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

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Hematopoietic Stem Cell Apheresis procedure in a context of related allogeneic transplant for acute myeloid leukemia: unexpected outcome, medical emergency and ethical issue.

Hematopoietic Stem Cell Transplant (HSCT) is recognized as a life-saving procedure for patients with severe hematological malignancies, increasingly performed in specialized centers around the world.

In autologous HSCT, Hematopoietic Progenitor Cells (HPC) are mobilized in 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 to 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 require the availability of HLA-compatible (un)related donors who have to consent to clinical evaluation and infectious diseases screening prior to G-CSF mobilization and apheresis procedure(s). Specifically, stem cells are not cryopreserved but transfused to the patient (recipient) at the latest 48 hours after collection. This is defined in the Marrow Donor Program Belgium 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 is a tricky situation, as quality standards and regulations applicable to HSCT Centers state that each 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 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 leukemia diagnosis (poor prognosis AML, FLT3 mutation) and Complete Remission (CR1) 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 (RIC) regimen was confirmed.

One donor was selected after initial assessment on June 7th at our HPC Collection Center, and signed the informed consent to donate. His eligibility was confirmed on July 19th (medical evaluation and infectious diseases serological results). 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.

While the donor presented to the Collection Center on August 2nd for the apheresis procedure, CD34 positive cells turned out to be far below 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 (MLUS), that theoretically would have contraindicated the HSC-A donation.

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

As the conditioning regimen of the recipient had already been initiated, we considered to come back to the first donor previously selected. After considering a benefit-risk balance, then achieving donor consent and receiving a favorable advice of the Ethical Committee of CHU UCL Namur, he was

referred to a collaborating center for HPC-M procedure. Marrow collection was performed on August 8th without complication. The recipient presented a proper hematopoietic reconstitution and was discharged on September 2nd.

We believe that such a situation raises important medical and ethical issues surrounding the allogeneic HSC transplant process.

Since a donor has theoretically 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 can have tragic consequences for the patient undergoing intensive chemotherapy.

Current guidelines focusing on HPC donors do not explicitly address that specific issue. Worldwide practices are largely in favor of transport and transplant of fresh allogeneic HPC-A or HPC-M (except for cord blood units that are cryopreserved and must be transported in dry shippers). [5] Main reasons stated against cryopreservation are possible adverse reactions to the cryoprotectant added to HPC (DMSO), bacterial contamination due to additional laboratory product manipulations, and impact of the cryopreservation and thawing process on the engraftment efficiency. Two recent studies underline the potential benefits of HPC cryopreservation in the context of allogeneic transplant, while emphasizing the need for further clinical evaluation. Currently we believe that there are no evidence-based clinical data that can unilaterally push forward the use of fresh HPC. [6, 7, 8]

The most appropriate rationale to support a fresh HPC collect and transplant *just in time* should be the concern to potentially avoid the performance of an unnecessary medical procedure for the donor, in 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 the harms shall not overcome the benefits, and in that context that the intensive conditioning regimen shall be rescued 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. That procedure could be performed between 30 and 15 days before transplantation, minimizing the risk of non-utilization of collected cells.

Finally, we have to deal at our Center with a high rate of HSC-A donors presenting psychological distress that can directly be related 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 positively impact on that emotional burden, and that should specifically be evaluated.

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