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Perspective

Addressing Ethical and Procedural Principles for Unrelated Allogeneic Hematopoietic Progenitor Cell Donation in a Changing Medical Environment

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INTRODUCTION

Since its establishment, the World Marrow Donor Association (WMDA) has developed standards in line with published international guidelines and policies to ensure the safety of adult volunteer donors and quality of hematopoietic progenitor cell (HPC) products [1]. The requirements for (written) informed consent at time of the various stages from recruitment to donation are described in the WMDA Standards [2]. Recruitment, high-resolution HLA typing, verification typing, and work-up for donation of standard cell products (bone marrow or peripheral blood stem cell [PBSC] donation or subsequent donation, including therapeutic T cells), are considered standard procedures as long as they themselves are not part of a research protocol [3]. However, in light of ongoing developments in the treatment of hematological disorders, immune deficiencies, and other diseases that are potentially curable by hematopoietic stem cell transplantation (HSCT), organizations providing HPCs are increasingly confronted with requests for (1) donations of other than standard cell products, (2) multiple donations, (3) genetic testing of donor material, or (4) donations for the treatment of new indications. As a consequence, HPC donor registries (DRs), donor centers (DCs), or collection centers are sometimes forced to adjust or override their procedures to meet nonstandard requests. A DR is a registry of volunteers recruited to be HPC donors. A DR can either function as a single DC or as a centralized hub for several DCs. Therefore, DRs and DCs are often combined (DR/DCs). Although criteria for informed consent procedures for unrelated HPC donors in general terms have been previously published [3], and the use of donors as research subjects has been extensively discussed by King et al. [4], in practice, HPC DRs are frequently confronted with additional requests that potentially may create considerable ethical dilemmas.

In this paper, ethical and procedural principles in the context of HPC donation and requests for nonstandard donations are further clarified based on examples from daily practice. The goal is twofold: to provide guidance on applying ethical principles and to create a basis for awareness and

Guidance paper.

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understanding for the position of HPC adult volunteer donors and the organizations providing HPCs from these donors in the dynamic field of allogeneic HSCT, by posing questions.

EXPECTATIONS AND COMMITMENT

During the process of unrelated donor search, donation, and transplantation, expectations of all parties involved may not always meet. From registration on, both donor and DR/DCs expect to rely on each other. This unwritten agreement is renewed each time a donor is approached by the DR/DC (eg, for extended HLA typing, work-up request), and may vary during different stages of the process [5]. Although donors are expected to be motivated and reliable, registration does not guarantee the obligation to donate, not even after a previous donation to a particular recipient. Commitment implies the donor's decision to fulfill a given task such as a HPC donation, but demands that HPC DRs set reasonable limits and act according to international criteria as published by WMDA, as levels of commitment may vary. The DR/DC has the responsibility to protect the donor's interest, while respecting the donor's rights in light of ethical principles. Very committed donors may not consider reasonable limits pertaining to their own safety. On the other end of the spectrum, there may be donors who are not aware of the consequences, if they opt out, thus causing ineffective donor searches. Donors, originally enlisted for bone marrow donation may instead be requested to donate mobilized PBSC. Consideration for each other's standpoint and an open dialogue between transplant center (TC), and DR/DC is crucial, as decisions can be seen as a matter of life and death. In this context it is essential that the DR/DCs function as connectors and facilitators. It is to the credit of joint efforts of the many international transplantation registry societies and their umbrella organization, the Worldwide Network for Blood and Marrow Transplantation, along with the WMDA, that this is possible. Standpoints of professional organizations may differ. It is, however, a challenge to see how expectations of both donors and recipients can be met in a timely manner, without jeopardizing any of the parties involved.

BENEFICENCE

The concept of beneficence is related to a group of norms for providing benefits, such as kindness, mercy, or charity, and sometimes referred to as the core value of health care ethics [6]. In this light, donation of cells or tissue is an altruistic act, driven by the motivation to do something with the intention to benefit another person. In health care, beneficence encompasses the idea that a physician should always act in the best interest of his patient. If the act poses a certain risk to the actor (the donor), it is important to address this risk and balance the benefits for both donor and patient [7]. In other words, the physician should prevent the donor from entering potentially harmful situations. An HPC donor is considered a healthy person (ie, *not* a patient) and donation of HPCs is not in his/ or her own physical interest. New procedures may not only affect the burden of the donation procedure (longer or multiple sessions to reach the requested number of cells), but also place commitment at risk (multiple preplanned donation requests), and have an impact on the donor's mental or physical health. The WMDA Standards are the basis of assuring the principle of beneficence [2].

Aspirated bone marrow, PBSCs collected by apheresis after "mobilization" of the donor with a cytokine like filgrastim (granulocyte colony-stimulating factor), and umbilical cord blood are considered standard HPC products to be used for HSCT for a number of routine indications [8]. Also, PB mononuclear cells collected by "unmobilized" apheresis from HPC donors after previous HPC donation is also considered a standard cell product. A request for a standard product to be used for a nonroutine indication, or a nonstandard product for a routine indication, are considered nonstandard requests.

For HPC collections not generally considered as standard, an approved protocol must be presented before a DR/DC can agree to proceed; extensive (written and when necessary translated) information for the donor must be available before informed consent can be requested. King et al. [4] stated that if a research protocol requires that the HPC collection procedure be altered in any way, the HPC collection procedure becomes a research activity and the donor a research subject. For instance, for the collection of large numbers of cells, the apheresis procedure may have to be prolonged or modified (see case A) (Box 1).

AUTONOMY AND NONMALEFICENCE

New insights are leading to the development of different (innovative) treatment protocols resulting in donation requests for other than standard products, or multiple donations. In turn, this may lead to significantly prolonged commitment of the donor. A donor who knows beforehand that subsequent donation is part of the treatment protocol, but has had a negative initial donation experience, may feel coerced to proceed. Investigation into how multiple donation requests affect the donor, both physically and mentally, should be incorporated into the development of new treatment protocols. New treatment protocols involve the infusion of more than 1 donor-derived product, such as preemptive donor lymphocyte infusions at fixed times after transplantation. Multiple donation requests or extended collection procedures add to not only the physical burden, but also the mental burden for the donor. The number of worldwide requests for therapeutic T cells increased from 94 (1997) to 1310 donations in 2016 (see Figure 1). An increase in the number of bone marrow and PBSCs for subsequent infusion was also seen (Figure 2). Although new treatment protocols are initially approved by medical ethical committees or institutional review boards, the care for the donor and how the protocol affects the donor is often scantily addressed in these protocols, especially when numbers of requests per donor are increasing. A TC may interpret the donor's consent to the first donation, as an automatic unconditional permission for all subsequent donations.

Respect for autonomy is one of the fundamental principles of bioethics, and as such it is a norm for regarding the decision-making capacities of an individual [9]. Regard for autonomy is in line with respect for integrity. Even though an autonomous person is, fundamentally, one who is able to act according to his or her own direction, it is a physician's obligation to set the preconditions that are necessary for deliberate decision making, keeping in mind the uniqueness of the person. In the context of HPC donation, autonomy is at the basis for the decision to become a HPC donor, as well as informed consent at the several stages of the donation process. During this process (eg, extended typing, verification typing, work-up), a donor may express a preference for bone marrow donation under general anaesthesia or a PBSC collection, after administration of hematopoietic growth factors, or decide not to proceed to donation. This right to self-determination has to be respected, even if the consequence for the recipient is undesirable.