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Review

How to manage poor mobilizers for high dose chemotherapy and autologous stem cell transplantation?

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ABSTRACT

Today, peripheral blood stem cells are the preferred source of stem cells over bone marrow. Therefore, mobilization plays a crutial role in successful autologous stem cell transplantation. Poor mobilization is generally defined as failure to achieve the target level of at least 2×10^6 $CD34^+$ cells/kg body weight. There are several strategies to overcome poor mobilization: 1) Larger volume Leukapheresis (LVL) 2) Re-mobilization 3) Plerixafor 4) CM + Plerixafor (P) + G-CSF and 5) Bone Marrow Harvest. In this review, the definitions of successful and poor mobilization are discussed. Management strategies for poor mobilization are defined. The recent research on new agents are included.

Contents

1. Introduction

High dose chemotherapy (HDC) supported with autologous hematopoietic stem cell transplantation (ASCT) is an established treatment option for some solid tumors and many hematological malignancies such as multiple myeloma (MM), non-Hodgkin lymphoma (NHL) and Hodgkin's disease (HD) [1–4]. Currently, peripheral blood stem cells (PBSC) are the preferred source of stem cells over bone marrow (BM) for which the harvest procedure requires multiple BM aspirations and general anesthesia. Moreover, the hematopoietic and immune functions restore more rapidly in transplants performed with PBSC compared to BM stem cells [5].

PBSC apheresis requires mobilization of stem cells to peripheral blood and collection with a continuous flow apheresis procedure. Generally there are two approaches for stem cell mobilization: mobilization using cytokines alone (or in combination) and chemomobilization(CM) using chemotherapy followed by cytokine administration [6–15]. In cytokine-only mobilization, recombinant human granulocyte colony stimulating factor (Rh-GCSF) is commonly administered at 10–16 mcg/kg/day for 4 days and PBSCs are collected by apheresis from day 5 onwards and G-CSF is continued until the last day of apheresis [15,16]. In various reports, it was shown that administration of chemotherapy before growth factors improved stem cell mobilization and collection yields [17–20]. However, unpredictable timing of apheresis, require-

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ment for hospitalization, the risk of infections during neutropenic period and transfusion of blood products and associated costs are the drawbacks for using CM especially for sole mobilization purposes. Cyclophosphamide (CY) is the most commonly used chemotherapeutic agent which has been tested at various doses and is used at the dose of 3–4 g/m^2 followed by G-CSF [21–23]. Although the mobilization failure rates overall seem to be similar to cytokine-only mobilization, recent studies have shown that CM may improves mobilization yields in difficult to mobilize patients, particularly those with lymphoma [17,24–27]. We have to emphasize that CM especially is used in patients who need cytoreduction and elimination of residual disease as much as possible, if needed [10,11,28,29]. Therefore, disease-specific intensive chemotherapy plus G-CSF followed by PBSC mobilization is an effective approach in lymphoma patients who require salvage therapy. Demirel et al. reported that CY + Etoposide + G-CSF is superior to G-CSF alone or CY + G-CSF based on mean daily CD34+ cell collection yield in patients with MM [10] and based on the average daily CD34+ cell yield, combination chemotherapy regimens were superior to single agent CY [11]. CM mobilization regimens include DHAP [30], ESHAP [31–33], a combination of CY + etoposide [34] and ifosphamide, carboplatin and etoposide (ICE) [35] followed by G-CSF among others. Although CM intuitively would seem to reduce graft contamination by malignant cells, in practice it has demonstrated no impact on transplantation outcomes, such as complete response rate, time to progression, event-free survival, or overall survival [36,37]. One has to keep in mind that the risk of myelodysplastic syndromes may be associated with administration of alkylating agents to mobilize stem cells

The major aim for a successful mobilization is to collect sufficient stem cells after an acceptable number of apheresis sessions to proceed to ASCT, to reduce overall failure rates to <5%, to minimize mobilization-related complications, and to optimize resource utilization. It is essential to obtain a minimum threshold of $\geq 2 \times 10^6$ CD34/kg for successful and consistent multi-lineage engraftment as well as sustained hematopoietic recovery [7–9,12,15]. The recommended stem cell collection target in general is 3–5 $\times 10^6$ CD34$^+$ cells/kg. Higher targets are necessary if multiple transplantations are planned [12]. For example, International Myeloma Working Group suggested a minimum collection target of 4 $\times 10^6$/kg CD34+ cells and if feasible 8–10 $\times 10^6$ notkg in order to perform two transplants [38]. In this review, we will focus on the poor mobilizers and review of various approaches for how to deal with this subgroup of patients.

2. Definition of poor mobilizers

Poor mobilization is generally defined as failure to achieve the target level of at least 2 $\times 10^6$ CD34$^+$ cells/kg body weight [39]. Patients whose peripheral blood CD34 + cell counts are too low (<10 $\times 10^6$/L in many centres) to start apheresis or patients who require 3–5 apheresis to collect a minimum of at least 2 $\times 10^6$/kg CD34$^+$ cells are also regarded as poor mobilizers [40]. One has to note that mobilization failure rates with traditional strategies are as high as as 40% [41]. Hopman et al. reported that the mobilization failure rate is detected up to 23% in heavily pretreated patients with plasma cell myeloma and non-Hodgkin's lymphoma [42]. Several risk factors associated with mobilization failure are older age, extensive BM involvement with malignancy, diagnosis of NHL, prior radiotherapy, prior treatment with alkylating agents, fludarabine, platinum containing regimens, prior prolonged exposure to lenalidomide, prior exposure to multiple chemotherapy regimens, prior mobilization failure, presence of baseline thrombocytopenia, diabetes and smoking [43]. One study which was conducted by Bensinger et al. using analysis by linear regression of the logarithm of CD34+ cells collected found lower age, marrow free disease, lack of prior radiation, and lower number of prior chemotherapy regimes were important factors influencing the large numbers of CD34+ cells in collections [44]. However, these factors account for only about half of the interpatient variability and do not fully explain differences [7,45,46]. In a study that included 840 patients with MM (n = 602) and NHL (n = 238), 129 of them (15.3%) were considered to be poor mobilizers, in which total number of cycles of prior chemotherapy (P = 0.0034) and previous treatment with melphalan (P = 0.0078) had a significant impact on the yield of PBSC mobilization [47,48].

It has been shown that some findings at the time of mobilization,especially PB CD34+ cell counts, may be predictive of poor mobilization. For example, in G-CSF only mobilization, blood CD34+ cell counts <10 $\times 10^6$/L on day +4 and <20 $\times 10^6$/L on day +5 may indicate a hard-to-mobilize patient and may be a warning sign for inadequate CD34+ cell collection yield [49,50]. Again, in patients receiving CM, slow leucocyte and platelets recovery as well as an anemia after mobilization may indicate poor marrow reserves. Slow increase in blood CD34+ cell counts (e.g. < 10 $\times 10^6$/L) at the time of marrow recovery (WBC 5–10 $\times 10^9$/L), may also be indicative of a hard-to-mobilize patient [51].

Gruppo Italiano Tra-pianto di Midollo Osseo GITMO (Italian Group for Stem Cell Transplantation) presented a hierarchic model in description of poor mobilization in lymphoma and myeloma patients. Proven poor mobilizer is defined as mobilization failure (CD34+ cell peak <20/μL) after adequate mobilization (G-CSF 10 μg/kg alone after 6 days or ≥5 μg/kg after chemotherapy after 20 days) or <2.0 $\times 10^6$ CD34+ cells per kg in ≤3 apheresis. On the other hand, predicted poor mobilizer is defined as if a patient failed a previous collection attempt, previously received extensive radiotherapy or if a patient meets two of the following criterias: (≥2 lines of chemotherapy, refractory disease, extensive bone marrow involvement or cellularity <30% at the time of mobilization, age ≥65) [52]. Mobilization strategy should be tailored in case of a patient fits to predicted poor mobilizer category.

3. How to manage the poor mobilizers?

In this modern era, several medical and technical options offer the possibility to convert "poor-mobilizers" into "good-mobilizers" or "appropriately-collected" patients; thus "poor-mobilization" is only a relative rather than definitive status. Based on the current accumulated literature data, there are several strategies to increase the apheresis yields such as: 1) Larger volume Leukapheresis (LVL) 2) Re-mobilization 3) Plerixafor 4) CM + Plerixafor (P) + G-CSF and 5) Bone Marrow Harvest. We will focus on these approaches, below, one by one.

1) Larger volume leukapheresis

Stem cell apheresis can be performed as a standard lower-volume procedure with a typical processing volume of 10–15 L based on 2–3 times the patient's blood volume. LVL processes 15–30 L (3–6 blood volumes) which results an increase in CD34+ cell yield per apheresis session owing to continued mobilization of stem cells from the marrow during the prolonged apheresis session [53–55]. But current literature data regarding LVL is somehow conflicting. For example Demirer et al. showed that there was no difference between 8L and 12L volumes in regard to collected CD34+ cells/kg in normal mobilizers and also the use of 12 L leukapheresis volume did not decrease the number of leukapheresis performed compared with a 8 L leukapheresis volume in normal mobilizers. In fact, the useage of larger leukapheresis volume had the disadvantage of adding 60 min to time the patient was on the