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Review article

Medical and ethical considerations on hematopoietic stem cells mobilization for healthy donors

Aspects médicaux et éthiques de la mobilisation de cellules souches hématopoïétiques chez les donneurs sains

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Abstract

Hematopoietic stem cell transplantation is a common procedure potentially beneficial to many individuals with cancer, hematological, or inherited disorders, and has highlighted the need of related or unrelated donors to perform allograft. Donation of hematopoietic stem cells, either through bone marrow harvest or peripheral blood stem cell collection, is well-established and widespread. Over the past two decades, the peripheral blood stem cell collection by aphaeresis has become the main source of hematopoietic stem cells for transplantation, due to faster engraftment and practicability and lower risk of relapse for high-risk patients. For peripheral blood stem cell donation, donors require mobilization of hematopoietic stem cells from bone marrow into the blood stream. This is performed by growth factors injections. This article is a review of reported applications of growth factors (original granulocyte colony stimulating factor and its biosimilars), for healthy donors' peripheral blood stem cell mobilization, in terms of toxicity, side effects, efficacy and follow-up. There is still an ethical dilemma for clinicians involved in allograft, because they expose healthy donors to drugs. It is important to dispel some of the critical concerns regarding their use in healthy volunteers, particularly because they receive no personal therapeutic benefit from this procedure.

Keywords: Granulocyte colony stimulating factor; Biosimilars; Donor; Hematopoïetic stem cells; Side effects

Résumé

La transplantation de cellules souches hématopoïétiques est une procédure établie depuis de nombreuses années pour le traitement de patients atteints de pathologies hématologiques, de certaines tumeurs solides ou de maladies génétiques. Les cellules souches hématopoïétiques sont issues d'un prélèvement se faisant par recueil des cellules souches soit dans la moelle osseuse, soit dans la circulation sanguine après une phase dite de « mobilisation ». Ce second type de prélèvement est majoritaire depuis de nombreuses années, car un prélèvement des cellules souches dites périphériques permet une prise de greffe plus rapide et un moindre risque de rechute chez les patients à haut risque. Le recueil de cellules souches périphériques par technique d'aphérèse nécessite au préalable la mobilisation des cellules souches hématopoïétiques de la moelle osseuse vers la circulation sanguine du donneur. Cela est généré par l'injection de facteurs de croissance. Cet article se propose de faire le point sur les molécules utilisées pour la mobilisation chez les donneurs volontaires (G-CSF princeps et biosimilaires), en termes de toxicité, d'effets secondaires, d'efficacité de la mobilisation et de suivi des donneurs. Il existe toujours un problème éthique pour les cliniciens, quant à la prescription d'un facteur de croissance chez un donneur sain. Il est important de garder à l'esprit que le donneur ne retire aucun bénéfice thérapeutique personnel de son don. Il faut donc proposer au donneur volontaire une procédure du don la plus efficace et la plus sure possible.

Mots clés : G-CSF ; Biosimilaires ; Donneur volontaire ; Cellules souches hématopoïétiques ; Effets secondaires

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Allogeneic stem cell transplantation is a standard therapy for hematological malignant or non-malignant diseases. The ability to perform hematopoietic stem cell transplantation (HSCT) depends on the availability of a suitable HLA (human leucocyte antigen) matched donor. In fact, HLA compatibility is a crucial parameter that influences the clinical outcome of HSCT. Unfortunately, on the basis of average of family size, less than 30% of patients will have a 100% HLA compatible sibling donor. Then, HSCT could be performed with an unrelated totally HLA matched donor, from the 30 million of anonymous donors registered around the world. It could also be performed with an alternative donor (donor with a mismatch on a HLA locus called 9/10 or donor matched on one HLA haplotype called haplo-identical donor).

There are three sources of hematopoietic stem cells:

- bone marrow (BM);
- peripheral blood stem cells (PBSC);
- umbilical cord blood.

Mobilized PBSC in replacing BM have been increasingly used to collect hematopoietic stem cells. This procedure requires mobilization of hematopoietic stem cells from bone marrow into bloodstream, before collection [1].

This article focuses on healthy donors PBSC mobilization, using mobilizing agents such as original granulocyte colony stimulating factor (G-CSF) or its biosimilars. Many ethical concerns have been raised about their administration in healthy volunteers. Their use could possibly constitute a risk for healthy donors either in a short term or as a delayed effect. This article provides a review of administration of G-CSF or its biosimilars to healthy donors, in terms of toxicity, side effects, efficacy and follow-up.

A stem cell is defined by two key-properties: ability of self-renewal and pluripotentiality. Hematopoietic stem cells (HSC) are able to give rise to any and all of the mature functional hematopoietic cell types from different lineages (erythrocytes, megacaryocytes, granuloctes, monocytes, lymphocytes, macrophages and mast cells). HSC is a rare but important cell in bone marrow (estimated frequency of one in 10,000 cells). The HSC population is heterogenic and varying nomenclature has been used to name these cells. The clonal composition within the HSC compartment changes according to the increasing age, the decreasing ability to self-renewal and the differentiation manner. Lineage reconstitution kinetic after HSCT depends on three HSC subpopulations, based on reconstitution time period:

- long-term stem cells (LT-HSC);
- intermediate term stem cells (IT-HSC);
- short term stem cells (ST-HSC).

Ema et al. have proposed a reclassification based on granulocyte reconstitution levels: ST-HSC play a role within 6 months after ST-HSC transplantation, IT-HSC is involved in immune reconstitution up to 12 months after IT-HSC transplantation, whereas LT-HSC play a role for the hematopoietic reconstitution over months (greater than 12 months) [2].

HSC compartment contains more than one population phenotypically identifiable. CD34 is a transmembrane phosphoglycoprotein, which has become the main marker for HSC and progenitors cells. Many studies have correlated the total number of cells, or the number of CD34 positive cells and hematopoietic reconstitution. However, this marker is not specific, because many others cells express CD34, as endothelial cells for example. Moreover, some hematopoietic stem cells, considered as very primitive, do not express the marker CD34. In many publications upon healthy donors' mobilization, CD34 positive cell count has been used as a predictive marker of good yield. Unfortunately, CD34 negative HSC could be mobilized into blood stream as the same manner than CD34 positive HSC and clinicians must keep in mind that CD34 negative cells could have both clinical significance and therapeutic potential. So, there is frequently a misconception that HSC is a synonym of CD34 positive cell. The term CD34+ cell should be restricted to functionally cell entities [3].

Regarding CD34 positives cells, G-CSF permits to collect a graft with different subpopulations: CD34+/CD38+ cells (for early hematopoietic reconstitution) and CD34+/CD38- or CD34+/HLA-DR- (for late and durable hematopoietic reconstitution). G-CSF has two roles: mobilization and differentiation, both mediated by its action on the G-CSF receptor [4].

G-CSF is also able to promote immunomodulatory effects on lymphocytes compartment in the graft, especially on T lymphocytes by skewing the Th1/Th2 cytokine balance toward increased levels of Th2 cytokines. The decrease of pro-inflammatory cytokines (Th1) and the Th2 cytokines production could explain that patients, who underwent PBSC transplantation, are less exposed to the common side effect of graft versus host disease (GVHD). G-CSF tempers T cell alloreactivity, but decreases graft versus leukemia (GVL) effect too [4].

In France, the molecule used to mobilize and collect hematopoietic progenitor cells from healthy donors is recombinant human granulocyte colony stimulating factor. G-CSF is a protein that stimulates the proliferation of myeloid progenitor cells and their differentiation into functionally mature neutrophils, and that accelerates neutrophil release from the bone marrow [5]. Two recombinants granulocyte growth factors are widely approved for healthy volunteer's mobilization: the filgrastim (Neupogen®) and the lenograstim, glycosylated formulation (Granocyte®). The use of G-CSF is generally standardized and donors are treated with a posology of 10 μg/kg/day for a maximum of 5 days. These molecules have the same efficacy to mobilize peripheral blood stem cells from healthy donors; the majority of volunteers could achieve the required dose of 4×10^6 CD34 + cells per kg recipient weight, in a single aphaeresis procedure [6,7]. Clinical data from healthy donors suggest that there is no reason to prefer one to each other [8].

Large individual variations exist within the population of healthy volunteers treated with the same dose of G-CSF. Some healthy donors (2% called poor mobilizers) may show poor mobilization response to G-CSF and poor subsequent CD34+

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