New option for improving hematological recovery: suppression of luteinizing hormone

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Current treatment modalities in leukemia are limited by Bone Marrow (BM) toxicity, a common adverse effect of cytotoxic chemotherapy and transplant-related conditioning regimens, resulting in an increased risk of bleeding and infections. Strategies to protect the BM from cytotoxic injury could augment haematopoietic recovery and improve overall patient outcomes.

Haematopoietic recovery following cytotoxic therapies and irradiation is dependent on the maintenance of a rare population of haematopoietic stem cells (HSCs) - which have the ability to sustain long-term haematopoietic recovery (1, 2). Following HSCT, there is evidence of decreased bone marrow cellularity (3) and diminished colony-forming capacity (4-6) which could last upto ~5 years. Growing evidence attribute these functional defects to several intrinsic and extrinsic regulators which orchestrate radiation-induced senescent and pro-apoptotic programs, thereby dictating HSC fate (7, 8). Several radioprotective agents have been identified (9), but very few mitigate radiation toxicity in the postinjury setting. Historically, mouse studies have informed post-irradiation strategies to promote HSC regeneration which are either cytokine-based, such as a combination of Stem Cell Factor (SCF), FMS-like tyrosine kinase 3 (Flt-3) ligand, Megakaryocyte Growth and Development Factor (MGDF) and Interleukin-3 (IL-3) (10), single agent IL-33 (11), or inhibitors targeting PTPσ (12)- none of which have been confirmed in the clinical setting. Cognate receptors for sex hormones and LH-releasing hormone (LHRH) have been identified on HSCs and implicated in their function (13-15). For example, LH can induce HSC expansion in vitro (13). Moreover, preclinical studies targeting the sex-steroid axis,
have demonstrated enhanced hematopoietic stem cell function and immune recovery, following sex-steroid ablation (16-18) and LHRH-antagonism (13).

In this issue of Haematologica, Dalle and colleagues (19) provide clinical evidence of BM recovery and long-term haematopoietic reconstitution following targeted therapy of the sex-steroid axis. They conducted a retrospective study of premenopausal women with leukemia treated with intensive chemotherapy and investigated the impact of leuprolide (Gonadotropin-releasing hormone, GnRH analogue) on long-term hematopoietic reconstituting ability. Their findings established an association between leuprolide use in leukemic patients and sustained recovery in blood counts. Additionally, patients with AML treated with leuprolide showed higher long-term hemoglobin levels and fewer blood transfusions. Notably, leuprolide treatment had no impact on either overall or event free survival. Finally, multivariate analysis confirmed that leuprolide administration showed an independent association with long-term hematological recovery.

This retrospective clinical study seeks to build upon previous work showing that sex steroid ablation and abrogation of LH can have beneficial effects on hematopoietic reconstitution in preclinical mouse models. However, the study raises several unanswered questions. Firstly, what would be an ideal clinical window and dosage for leuprolide administration following chemotherapy and whether that impacts association with recovery? The preclinical studies with LHRH-antagonists were protective when administered within 24 hours after radiation (13). The current study was limited by sample size to determine statistical significance. Secondly, in relapse cases, where reinduction chemotherapy and irradiation is the standard of care- is additional leuprolide required to help boost hematological tolerance, thereby mitigating hematopoietic stress and temporary cytopenias? Thirdly, are the effects of leuprolide on hematopoietic recovery restricted to bone marrow malignancies or could it be repurposed for
treatment of other malignant and non-malignant diseases with bone marrow involvement? Finally, from a mechanistic perspective—recent work demonstrating a role for estrogens in regulating HSC proliferation and function (14, 15) begs the question: are these effects specific to LH or sex steroids? Considering the rationale for leuprolide to protect against chemoradiation induced premature ovarian failure (20, 21)—preserved estrogen levels could explain the indirect beneficial effects of leuprolide on hematopoietic recovery. Hence, this warrants additional clinical studies accounting for ovarian failure, as that interpretation would restrict the potential utility of this therapy to a younger cohort. These findings also suggest a role of HSC extrinsic factors and raises the question whether leuprolide has a similar cytoprotective effect on the BM microenvironment?

In conclusion, the work by Dalle et al. (19) highlights a potential new therapeutic option for improving hematological recovery in patients undergoing intensive chemotherapy and transplant conditioning regimens, by boosting postinjury long-term hematopoietic reconstitution; although follow-up clinical investigations are warranted for the rational development of leuprolide as a stand-alone therapy, or in conjunction with other agents. This study also underscores the relevance of mouse models to explore additional markers and molecular underpinnings which confer survival advantage in post-irradiated HSCs and BM, as those discoveries will direct us to novel non-cellular approaches to promote hematopoietic recovery and serve as effective therapies against BM toxicity.
References


FIGURE LEGEND
Figure 1. Schematic model of LHRH antagonism mediated cytoprotection which promotes HSC recovery following haematopoietic injury. Dalle et al. provide clinical evidence for BM recovery and long-term hematopoietic reconstitution with LHRH antagonism (leuprolide) in leukemia patients following chemotherapy. HSC: Haematopoietic Stem Cell; HSPC: Haematopoietic Stem and Progenitor Cell; LHCGR: Luteinizing Hormone/Choriogonadotropin Receptor; LH: Luteinizing Hormone. LHRH antagonism: Degarelix and Leuprolide. Figure created with BioRender.com
Steady-state

Self-renewal → LHCGGR → HSC → HSPC → HSPC

Radiation chemotherapy

Hyperproliferative signal → LHCGGR → HSC → HSPC

Loss of Self-renewal

LEUPROLIDE DEGARELIX → LHCGGR → HSC → HSPC → HSPC

Maintenance of Self-renewal