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Move on air: Webinar for education in stem cells mobilization Report I

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CLINICAL EVALUATION OF PATIENTS TO MOBILIZE

Autologous stem cell transplantation (ASCT) is a mainstream therapy for patients with chemosensitive lymphoma or multiple myeloma (MM); transplants are frequently performed using mobilized hemopoietic stem cells (HSC).
However 5 to 40% of MM or lymphoma patients fail to mobilize an adequate number of peripheral blood stem cells (PBSCs) and cannot proceed to the planned ASCT.
During these years, various criteria have been proposed to define a successful CD34+ cell mobilization and an adequate aphaeresis yield, particularly to individuate the "perfect collection".
These guidelines showed the minimum threshold of CD34+ cells to be infused must be ≥2-2.5x10^6 kg for every single ASCT, although the optimal dose for platelet engraftment is about 4-6x10^6 CD34+ kg.
In Europe, the combination of plerixafor + granulocyte colony-stimulating factor (GCSF) is approved for the mobilization of hematopoietic stem cells for autologous transplantation in patients with lymphoma and myeloma whose cells mobilize poorly; in fact, this kind of mobilization allowed the majority of patients with myeloma or non-Hodgkin's lymphoma to undergo transplantation with minimal toxicity (1).

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The identification of the so-called "poor mobilize" (PM), a subgroup of patients who do not respond to such mobilization protocols, is also very important.
The main parameters to identify the PM are: the ability to mobilize and then to get a consistent CD34+ circulating concentration, obtaining an adequate apheresis product, and the transplant outcome related to the kinetics of engraftment, closely related with the infused cells (2).
In this regard, the GITMO-WG proposed a project that aims to optimize the identification of "poor mobilizer" patient. Particularly:

1. prior to mobilization, assess risk factors such as age and previous chemo or radiotherapy;
2. during the mobilization, monitoring markers in peripheral blood, as the CD34+ peak, WBC, MNC and platelets;
3. after mobilization, measure the mobilization capacity and the performance of apheresis procedure (3).

ELEGIBILITY OF PATIENTS TO THE MOBILIZATION AND COLLECTION OF STEM CELLS

The main criteria to define the eligibility of patients to the mobilization and collection of stem cells are the CD34+ cells concentration in peripheral blood, the timing of collection and the blood volume processing. As regards to the concentration of CD34+ cells, if these are >20 µL and leukocytes >500 µL in daily monitoring, we can start collecting; if the CD34+ cells are between 20 and 5/ µL and leukocytes >5,000 µL, it involves the use of plerixafor "on demand"; if despite the plerixafor the CD34+ cells are <10 µL and leukocytes >10,000, the patient is excluded from apheresis; If a sub optimal collection of CD34+ is reached (<20 and >10 µL) and leukocytes >10,000 µL, we consider good a collection of $1.2x10^6$ kg HSC for each apheresis (4). The definition of blood volume processing is also very important: if the volume is high (>80 CD34+ µL) or low (<20 CD34+ µL) it could be better apply algorithms that help us to identify the volume processed. To this end, Pierelli et al. has developed a PREDICTIVE FORMULA that allows you to predict the yield or blood volume processing (5).
Hematopoietic progenitor cell mobilization and collection is an evolving area with wide variation in clinical practice. The patient's ability to endure the extracorporeal volume, calcium depletion and electrolyte changes, anticoagulation and depletion of platelets and red blood cells are variable to be considered (6).
About the CD34+ cells concentration, it has been shown a positive correlation between clinical effect and dose of CD34+ cells, but some patients, despite a good harvest, show a delay in platelets recovery (7). To better investigate this phenomenon, a retrospective study (2009-2012), involving 8 Italian transplant centers, was performed and 762 patients were enrolled. The primary endpoint was to evaluate the influence on time to engraftment of high number of total nucleated cells (TNC). By a multivariate analysis this study showed that the dose of CD34+ cells was always significant for the platelet engraftment. There was also a statistical parameter, the relationship between the dose of CD34+ cells

(millions/kg) and the total number of cells infused (hundreds of millions/kg) (Dose/TNC/kg).
When this ratio is >10, the patient has a faster platelet recovery, indicating a collection with increased mononuclear cell contamination goes to affect negatively the engraftment, albeit with a good dose of CD34+ cells.
On this basis, a score that allows to evaluate the impact of various risk factors on platelet recovery was therefore proposed.
Also neutrophil recovery was affected by effect dose and also by Dose/TNC/kg: when this is >10 there was an improvement of the neutrophil engraftment (8).

STRATEGIES TO IMPROVE THE SUCCESS LIKELIHOOD IN POOR MOBILIZER PATIENTS

Among the strategies to improve the mobilization in patients at risk of failure, plerixafor plays a key role, even if there is still no consensus on its exact use. A recent study showed that the use of plerixafor led to a successful mobilization in patients "poor mobilizer" both proven and "predicted" (9).
European data emphasize the role of plerixafor in poor mobilizers: in a recent study 580 poor mobilizers with non-Hodgkin's lymphoma, Hodgkin's lymphoma and multiple myeloma were enrolled and all patients received plerixafor plus GCSF with or without chemotherapy. This analysis documents the effectiveness of plerixafor in patients who have previously mobilized poorly, but further strategies to improve the apheresis yield, especially in patients with NHL, are required (10).
To optimize the use of plerixafor various algorithms have been proposed, that take into account the amount of CD34 + (11) but also the kinetics (12) and the CD34+/WBC ratio (13) are important.

MOBILIZATION PROTOCOLS

During the last decades, CD34+ stem cells mobilization protocols have been characterized by considerable improvements.
Protocols based on chemotherapy and/or growth factor administration allowed to obtain brilliant results and thus are currently widely exploited in the clinical setting as induction regimens.
However, the "poor mobilizers" phenomenon still affects a portion of patients ranging from 11 to 50% of the total.
As a poor mobilization condition often forces physicians to adopt alternative induction protocols resulting in lower patient's compliance and increased costs for the health-giving structure, this phenomenon should be kept in strict consideration.
Plerixafor, is however allowing to overcome the poor mobilizing problem in a safe, specific fashion; the drug indeed is able to mobilize CD34+ cells only, therefore avoiding the induction of malignant cells, and is currently adopted in different schedules.
Among the different treatment schedules, the on-demand (or pre-emptive) administration of plerixafor allows to overcome a poor or null mobilization condition even if previous chemotherapy and/or C-GSF-based treatments have been ineffective - therefore, in presence of the so-called proven poor

mobilizers. This kind of administration of plerixafor is supported by several international studies, with particular regards to Non-Hodgkin Lymphoma and Multiple Myeloma patients; overall, the results of these studies highlight that plerixafor is actually able to correct "on the go" an eventual not-sufficient classical mobilization protocol, starting from CD34+ counts of 10 cells/μL (14-15).
On the base of the brilliant clinical advantages which have been documented, the on-demand administration of plerixafor is increasingly emerging. However, as of today there is no well-defined protocol establishing standardized procedures in terms of timing and treatment schedule, and therefore the therapeutic success of this agent is linked to the single experiences reported by different health-giving centers.
This "dynamic approach" is thus related to the development of algorithms which evaluate all the diverse factors in order to better establish the most suitable moment and schedule which may relate to higher yields at the harvest.
This consideration is nonetheless valid with regards to CD34+ cells counts ranging between 10 and 20 units per μL - the so-called grey-area. Therefore, novel perspective studies are strongly required.

HARVEST TIMING

As of today, the definition of the most suitable harvesting timing is mostly related to the number of CD34+ cells/kg observed prior to the procedure.
It is generally accepted that the monitoring of the number of CD34+ cells is the most important factor to evaluate in order to obtain better yields at the harvesting time, but there is actually no international consensus regarding the precise number of CD34+ to consider.
On the other hand, international guidelines agree on the target value to reach (4 millions of cells/kg) which empirically correlates with a lower incidence of adverse reactions and a reduced mortality.
In the contexture of a better definition of the harvesting time, there are besides many factors to consider in addition to the CD34+ count. Red blood cells and mononuclear cells count, as an example, has been demonstrated to be a valid tool for the prediction of the obtainment of yields values higher than $4x10^6$ kg, with an inverse correlation to the number of CD34+ at the harvesting time.
Moreover, the timing of the administration of the mobilizing agent can potentially elicit a strong influence on the yield, as highlighted by the Pescara group; thus, a correct evaluation of the timing and an effective synchronization can exert a strong influence on the number of CD34+ cells obtained.
In addition, the volume of whole blood which has been processed can be considered as another important variable to consider in perspective of better yields, as it is directly associated to higher CD34+ cells counts at the harvest.
Specifically, for every liter of processed whole blood, the probability of obtaining CD34+ yields higher than the target value of 8 millions/kg increases of a 22%. Additional factors influencing the quality of a CD34+ harvest are moreover related to the type of instrument

utilized, in association to the amount of hematocrit which is detected (16).
In order to obtain optimal yields at the harvesting time, the factors to consider are therefore multiple and deeply linked each to the others (17). A dynamic multiparametric evaluation in accordance with novel optimized algorithms, is therefore necessary, as it would increase the success rate for CD34+ harvest (5, 18, 19).

Slides and webinars are available on: https://project.prex.it/moveonair/

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