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Review

Management of mobilization failure in 2017

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ABSTRACT

In contemporary clinical practice, almost all allogeneic transplantations and autologous transplantations now capitalize on peripheral blood stem cells (PBSCs) as opposed to bone marrow (BM) for the source of stem cells. In this context, granulocyte colony-stimulating factor (G-CSF) plays a pivotal role as the most frequently applied frontline agent for stem cell mobilization. For patients classified as high-risk, chemotherapy based mobilization regimens can be preferred as a first choice and it is notable that this also used for remobilization. Mobilization failure occurs at a rate of 10%–40% with traditional strategies and it typically leads to low-efficiency practices, resource wastage, and delayed in treatment intervention. Notably, however, several factors can impact the effectiveness of $CD34^+$ progenitor cell mobilization, including patient age and medical history (prior chemotherapy or radiotherapy, disease and marrow infiltration at the time of mobilization). In recent years, main (yet largely ineffective) approach was to increase G-CSF dose and add SCF, but novel and promising pathways have been opened up by the synergistic impact of a reversible inhibitor of CXCR4, plerixafor, with G-CSF. The literature shows to its favorable results in upfront and failed mobilizers, and it is necessary to use plerixafor (or equivalent agents) to optimize HSC harvest in poor mobilizers. Different CXCR4 inhibitors, growth hormone, VLA4 inhibitors, and parathormone, have been cited as new agents for mobilization failure in recent years. In view of the above considerations, the purpose of this paper is to examine the mobilization of PBSC while focusing specifically on poor mobilizers.

Contents

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1. Introduction

Numerous hematological malignancies and some solid tumors are treated via hematopoietic cell transplantation (HCT). There are two sources of hematopoietic stem cells (HSCs), namely, the bone marrow (BM) and the peripheral blood (PB). HSCs can be collected directly from the bone marrow or via apheresis from the PB [1,2]. Autologous transplantations and most allogeneic transplantations are currently performed primarily with peripheral blood stem cells (PBSCs) rather than stem cells from the BM. The reason for this is that a greater number of cells can be collected from the PB with no need for general anesthesia, the pain caused by multiple BM aspirations is avoided, faster hematopoietic recovery with less necessity for blood transfusions, and hospital stay and overall costs can be cut down [3].

From a clinical perspective, the discharge of hematopoietic stem and progenitor cells into the PB after cytokine treatment and/or chemotherapy is known as mobilization. The $CD34^+$ cells do not exceed 0.05% of white blood cells (WBCs) under steady-state conditions. The number of PBSCs increases 5–15 times after chemotherapy [4]. Combining chemotherapy and growth factors increases $CD34^+$ cells up to 6% of WBC [5]. The HCT depends significantly on mobilization and collection of HSCs.

Stem cells can be mobilized in two ways, namely, cytokine mobilization based on cytokines like filgrastim [granulocyte-colony stimulating factor (G-CSF)], pegfilgrastim, or sargramostim [granulocyte macrophage-colony stimulating factor (GM-CSF)] that can be used either alone or combined, and chemomobilization (CM) using chemotherapy followed by cytokine administration [6].

There are significant differences in the practices of mobilization and collection. To be considered optimal, a mobilization practice should enable an appropriate number of $CD34^+$ cells to be collected for transplantation, minimize toxicity, and immediately yield a long-lasting engraftment. It is well-known that the number of stem cells collected for HCT and engraftment kinetics are closely correlated. If the number of collected HSCs is sufficient, hematopoietic recovery will occur faster and hospital stay is shorter, fewer blood products are used, and the risk of infections is reduced [7,8].

The minimal cell dose that can be used for allogeneic stem cell transplants (AlloSCTs) is 2×10^6 $CD34^+$ cells/kg. Existing data suggest that the most appropriate dose for allogeneic transplantation in adult patients is $4–5 \times 10^6$ $CD34^+$ cells/kg. If the cell dose exceeds 8×10^6.

$CD34^+$ cells/kg, the likelihood of extensive chronic graft versus host disease (GVHD) occurring will be heightened, while survival will not be increased. In the case of haplotype mismatched transplantations, the risk of unsuccessful engraftment is frequently attenuated by using doses of $\geq 10 \times 10^6$ $CD34^+$ cells/kg [9–12]. The minimum dose considered to be safe in case of autologous stem cell transplantation (ASCT) is 2×10^6 $CD34^+$ cells/kg per transplant. If the dose is lower than this, delayed neutrophil and platelet engraftment will be more likely to occur. To ensure the success of transplantation, the ideal dose is deemed to be 5×10^6 $CD34^+$ cells/kg. Furthermore, it has been observed that doses of $CD34^+$ cells exceeding 6×10^6/kg associated with faster hematopoietic recovery and improved overall survival [13–16].

Mobilization approaches, including plerixafor, have been considerably improved, but there is still a significant amount of mobilization failures (15–30%) [17–20]. Aside from collecting a large enough stem cell dose for ASCT, ideal mobilization should also reduce the number of necessary apheresis sessions, be more cost-effective, and prevent any associated complications. Given these considerations, the purpose of the present review is to define mobilization failure and identify underlying risk factors as well as to explore the different approaches that could reduce mobilization failure.

2. Definition and risk factors of mobilization failure

Mobilization failure, is defined as failure to attain the target level of at least 2×10^6 $CD34^+$ cells/kg body weight. Patients are deemed poor mobilizers if their count of $CD34^+$ cells in PB is lower than 10×10^6/L before starting apheresis or if they need more than four apheresis sessions to collect at least 2×10^6/kg $CD34^+$ cells [17].

Poor mobilization in lymphoma and myeloma patients has been characterized by the Gruppo Italiano Tra-pianto di Midollo Osseo GITMO (Italian Group for Stem Cell Transplantation) based on a hierarchic model. Proven poor mobilizer is characterized as mobilization failure ($CD34^+$ cell peak <20/μL) after adequate mobilization (G-CSF 10 μg/kg alone after 6 days or ≥5 μ g/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) they have failed from a previous collection attempt; or (b) they previously received extensive radiotherapy or chemotherapy impacting affecting peripheral blood stem cell mobilization; and/or (c) two of the following criteria are fulfilled: advanced disease (≥2 lines of chemotherapy), refractory disease, extensive bone marrow involvement, cellularity < 30% at the time of mobilization, or age >65 years) [21].

Among the risk factors that could cause mobilization failure is previous mobilization failure, previous radiotherapy, previous therapy with alkylating agents, older age, extensive involvement of BM with malignancy, non-hodgkin lymphoma (NHL) diagnosis, fludarabine, regimens with platinum content, presence of baseline thrombocytopenia, previous exposure to lenalidomide for a long time, previous exposure to more than chemotherapy regimen, diabetes and smoking [22].

Outcomes are usually poor in the case of BM involvement with malignancy. The impact of malignant cells in the BM on healthy niches or niche competition among HSCs and malignant cells may contribute to the lower counts of HSCs. Meanwhile, mobilization failure has been associated with the independent risk factors of Hodgkin's lymphoma (HL) and NHL, indolent lymphoproliferative diseases and acute leukemia [23,24]. Another major predictor of mobilization failure is considered to be BM cellularity of less than 30% [25].

Previous exposure to myelotoxic chemotherapy is the most common reason for mobilization failure in autologous donors. The stem cells and marrow niches are damaged by the DNA cross-linking agents like melphalan, carmustine and purine analogs such as fludarabine that they contain [26,27]. Intensive chemotherapy regimens such as the hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone with methotrexate and cytarabine) are associated with a high risk of mobilization failure if more than two cycles of therapy [28]. Moreover, the risk of mobilization failure is enhanced by lenalidomide, particularly after four or more cycles [29]. In addition, the HSC niche function could be impaired if imatinib is administered for long periods of time, as it has been observed to diminish bone turnover. Discontinuation of imatinib for three weeks prior to collection led to yield improvement [30]. Furthermore, chemotherapies with toxicity for stem cells should not be conducted if autologous HSCT is scheduled.

Mobilization may also fail because of past extensive radiotherapy to BM areas, as this procedure is toxic to HSCs and niche environments [21,31]. Thus, collection of HSCs prior to radiotherapy is usually suggested.

Older age (>60 years) has been related with the higher risk of mobilization failure [31]. Pre-mobilization low numbers of platelets have been identified in numerous studies as an indepen-

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