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Review Article

Chemokine Receptor Antagonist - Plerixafor, a Novel Strategy for Blood Stem Cell Mobilization

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ABSTRACT

On December 15, 2008, the US Food and Drug Administration approved plerixafor (Mozobil; Genzyme Corp.), a new small-molecule inhibitor of the CXCR4 chemokine receptor, for use in combination with granulocyte colony-stimulating factor (G-CSF) to mobilize hematopoietic stem cells (HSC) to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM). The use of mobilized peripheral blood stem cells (PBSCs) has largely replaced the use of bone marrow as a source of stem cells for both allogeneic and autologous stem cell transplantation. G-CSF with or without chemotherapy is the most commonly used regimen for stem cell mobilization. This article reviews the clinical efficacy and tolerability of subcutaneous plerixafor for stem-cell mobilization in patients with lymphoma or MM, as well as summarizing its pharmacological properties.

Key words: Chemokine receptor antagonist, Plerixafor, blood stem cell mobilization

INTRODUCTION

Chemokines and their receptors have been identified as mediators of chronic inflammation, which play a key role in the initiation or progression of cancers of the lung, colon, liver, breast, cervix, prostate, bladder, ovary, esophagus, skin and lymphatics.[1-4] Early work has shown that cancer cells from a variety of types of solid cancers expressed higher levels of the chemokine receptors CXCR4, CCR7, CCR9 and CCR10 11–13 (Table 1).[3-6] The ligand of CXCR4, CXCL12, is expressed at high levels in various organs, including the lung, liver, and lymph nodes, which are frequently involved in tumor metastasis. Similarly, CCL21, the ligand of CCR7, is produced by lymph nodes, and CCL27, the ligand of CCR10, is secreted by the skin[7] Based on the demonstration of the roles of chemokines and their receptors in tumor growth, angiogenesis, and metastasis, and upon the availability of drugs targeting these molecules in other diseases, several clinical trials have been launched (Table 2). Compared to clinical trials targeting

chemokines or chemokine receptors for other diseases such as arthritis or asthma, the trials targeting chemokines or their receptors in cancer remain quite limited. These trials have targeted mainly CXCR4, and to a lesser extent CCR4, CCR5 and CCL2. [8-12]

Table-1: Summary of chemokines and chemokine receptors in cancer*

	Ligands	Receptors
Epithelial cells	CXCL1, 3, 5, 6, 8, 10	CXCR1, 2, 4, 6, 7
	CCL2, 4, 5	CCR1, 2, 5, 6, 7, 9, 10
	CX3CL1	CX3CR1
Cancer-associated fibroblasts	CXCL1, 2, 5, 6, 8, 12	CCR5
Endothelial cells	CXCL1, 2, 3, 8	CXCR 2, 3, 4, 7
	CCL2	
	CX3CL1	
Infiltrating leukocytes	CXCL 5, 8	CXCR1, 2
	CCL2, 3, 4	CCR2, 4, 5

* Only chemokines or chemokine receptors expressed at higher levels in epithelial cells compared to normal tissues or expressed by cancer-associated fibroblasts, endothelial cells and infiltrating leukocytes are indicated here

Table-2: Survey of the clinical trials targeting chemokines in cancer.

Target	Drug	Type	Company	Clinical phase	Indication
CXCR4	AMD 3100	Small molecule inhibitor	Genzyme	Phase II/III	Multiple myeloma, acute myeloid leukemia, solid tumors
	MDX-1338	Antibody	Medarex	Phase I	Acute myeloid leukemia
	BKT 140	Small molecule inhibitor	Biokine Therapeutics	Phase I/II	Multiple myeloma
	CTCE-9908	Peptide antagonist	Chemokine Therapeutic Corp.	Phase I/II	Solid tumors
	MSX-122	Small molecule inhibitor	Metastatis Inc	Phase I suspended	Solid tumor
CCR4	KW0761	Antibody	Kyowa Hakko Kogyo Co.	Phase II	Adult T-cell leukemia and lymphoma, peripheral T-cell leukemia
CCR5	Sch-C	Small molecule inhibitor	Schering-Plough	Phase I	Cancer
CCR9	CCX282	Small molecule inhibitor	ChemoCentryx	Phase III	Crohn's disease
CCL2	CNTO 888	Antibody	Centocor	Phase I	Solid tumors
	MLN 1202	Antibody	Millenium	Phase II	Bone metastasis

Plerixafor originally developed as need for new class of antiretroviral drugs. Antiretroviral drugs act at several steps involved in HIV replication. These steps can be divided into entry steps, in which viral envelop glycoprotein and their receptors are involved, and post entry steps, involving viral accessory gene products and the cellular protein with which they interact. Most regimens are combinations of inhibitors of two viral enzymes- reverse transcriptase and protease. There is increasing concern about the long term toxic effect of existing drugs. New treatment option target viral entry into the cell. Plerixafor developed as a new HIV entry inhibitor that inhibit HIV infection through a specific blockade of CXCR4 receptor and inhibit HIV replication at nanomolar concentrations while not being toxic to the host cells at 100000 fold higher concentration. [13,14]

On December 15, 2008 the US Food & Drug Administration approved plerixafor, for use in combination with granulocyte colony stimulating factor (G-CSF) to mobilize hematopoitic stem cells (HSC) to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma (NHL) & multiple myeloma (MM). [15] On medline search we found that in India,

plerixafor was approved on 31 Jan. 2012 for similar indication as an injectable preparation.

Pharmacodynamic & Pharmacokinetic:

Plerixafor is a bicyclam derivative that antagonizes CXCR4 by binding to three acidic residues in the ligand – binding pocket i.e. Asp 171, Asp 262 & Glu 288. CXCR4 receptors also present on CD 34 + cells. It reversibly blocks binding of the ligand, stormal cell- derived factor-1-alpha (SDF-1α). By blocking the interaction between SDF-1α and CXCR4 with plerixafor, mobilization of progenitor cells is triggered. Early clinical trials of plerixafor revealed a remarkable ability to increase CD34 cells in peripheral blood. Blood levels of CD 34 + cells peaked at 9 hours after administration in a dose 0.24 mg/kg in healthy subjects whereas in patients of NHL or MM, blood levels of CD 34 + peaked at 6 hours. In combination with a G-CSF, circulating CD34+ cells in peripheral blood peaked at 9-14 hour.

Pharmacokinetic profile follows a two-compartment model with first-order absorption. A median peak plasma concentration of 0.24 mg/kg of plerixafor occurs 30-60 minutes after subcutaneous dose. Fifty eight percent of drug binds to plasma protein with a 0.3 L/Kg volume of distribution. There is no evidence of involvement of CYP isoenzyme in the process of metabolism. It is eliminated primarily by the renal route. Almost 70 % of the parent drug is excreted in urine in the first 24 hours. Dose must be adjusted for patients with renal impairement. It's renal clearance is 3.5 L/h. It is rapidly cleared with a terminal half life of 4.4 hours in NHL patients, 3.5 hours in Hodgking's lymphoma (HL) and 5.6 hours in MM patients. [16]

Adverse effects:

Plerixafor is well tolerated; the most common adverse effects associated with its use are injection site reactions, gastrointestinal disturbances, dizziness, fatigue and headache. [15]

Indications:

In patients with hematolgic malignancies (i.e. NHL & MM), autologous hematopoietic stem cell (HSC) transplantation is a treatment strategy for restoring normal hematopoietic function. The number of CD34 (+) cells available for transplantation has been reported to be the strongest predictor of transplantation success, as measured by rapid and durable hematopoietic recovery. Currently, granulocyte colony-stimulating factor (G-CSF) alone or G-CSF plus chemotherapy are the most commonly used methods for stem cell mobilization. Unfortunately, 5-30% of patients do not respond to these agents. Results of clinical trials have shown that plerixafor plus G-CSF allow for the collection of a high yield of HSC with fewer apheresis sessions in patients with NHL and MM. Plerixafor has also shown promising results in small studies enrolling patients with Hodgkin's lymphoma. [17] It is mainly used in combination with G-CSF to mobilize haematopoitic stem cells to blood stream for collection and subsequent autologus transplantation in patient with NHL & MM. Considering the previous studies; we also found that plerixafor has a crucial role in lung cancer & HIV infections. Lung cancer cells express CXCR4 (CD 184), a seven transmembrane G-protein coupled chemokine receptor. Stromal cells within the tumor microenvironment constitutively secrete SDF1 / CXCL12, the ligand for CXCR4. Activation of CXCR4 induces lung cancer cell migration and adhesion to stromal cells, which in turn provides growth and drug resistance signals to the tumor cells. CXCR4 antagonist and T 140 analogues can disrupt CXCR4 mediated tumor cell adhesion to stromal cells and sensitize lung cancer cells to cytotoxic drugs. Therefore targeting the CXCR4-

CXCL12 axis is a novel attractive therapeutic approach in small cell lung cancer and non- small cell lung cancer. [18] It has been assumed a good therapeutic option in treatment of HIV infection also. [14]

Clinical trials:

A phase III, multicenter, randomized, double blind, placebo controlled study was conducted by Di Persi JF et al to evaluate the safety and efficacy of plerixafor in mobilizing hematopoitic stem cells for autologous stem cell transplantation in NHL patients. The primary end point was the percentage of patients who collected > or = 5 x 10(6) CD34+ cells/kg in 4 or fewer apheresis days. Patients received granulocyte colony-stimulating factor (G-CSF; 10 microg/kg) subcutaneously daily for up to 8 days. Beginning on evening of day 4 and continuing daily for up to 4 days, patients received either plerixafor (240 microg/kg) or placebo subcutaneously. Starting on day 5, patients began daily apheresis for up to 4 days or until > or = 5 x 10(6) CD34+ cells/kg were collected. Total number of patients included in this study was two hundred and ninety eight. After 12 months of follow up, Eighty-nine (59%) of 150 patients in the plerixafor group and 29 (20%) of 148 patients in the placebo group met the primary end point (P < .001). One hundred thirty-five patients (90%) in plerixaforgroup and 82 patients (55%) in placebo group underwent transplantation after initial mobilization. This finding justify that with plarixafor a significantly higher proportion of patients with non-Hodgkin's lymphoma achieve the optimal CD34+ cell target for transplantation in fewer apheresis days, compared with G-CSF alone. [19]

To evaluate the safety and preliminary efficacy of plerixafor, an open-lable, multicentric, exploratory trial in patients with MM & NHL undergoing stem cell mobilization was conducted by Dugan MJ et al. Forty (26 multiple myeloma and 14 non-Hodgkin's lymphoma) patients were treated with plerixafor. Plerixafor was well tolerated and its addition to a chemo-mobilization regimen resulted in an increase in the peripheral blood CD34+ cells. The mean rate of increase in the peripheral blood CD34+ cells was 2.8 cells/microl/h pre- and 13.3 cells/microl/h post-plerixafor administrations. The data obtained from the analysis of this pilot study suggest that plerixafor can safely be added to chemotherapy-based mobilization regimens and may accelerate the rate of increase in CD34+ cells on the second day of apheresis. [20]

The safety and efficacy of plerixafor were also demonstrated by two other multicentric, randomized, placebo controlled studies in patients with NHL & MM, who were eligible for autologous HSC transplantation. The two randomized studies combined enrolled 600 patients (298 with NHL and 302 with MM). Fifty-nine percent of patients with NHL who were mobilized with G-CSF and plerixafor had peripheral blood HSC collections of > or = 5 x 10(6) CD34+ cells/kg in 4 or fewer apheresis sessions, compared with 20% of patients with NHL who were mobilized with G-CSF and placebo ($p < 0.001$). Seventy-two percent of patients with MM who were mobilized with Mozobil and G-CSF had peripheral blood HSC collections of > or = 6 x 10(6) CD34+ cells/kg in 2 or fewer apheresis sessions, compared with 34% of patients with MM who were mobilized with placebo and G-CSF ($p < 0.001$). This report describes the FDA review supporting the approval of plerixafor. [15]

Addition of plerixafor to chemo-mobilization or G-CSF mobilization may be more cost-effective than its routine use, and it is worth considering in predicted or proven poor mobilizers. Novel mobilization strategies have allowed more successful

stem cell collection in autologous setting, although the effect of plerixafor on graft content and long-term patient outcomes needs further investigation. [21]

CONCLUSION

Plerixafor is a valuable stem cell mobilizer used in combination with G-CSF in patient with lymphoma or MM, particularly in patients who are poor mobilizers.

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