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Review

Mobilization and collection of peripheral blood stem cells in healthy donors: Risks, adverse events and follow-up

Mobilisation et recueil des cellules souches hématopoïétiques périphériques chez les donneurs volontaires : risques, effets secondaires et suivi

V. Moalic

Laboratoire de génétique moléculaire et d'histocompatibilité, pôle de pathologie biologie, CHRU Morvan, bâtiment 5bis, RDC, 2, avenue Foch, 29609 Brest cedex, France

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ABSTRACT

Allogeneic haematopoietic stem cell transplantation is the choice treatment for many haematological malignancies. Granulocyte-colony-stimulating factor (G-CSF) has been widely used to mobilize stem cells into the peripheral blood from healthy siblings or volunteer unrelated donors. To a large extent, the use of mobilized peripheral blood haematopoietic stem cells has replaced marrow-derived stem cells as the preferred source of donor haematopoietic stem cells. Clinicians have been aware since the first clinical use, that administration of G-CSF, even in a single short course, could possibly be a risk for healthy donors either in short-term or as a delayed effect. The immediate side effects of G-CSF have been established for a long time, most of them are frequent but transient, self-limited and without long-term consequences. Questions have been raised about potential long-term adverse effects such as an elevated risk of haematological malignancies after G-CSF administration. More long-term safety data from registries are needed to adequately evaluate such a relationship. Our objective in this article is to provide an in-depth review of reported adverse events associated with the use of G-CSF in healthy donors and to focus attention on unanswered questions related to their long-term follow-up.

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RÉSUMÉ

L'allogreffe de cellules souches hématopoïétiques est indiquée dans le cadre du traitement de nombreuses hémopathies. Le facteur de croissance hématopoïétique G-CSF est largement utilisé dans le but de mobiliser des cellules souches hématopoïétiques recueillies dans le sang périphérique chez les donneurs apparentés ou non apparentés aux patients. Ces cellules sont devenues la source cellulaire préférentielle pour les allogreffes par rapport aux cellules souches hématopoïétiques médullaires. Depuis la première utilisation du facteur de croissance hématopoïétique, le corps médical est conscient des risques potentiels encourus chez les volontaires sains à court et long terme. Les effets secondaires immédiats sont bien connus, le plus souvent transitoires et sans conséquence importante. En revanche, qu'en est-il des effets à distance pour les donneurs volontaires, concernant notamment le risque leucémogène non établi du G-CSF ? La question reste toujours en débat et le suivi sur plusieurs années de donneurs volontaires mobilisés est nécessaire pour établir une possible relation. Cet article se propose de faire le point sur les effets secondaires liés à l'administration du G-CSF chez les donneurs volontaires de cellules souches hématopoïétiques et souligne l'importance du suivi de ces donneurs afin de connaître les potentiels effets délétères à long terme d'une stimulation par G-CSF.

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Allogeneic stem cell transplantation, used for many years, represents an important therapeutic tool for treatment of malignant or non-malignant blood diseases. This latter is based on combined action of conditioning regimen, which allows reducing of tumoral cells, making room for the graft, and creating antitumoral control mediated by allogeneic T-cells named Graft Versus Leukemia effect (GVL). The origin of haematopoietic stem

E-mail address: virginie.moalic@chu-brest.fr

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cells is diverse: Bone Marrow (BM) derived stem cells collected from liquid marrow aspiration in the donor's pelvic bones during general anesthesia, Peripherical blood stem cells (PBSC) obtained by leukapheresis after mobilization of the donor for 4 or 5 days by an haematopoietic growth factor, or stem cells from cord blood units stored in public or private cord blood banks. The main rationale behind PBSC allografting is the consistent collection of larger numbers of haematopoietic precursors (CD34+ cells), which results in accelerated neutrophil and platelet recovery, when compared to patients undergoing bone marrow transplantation. However, there is an increase risk of chronic graft versus host disease (cGVHD) due to the significantly larger number of T lymphocytes in the graft. In France, as in many countries, PBSC has become the preferred source of haematopoietic stem cells for transplantation [1].

1. Growth factors used for peripherical blood stem cells mobilization

Granulocyte-Colony-Stimulating Factor (G-CSF) is the most frequent cytokine administered to French healthy donors as a part of the regimen to mobilize CD34+ cells into the peripherical blood. Two recombinant granulocyte growth factors can be used: the filgrastim (Neupogen®, Zarzio®, Ratiograstim®, and Tevagrastim®) and the lenograstim (Granocyte®). These two molecules are not identical: their amino acid sequence is different, and lenograstim is glycosylated whereas filgrastim is not. Healthy donors receive G-CSF subcutaneously at a dose of 10 μg/kg/day for 4 or 5 days, with harvest on the fifth or on the sixth day if necessary. The majority of donors could achieve the required recipient dose of 4×10^E6 CD34+ cells per kg in a single apheresis procedure [2]. Studies show no remarkable difference for obtaining PBSC between the two factors [3].

Pegfilgrastim (Neulasta®) is a glycosylated form of filgrastim with a long acting effect. Attachment of the polyethylene glycol chain reduces renal excretion and marks proteolytic cleavage sites resulting in elevated G-CSF serum levels. Its approved indication is only the reduction of febrile neutropenia when used as prophylaxis following chemotherapy [4,5]. Sarmograstim (Granulocyte Macrophage Colony Stimulating Factor or GM-CSF) is not used for PBSC mobilization, because it is less tolerated and less effective than G-CSF when used alone [5].

Plerixafor (Mozobil®) is a bicyclam compound, a competitive inhibitor of the SDF-1/CXCR4 axis. It reduces CD34+ progenitors anchoring to the bone marrow microenvironment. An upsurge of CD34+ cells is evident 9 hours after subcutaneous injection [6]. It can be used alone or in addition with G-CSF, for normal donors who failed to mobilize adequate numbers of stem cells with G-CSF. In France, this molecule is only approved for autologous stem cells mobilization in patients with multiple myeloma or non-Hodgkin's lymphoma. Pilot studies in normal donors to mobilize sufficient stem cells have been performed abroad. The collection of PBSC obtained with Plerixafor is rich in T lymphocytes, leading to an increased risk of GVHD. Short-term side effects are well known: gastro-intestinal discomfort, headache, pain at the injection site [7]. No long-term side effects have been reported to date (8 months for donor's follow-up) [8].

Due to the shortened mobilization following the subcutaneous injection, this drug has been used for an emergency PBSC mobilization in a normal donor for whom bone marrow harvest has been cancelled as the last minute. The donor received one dose of G-CSF (5 ug/kg SC) at 5.00 p.m., while plerixafor was given 6 hours later at 11.00 p.m. (240 μg/kg SC). At 9.00 a.m. the next day, the number of white blood cells in the donor was 61G/l, and the CD34+ cells count was 30 $X10^E6$/l. The leukapheresis performed the same day yielded 2×10^E6 CD34+ per kg of recipient body weight [9]. Similarly, Neumann et al. reported for the first time a successful PBSC mobilization by adding Plerixafor to G-CSF in a volunteer, who failed to mobilize with G-CSF alone [8].

2. Response parameters

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+ apheresis yields [10]. The reasons are yet unknown, but experiments in mice suggest the involvement of genetic factors [11]. In the study of Suzuya et al. [12], the most important factor for predicting a good CD34+ yield is donors' age. Advanced age is an unfavorable factor. Similarly, adequate donor's blood counts during treatment and just before mobilization correlate with good mobilization. On average, donors over 55 years are poor mobilizers [10,13]. In France, guidelines exist to protect donors and contra-indications to G-CSF injection published by the national registry of bone marrow donor volunteers are strictly observed (Table 1). Eighteen is the age of legal consent. Donors are eligible through their 50th year until their 51st birthday for PBSC collection. This age threshold was set up because older donors are at increased risk of medical complications. The donor's weight does not play an important role [10]. For Vasu et al. [14], three variables are correlated with poor mobilization: advanced age, female gender and white ethnicity. It would be necessary to focus as much as possible on young male donors [15]. The best predictive parameter for a good mobilization remains CD34+ cells count before apheresis [16].

3. Side effects after granulocyte-colony-stimulating factor administration in healthy donors

Numerous publications have reported common side effects following G-CSF injection in healthy donors (Table 2). In a retrospective analysis about more than 1400 donors from International Bone Marrow Transplant Registry (IBMTR) and European Group for Blood and Marrow Transplantation (EBMT) registers, the rate of serious complications post G-CSF administration would be 1.1% [17]. Some complications are due to a central venous catheter used for apheresis [17]. A recent alert from World Marrow Donor Association (WMDA) reported a donor death due to a tension haemo/pneumothorax related to the insertion of a central venous catheter. In France, central catheterization for PBSC collection is prohibited for anonymous donors, but is allowed for a sibling donor. Side effects are generally mild to moderate including bone pains (52% to 80%) [18], headache, fatigue and nausea, fever and insomnia [19,20]. Bone pains decrease under acetaminophen and disappear after the end of the treatment. The pain and the

Table 1
Main contra-indications to granulocyte-colony-stimulating factor injection in French healthy donors.

Age under 18 years and above 51 years
Pregnancy or breastfeeding
History of neoplasia
Splenomegaly
Auto-immunes diseases
Inherited thrombophilia disorders, myocardial infarction, coronary artery embolism, hypertension
Severe allergic reactions
Treatment with anticoagulants
General anesthesia prohibited if poor mobilization

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