs [1]. AMD3100 safely and rapidly mobilizes stem cells in healthy donors and in patients with lymphoma and myeloma, and it does so in synergy with the granulocyte-colony stimulating factor (G-CSF) [2]. A recent phase III clinical study on autologous stem cell transplantation showed that a combination of AMD3100 and G-CSF allowed for the collection of a large number of stem cells in fewer apheresis sessions and can help the patients in whom mobilization with G-CSF alone was ineffective [3]. On the basis of these findings, the FDA has recently approved the use of AMD3100 in combination with G-CSF for stem cell mobilization in patients with non-Hodgkin's lymphoma and multiple myeloma.

Leukemia and myeloma cells also express different levels of CXCR4 and respond to SDF-1, resulting in the migration and stable localization of these cells in the BM [4]. AMD3100 induces the segregation of leukemia and myeloma cells in the BM microenvironment, thereby mobilizing these cells to the peripheral blood and sensitizing them to chemotherapy [5]. Studies are underway for testing the use of AMD3100 as an adjunct to chemotherapy in patients with refractory acute myeloid leukemia (AML) and other hematologic malignancies; if successful, this strategy may be used to sensitize leukemic cells to chemotherapy and improve clinical outcomes.

SDF-1 alone has a minimal or negligible effects on the survival and growth of normal and malignant hematopoietic cells *in vitro*, but the SDF-1/CXCR4 axis is involved in the progression and dissemination of a variety of hematologic malignancies and solid tumors [6]. Patients with multiple myeloma and extramedullary plasmacytoma, which is a manifestation of an advanced stage of multiple myeloma, show elevated levels of serum SDF-1 and CXCR4 expression, respectively. Moreover, BM endothelial cells in multiple myeloma patients secrete CXC chemokines, including SDF-1, that mediate interactions with the myeloma cells. Similar findings have been reported in leukemia patients. For example, AML patients with high levels of CXCR4 in $CD34^+$ cells had a significantly lower survival rate and higher probability of relapse than those with low levels of CXCR4. A polymorphism in the SDF-1 gene correlated with the risk of distant tissue being infiltrated by AML cells. Compared to the Philadelphia chromosome (Ph)-negative $CD34^+CXCR4^+$ cells, the Ph-positive $CD34^+$ $CXCR4^+$ cells from chronic myelogenous leukemia patients showed limited migration. In addition, SDF-1 has been shown to play a role in tumor neoangiogenesis. On the

basis of these observations, the modulation of the SDF-1/CXCR4 axis has been suggested to influence the biological characteristics and disease course of hematologic malignancies.

Contradictory to early studies, CXCR4 antagonists have been shown to inhibit the survival and proliferation of leukemia and myeloma cells *in vitro*. AMD3100 and TC140012, another CXCR4 antagonist, significantly inhibited stroma-dependent proliferation of leukemia cells in a population of patients with acute lymphoblastic leukemia. In addition, AMD3100 and TC140012 were shown to enhance the cytotoxic and antiproliferative effects of the cytotoxic agents vincristine and dexamethasone [7]. AMD3100 arrested proliferation in AML cell lines and triggered changes that mimicked differentiation, including morphological changes and the expression of myeloid differentiation antigens [8]. A recent study has shown that another CXCR4 antagonist, BKT140 4F-benzoyl-TN14003 (BKT140), exhibited CXCR4-dependent preferential cytotoxicity toward malignant cells of hematopoietic origin. BKT140 significantly and preferentially stimulated apoptotic cell death in multiple myeloma cells. BKT140 treatment induced morphological changes and phosphatidylserine externalization; it also decreased mitochondrial membrane potential, caspase-3 activation, sub-G1 arrest, and DNA double-stranded breaks. *In vivo*, subcutaneous injection of BKT140 significantly reduced the growth of human AML and multiple myeloma xenografts in a dose-dependent manner. Compared to the tumor samples obtained from animals not treated with BKT140, those obtained from the animals treated with BKT140 were smaller in size and lower in weight and had larger necrotic areas and high apoptotic scores [9]. In this issue of the Korean Journal of Hematology, Kim *et al.* report that higher concentrations of AMD3100 enhanced the proliferation of AML cells during the early course of *in vitro* incubation. Conversely, after 5-7 days of culture, AMD3100 decreased the number of AML cells and induced cell apoptosis more rapidly than the control did [10].

In summary, recent studies have suggested that CXCR4 antagonists may potentially be used in the treatment of hematologic malignancies not only as stem cell mobilizers for transplantation and sensitizers to chemotherapy but also as direct cytotoxic agents.

REFERENCES

1. Larochelle A, Krouse A, Metzger M, et al. AMD3100 mobilizes hematopoietic stem cells with long-term repopulating capacity in nonhuman primates. Blood 2006;107:3772-8.
2. Vose JM, Ho AD, Coiffier B, et al. Advances in mobilization for the optimization of autologous stem cell transplantation. Leuk Lymphoma 2009;50:1412-21.
3. DiPersio JF, Micallef IN, Stiff PJ, et al. Phase III prospective randomized double-blind placebo-controlled trial of plerixafor plus granulocyte colony-stimulating factor compared with placebo plus granulocyte colony-stimulating factor for autologous stem-cell mobilization and transplantation for patients with non-Hodgkin's lymphoma. J Clin Oncol 2009;27:4767-73.
4. Laurence AD. Location, movement and survival: the role of chemokines in haematopoiesis and malignancy. Br J Haematol 2006;132:255-67.
5. Zeng Z, Shi YX, Samudio IJ, et al. Targeting the leukemia microenvironment by CXCR4 inhibition overcomes resistance to kinase inhibitors and chemotherapy in AML. Blood 2009;113:6215-24.
6. Tsutsumi H, Tanaka T, Ohashi N, et al. Therapeutic potential of the chemokine receptor CXCR4 antagonists as multifunctional agents. Biopolymers 2007;88:279-89.
7. Juarez J, Bradstock KF, Gottlieb DJ, Bendall LJ. Effects of inhibitors of the chemokine receptor CXCR4 on acute lymphoblastic leukemia cells in vitro. Leukemia 2003;17:1294-300.
8. Tavor S, Eisenbach M, Jacob-Hirsch J, et al. The CXCR4 antagonist AMD3100 impairs survival of human AML cells and induces their differentiation. Leukemia 2008;22:2151-5158.
9. Beider K, Begin M, Abraham M, et al. CXCR4 antagonist 4F-benzoyl-TN14003 inhibits leukemia and multiple myeloma tumor growth. Exp Hematol 2011;39:282-92.
10. Kim HY, Hwang JY, Oh YS, et al. Differential effects of CXCR4 antagonists on the survival and proliferation on myeloid leukemia cells in vitro. Korean J Hematol 2011;46:244-52.