Hematopoietic stem cell apheresis in the context of a related allogeneic transplant for acute myeloid leukemia: an unexpected outcome, medical emergency and ethical issue

Hematopoietic stem cell transplantation (HSCT) is recognized as a life-saving procedure for patients with severe hematologic malignancies and is being increasingly performed in specialized centers around the world.

In autologous HSCT, hematopoietic progenitor cells (HPC) are mobilized into the blood of patients, usually using chemotherapy and/or granulocyte colony-stimulating factors (G-CSF), in order to be collected (apheresis technique) and subsequently managed by a processing laboratory for cryopreservation. Stem cells are later thawed and reinfused into the patient after the conditioning regimen (intensive chemotherapy with or without radiotherapy), to allow the immune reconstitution.

Allogeneic HSCT is indicated for specific diseases/clinical conditions, and requires the availability of HLA-compatible donors, related or not, who have to consent to clinical evaluation and screening for infectious diseases prior to G-CSF mobilization and apheresis procedure(s). In Belgium, stem cells are not cryopreserved but transfused into the patient (recipient) at the latest 48 hours after collection. This is defined in the Belgian Marrow Donor Program Standards (for unrelated volunteer donors)[1]: "Cryopreservation of HPC-M or HPA-A is not recommended and should not be done, except for very specific cases and Medical Advisory Committee (MAC) approval is mandatory for Belgian donors".

This creates a tricky situation, as quality standards and regulations applicable to HSCT Centers state that every allogeneic donor (whether related or unrelated) shall have the right to refuse to donate after selection and consent, and concurrently "shall be informed of the potential consequences to a recipient of such refusal".[2] Hence, if HPC are not available in due time following the conditioning regimen, the patient's immune reconstitution is impossible.

We report here the case of a 58-year old man recently included in the allogeneic HSCT program of CHU UCL Namur. He was referred to our Center in June 2016 with a diagnosis of leukemia (poor prognosis acute myeloid leukemia, *FLT3* mutation) and a first complete remission was obtained after induction chemotherapy. As two HLA-compatible related donors were identified, the indication for allogeneic HSCT following a fludarabine/busulfan reduced intensity conditioning regimen was confirmed.

One donor was selected after initial assessment on June 7th at our HPC Collection Center, and signed informed consent to donate. His eligibility was confirmed on July 19th (after medical evaluation and results of serology for infectious diseases). The recipient's conditioning regimen was therefore initiated on July 28th in a protective isolation room of our Hematology Department, with the allogeneic transplant scheduled for August 3rd.

When the donor presented at the Collection Center on August 2nd for the apheresis procedure, the CD34-positive cell count was found to be far below the expected target after G-CSF mobilization (8/μL). Further investigation was performed (flow cytometry) resulting in the identification of a monoclonal lymphocytosis of undetermined significance, which would theoretically have contraindicated the donation of HPC.

Fortunately, the second HLA-compatible related donor could be contacted while on holiday abroad, and agreed to initiate G-CSF mobilization so that his HPC could be collected. A medical consultation was scheduled for August 5th at the Collection Center of CHU UCL Namur to screen for infectious diseases and confirm eligibility. Unexpectedly, the donor developed a severe allergic reaction following the first subcutaneous administration of G-CSF on August 4th and was admitted to the Emergency Department of an external hospital, with a favorable outcome. To our knowledge such a clinical event has rarely been reported.[3,4]

As the recipient's conditioning regimen had already been initiated, we considered returning to the previously selected, first donor. After weighing the benefit-risk balance, obtaining the donor's consent and receiving a favorable opinion from the Ethical Committee of CHU UCL Namur, he was referred to a collaborating center for the collection of bone marrow HPC. The marrow collection procedure was performed on August 8th without complications. The recipient achieved proper hematopoietic reconstitution and was discharged on September 2nd.

We believe that this situation raises important medical and ethical issues surrounding the allogeneic HSCT process.

Since a donor theoretically has the possibility to retract after the initiation of the recipient's conditioning regimen, a retraction or an unexpected medical event immediately preceding or directly related to the HPC collection procedure could have tragic consequences for the patient undergoing intensive chemotherapy.

Current guidelines focusing on HPC donors do not explicitly address this specific issue. Worldwide practice is largely in favor of transport and transplant of fresh allogeneic HPC collected by apheresis or from bone marrow (excluding cord blood units that are cryopreserved and must be transported in dry shippers).[5] The main reasons for objections to cryopreservation are possible adverse reactions to the cryoprotectant (dimethylsulfoxide) added to HPC, bacterial contamination due to additional manipulation of the product in the laboratory, and an impact of the cryopreservation and thawing process on engraftment efficiency. Two recent studies underline the potential benefits of HPC cryopreservation in the context of allogeneic transplantation, while emphasizing the need for further clinical evaluation. We believe that there are currently no evidence-based clinical data that can unilaterally push forward the use of fresh HPC.[6-8]

The best rationale supporting collection and transplantation of HPC *just in time* should be the concern to avoid performing an unnecessary medical procedure in a donor, in the case of late transplant cancellation (recipient's worsening condition or death). This is an ethical and medical issue, which needs to be discussed in view of our recent experience.

It is the responsibility of the medical team to ensure that harm shall not overcome benefits, and in this context that the patient shall be rescued from the intensive conditioning regimen with HPC available for transplantation. We believe that to this end a scheduled anticipated HPC collection and cryopreservation procedure could be the most appropriate option. This could be performed between 30 and 15 days before transplantation, minimizing the risk of non-utilization of collected cells.

Finally, at our Center, we have to deal with a high rate of HPC-apheresis donors with psychological distress, which can be related directly to the donation process and their responsibility in that context.[9] Anticipating the apheresis procedure while the recipient is not yet undergoing intensive chemotherapy could have a positive

impact on this emotional burden, an aspect that should specifically be evaluated.

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