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Deconstructing Blood Cell Research
Building the Hematology Community

Exploring Experimental Hematology: January 2021 (Volume 93)

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Exploring *Experimental Hematology*: AMD3100 re-dosing fails to repeatedly mobilize hematopoietic stem cells in the non-human primate and humanized mouse

Introduction:

In this issue of Simply Blood, we are highlighting and deconstructing one of the journal's latest manuscripts by first author Clare Samuelson. In a recent study in the laboratory of Dr. Hans-Peter Kiem (Fred Hutchinson Cancer Research Center), Samuelson et al. examined the mobilization of hematopoietic stem/progenitor cells (HSPCs) with repeated doses of AMD3100 (plerixafor). (Samuelson et al., 2020).

Stem cell transplantation (SCT), using bone marrow (BM) or mobilized peripheral blood (PB) HSPCs, is a therapy used to cure several cancers, including multiple myeloma, leukemia, lymphomas, and non-malignant hematological diseases. HSPCs are enriched in the PB using a mobilization agent(s), which is a non-invasive procedure compared to a BM harvest and may offer faster hematopoietic reconstitution. AMD3100 (plerixafor) is an antagonist of the CXCR4 receptor, which blocks the CXCR4/CXCL12 (SDF-1) axis that mediates the retention of stem cells in the BM. It is an FDA approved drug used for BM HSPC mobilization to the PB. Unlike granulocyte colony-stimulating factor (G-CSF), which is the most frequently used mobilizing agent in PB SCT donors, AMD3100 is usually associated with minimal side-effects, improved mobilization, and is safe to use in sickle cell disease patients. In some cases, repeated HSPC mobilization is required because of insufficient cell numbers from the first collection, graft failure or disease relapse. However, the efficacy of AMD3100 after repeated dosing has not been fully evaluated.

My reason for reading this paper:

SCT is the ultimate treatment to cure patients with hemoglobinopathies including sickle cell disease (SCD). Unfortunately, obtaining donor HSPCs for transplant is challenging in that less than a quarter of qualified patients find compatible donors. Autologous HSPC transplant using gene-edited cells is an alternative strategy and is successful in clinical trials that included a small cohort of patients. However,

procurement of HSPCs in patients with SCD may require repeated mobilization to achieve an adequate cell dosage for manufacturing and infusions. Due to the risk for SCD-related morbidity with bone marrow harvest, HSPC mobilization using AMD3100 is favorable. Therefore, it is important to examine the efficacy of multiple AMD3100 dosages to understand the limitation of this drug.

Strategy used in this paper:

The authors examined the effect of AMD3100 re-dosing on white blood cells (WBC) and HSPCs using two models: the rhesus macaques (Macaca mulatta) as a non-human primate (NHP), and a humanized NSG mouse model. NHP is an established model for studying the biological mechanisms for translational applications. NHP was used to characterize the mobilized HSPCs by examining the CD34+ and CD90+ cells in the PB at baseline after repeated administration of AMD3100 with 4-16 weeks intervals between doses. To complement their findings in NHPs, they utilized humanized NSG mice that were engrafted with human G-CSF–mobilized, CD34+-enriched PB WBC. These mice were treated with AMD3100 after 20 weeks with 3-4 weeks intervals between doses. PB cells were collected from these mice after each dosing and analyzed for hCD45+ and CD34+ cells, and CXCL12 plasma concentration.

Reasons you should read this paper:

AMD3100 has been used in the clinic for over a decade yet, outstanding questions about the efficacy of redosing in healthy and disease patients remain. The research by Samuelson et al. is the first to show the impact of repeated AMD3100 administration in a clinically relevant pre-clinical animal model, NHP. The decline in mobilization efficacy shown by the authors and from other studies that focused on another agent, G-CSF underscores the complex interplay between these drugs and the HSPCs / BM microenvironment. The question of whether HSPCs orchestrate a tolerance for AMD3100 causing the drop in efficacy or whether a limited number of AMD3100-sensitive cells exist in the BM pool is open for further investigation. Furthermore, their findings propose the need to develop alternative mobilization agents when repeated AMD3100 dosing eventually becomes ineffective, especially for sickle patients, which cannot tolerate G-CSF.

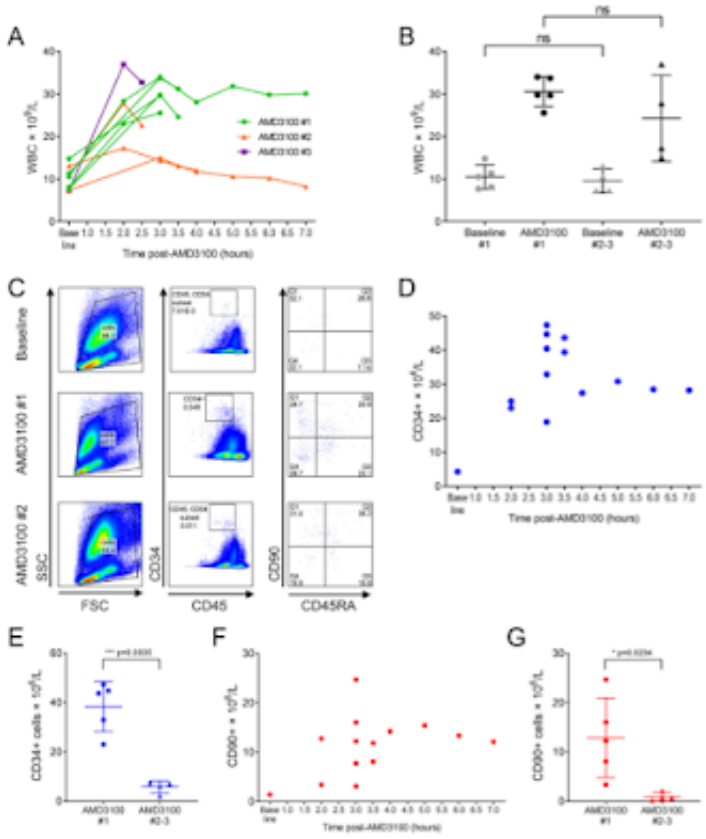

Figure 1: White blood cell counts, CD34+ HSPCs and HSC-enriched CD90+ subpopulation counts in NHPs treated with one or repeated AMD3100 doses.

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