

# Mobilization of hematopoietic progenitor cells for autologous transportation: consensus recommendations

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## SUMMARY

Selected patients with certain hematological malignancies and solid tumors have the potential to achieve long-term survival with autologous hematopoietic progenitor cell transplant. The collection of these cells in peripheral blood avoids multiple bone marrow aspirations, results in faster engraftment and allows treatment of patients with infection, fibrosis, or bone marrow hypocellularity. However, for the procedure to be successful, it is essential to mobilize a sufficient number of progenitor cells from the bone marrow into the blood circulation. Therefore, a group of Brazilian experts met in order to develop recommendations for mobilization strategies adapted to the reality of the Brazilian national health system, which could help minimize the risk of failure, reduce toxicity and improve the allocation of financial resources.

**Keywords:** Hematopoietic stem cell mobilization; Autologous transplantation; Plerixafor; G-CSF

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## INTRODUCTION

Autologous transplantation of hematopoietic progenitor cells from peripheral blood is a well-established therapy for some hematological malignancies, such as multiple myeloma, non-Hodgkin's and Hodgkin's lymphoma, as well as for some solid neoplasms, such as germ cell tumors.<sup>1,2</sup> Mobilization and collection are crucial steps in this procedure, which aim not only at obtaining enough stem cells for transplantation but also at minimizing the number of apheresis sessions, reducing the risk of complications, preventing failure and optimizing resource allocation.<sup>3</sup> The choice of the mobilization regimen should take into account factors such as efficacy, safety, convenience and cost-effectiveness.<sup>4</sup> Even though they are well established in everyday practice of Hematology and Transplant centers, mobilization regimens can vary greatly from one institution to another and differ in terms of clinical and pharmaco-economic outcomes.<sup>5-7</sup>

Of the currently available regimens, the one most commonly used involves the isolated use of the granulocyte-colony stimulating factor (G-CSF), which has the advantages of being well tolerated and allowing the programming of apheresis procedures.<sup>8,9</sup> The combination of chemotherapy and G-CSF has shown to improve the

collection of CD34 + cells and reduce tumor activity, but at the expense of increased risk of complications such as fever and neutropenia. In turn, the combination of G-CSF and plerixafor has been shown to result in reduced risk of mobilization failure, improves the collection of CD34 + cells and a favorable tolerability profile, but at a higher cost.

Thus, the combination of G-CSF and plerixafor has been used as the initial regimen for patients with risk factors for poor mobilization, preemptively in patients with early signs of mobilization failure, as well as a rescue strategy in cases of failed mobilization with other regimens.<sup>9-12</sup> Other currently available rescue strategies include the re-mobilization with the same regimen used previously, the segmentation of the G-CSF doses and collection of cells directly from bone marrow.<sup>13</sup>

Recently, the American Society for Blood and Marrow Transplantation<sup>4</sup> and a panel of US experts<sup>3</sup> published their guidelines and recommendations to optimize the mobilization of hematopoietic stem cells from peripheral blood. Considering the peculiarities of the Brazilian public health system and the need for more standardized approaches in our country, a panel of national experts was summoned to meet and develop consensus recommendations adapted

to our reality and that could serve as a starting point for broader efforts to improve clinical outcomes of patients submitted to autologous hematopoietic stem cell transplantation from peripheral blood in Brazil.

## PREDICTIVE FACTORS OF POOR MOBILIZATION

The identification of risk factors associated with the disease and the patient that can predict poor mobilization of hematopoietic progenitor cells is of utmost importance for the optimization of both the therapy and resource allocation. Several studies carried out to investigate this question showed that the diagnosis of lymphoma,<sup>14-19</sup> thrombocytopenia,<sup>14,20-23</sup> older age<sup>18-21,23-25</sup> and polytreatment<sup>14,16,19,25,26</sup>, among other factors, emerged as the main potential factors for the prediction of poor recruitment of hematopoietic stem cells.

However, the retrospective characteristic of these studies, the relatively low number of assessed patients, the heterogeneity of the studied populations, the use of different mobilization regimens and lack of uniform criteria for the definition of failure contributed to the achievement of conflicting results,<sup>11,27-29</sup> making data interpretation and the drawing of definitive conclusions about the role of these factors in therapeutic decision-making difficult. The most robust factor for the prediction of collection efficiency is the CD34+ cell count in peripheral blood before apheresis and its implementation in daily practice has the added potential to save financial resources.<sup>7,30-34</sup>

*Recommendation: the isolated use of pre-treatment clinical and laboratory factors to identify patients at risk of poor mobilization and to select the best therapeutic approach shows conflicting results in the literature. However, potentially more effective mobilization strategies – such as chemo-mobilization and plerixafor-based regimens should be considered for patients who have these factors. A low number of CD34+ cells in peripheral blood before apheresis is the most robust predictor of collection failure; thus, the cell count should be performed in all patients submitted to autologous transplantation of hematopoietic progenitor cells.*

## MEASUREMENT OF CD34+ CELL COUNT IN PERIPHERAL BLOOD

The use of flow cytometry for CD34 + cell count in peripheral blood has become a standard technique to evaluate the recruitment of these progenitor cells and to optimize mobilization strategies,<sup>3,4,7</sup> having been implemented in the routine practice in the vast majority of treatment centers.<sup>35,36</sup> Although several methodologies and cytometric assays have been described, there can be great variability

among the observed cell counts and the lack of standardized methods has led to the obtaining of widely differing results.<sup>35,37</sup> The sample type and condition, the used reagent and the characteristics of the employed anti-CD34 monoclonal antibodies are some potential error sources for the cytofluorimetric measurement of CD34 + cell count.<sup>38</sup>

The three main techniques of hematopoietic progenitor cell count include the Milan/Mullhouse two-platform protocol and the two-platform and single-platform analysis systems of ISHAGE (International Society of Hematotherapy and Graft Engineering). In the two-platform method, the percentage of CD34 + cells is determined by flow cytometry and the leukocyte count is performed in an automated hematology analyzer. The development of single-platform methods allowed the absolute count of CD34+ cells through a single device - the flow cytometer.<sup>39</sup> The results obtained with the three methods are apparently comparable, with a low rate of divergence.<sup>39,40</sup> Given their presumed interchangeability, the choice between these three methods can be based on subjective criteria, such as convenience, cost, and simplicity.<sup>39</sup>

*Recommendation: the exact quantification of CD4+ cells in peripheral blood is currently a highly relevant factor for a successful autologous hematopoietic stem cell transplantation. The purchase notices of kits for the analysis of this parameter should be carefully prepared, aiming at the acquisition of accurate, reliable products that have been submitted to quality control testing.*

## MOBILIZATION WITH G-CSF

G-CSF is the most commonly used mobilizing agent, either alone or in combination with chemotherapy. The generally applied dose is 10 µg/kg subcutaneously, with apheresis being started on the fifth or sixth day, until the number of target cells is achieved.<sup>41,42</sup> Some studies postulated that G-CSF dose division could result in better mobilization. The pharmacological profile of G-CSF demonstrates a maximum serum concentration within 2 to 8 hours after subcutaneous administration.<sup>43</sup>

Considering an elimination half-life of 3 to 4 hours, the dose division could result in higher basal serum concentrations and, consequently, better mobilization.<sup>44</sup> However, studies comparing a single daily dose versus divided dose of G-CSF showed conflicting results.<sup>5,44</sup> Higher doses of G-CSF (8 to 12 µg/kg/12h) resulted in the collection of a higher number of CD34 + cells with fewer apheresis procedures, suggesting the existence of a dose-effect response.<sup>45-47</sup>

The use of G-CSF has the advantage of allowing the mobilization planning, resulting in more predictability,

when compared to chemotherapy. Moreover, G-CSF can be administered at home, resulting in greater convenience for patients. G-CSF also has a favorable toxicity profile, with the most frequent adverse events being mild to moderate musculoskeletal pain (usually controlled with conventional analgesics), as well as dysuria, fever, headache, nausea and asymptomatic increase in alkaline phosphatase and gamma-glutamyl transferase.<sup>48,49</sup> Retrospective and prospective randomized studies suggest that the granulocyte-monocyte colony stimulating factor (GM-CSF) is less effective than G-CSF in mobilizing hematopoietic progenitor cells, either alone or in combination with chemotherapy, with an additional less favorable profile of safety and tolerability.<sup>48,50</sup> The combination of G-CSF and GM-CSF did not result in significant clinical benefits in comparison with isolated G-CSF.<sup>51</sup> Pegfilgrastim has not been widely accepted by transplant centers, due to the fact that G-CSF is easy to use and the accumulated experience using it, as well as cost-related matters.<sup>42</sup>

*Recommendation: G-CSF can be used alone to mobilize hematopoietic progenitor cells at doses of 10 to 20 µg/kg, divided into 2 to 4 equal daily applications, or with a higher dose in the morning.*

## CHEMOMOBILIZATION

The decision between mobilization with G-CSF alone or a combination of chemotherapy and G-CSF should take into account factors such as the remission status of the underlying disease and the probability of poor mobilization.<sup>52</sup> The combination of G-CSF with chemotherapy accomplishes the double purpose of promoting both the mobilization of hematopoietic progenitor cells and the reduction of antitumor activity, with the latter effect being demonstrated in cases of lymphoma and also of multiple myeloma. Moreover, the combination of chemotherapy and G-CSF has the advantage of resulting in the collection of a higher number of CD34 + cells and requiring fewer apheresis procedures, when compared with the isolated use of G-CSF. In contrast, chemomobilization is associated with lower predictability to the start of apheresis, as well as the toxicity and complications from the chemotherapy regimen used, including febrile neutropenia and need for hospitalization.<sup>10,42,50,52</sup> Moreover, when the chemomobilization is used as a cycle of part of the induction or rescue therapy, additional expenses with the chemotherapy itself and also hospitalization for treatment administration and management of complications result in higher costs related to the isolated use of G-CSF.<sup>6</sup>

The combination of G-CSF with high-doses cyclophosphamide was shown to improve the efficiency of col-

lection and increase the correlation between the CD34+ cell counts in peripheral blood and in the final collection.<sup>8,49</sup> Etoposide, in turn, has shown to be effective in the treatment of Hodgkin's and non-Hodgkin's lymphoma; thus, its inclusion in the mobilization regimens of patients with these tumors has the advantage of providing treatment during the mobilization phase<sup>49</sup>. The combination of vinorelbine and G-CSF is an excellent alternative in comparison with G-CSF alone or in combination with cyclophosphamide, showing a more favorable toxicity profile, resulting in earlier collection and lower costs. Furthermore, outpatient administration with one in bolus injection and better predictability of apheresis improve patient comfort and simplify the collection procedure, both in multiple myeloma and in malignant lymphoma.<sup>53-55</sup>

The use of several cytotoxic combination regimes have also been described, including cisplatin, cytosine arabinoside, dexamethasone (DHAP); ifosfamide, carboplatin and etoposide (ICE); etoposide, methylprednisolone, cytarabine and cisplatin (ESHAP); cyclophosphamide, mitoxantrone, dexamethasone (CMD); dexamethasone, carmustine, etoposide, cytarabine, melphalan (Dexa-BEAM); ifosfamide, epirubicin, etoposide (IEE); cyclophosphamide and etoposide with or without cisplatin; and etoposide and rituximab.<sup>8</sup>

*Recommendation: mobilization with chemotherapy combined with G-CSF (beginning on the day after completion of chemotherapy) can be performed with cyclophosphamide 2 to 3 g/m<sup>2</sup> or vinorelbine 35 mg/m<sup>2</sup> in a single dose<sup>61</sup> or etoposide 375 mg. The selection of other chemomobilization regimens should preferably take into account the sensitivity of the underlying malignancy to the different cytotoxic agents.*

## MOBILIZATION WITH PLERIXAFOR

Plerixafor is a reversible antagonist of chemokine receptor type 4 (CXCR4), which blocks the interaction between the receptor and its ligand - the CXC chemokine type 12 - and causes the release of CD34+ cells from the bone marrow into blood circulation. The efficacy and tolerability of the combination of Plerixafor and G-CSF in promoting the mobilization of progenitor cells in patients with previous failed mobilization attempts has been demonstrated in several prospective trials, with success rates ranging from 60 to 90%, even among patients aged ≥60 years.

Furthermore, the combination of Plerixafor and G-CSF has also been successfully used in patients with poor mobilization risk factors. Compared to chemomobilization, the combination of Plerixafor and G-CSF provides

greater predictability of the time to obtain CD34+ cell count peak, resulting in improved collection efficiency and fewer apheresis sessions. In the absence of a clear chemotherapy indication, the combination of Plerixafor and G-CSF may be preferred to chemomobilization in patients at high risk of failure. On the other hand, only one formal phase II study on the combination of plerixafor, chemotherapy and G-CSF has been published to date, so that the evidence for the use of this regimen is scarce.<sup>10,56,57</sup>

Plerixafor can also be used preemptively in patients with early signs of poor mobilization, even in the absence of known risk factors. Several algorithms have been developed to guide the preemptive use of plerixafor. Evidence indicates that the number of collections and failure rates can be substantially reduced with the use of this strategy, although a group of patients may still develop with poor mobilization. In patients undergoing mobilization with G-CSF alone, the decision to preemptively add plerixafor usually occurs after 4 days of the mobilization onset and depends on the target for collection. Usually, the addition of plerixafor is indicated for patients with CD34+ cell count  $<10/\text{mm}^3$  on day +4. This strategy has been shown to result in similar or lower total costs compared to traditional mobilization methods, when taking into account the management of adverse events and complications associated with alternative regimens of mobilization and mobilization failure.<sup>56-58</sup>

*Recommendation: plerixafor, at a dose of 240 mg/kg subcutaneously, should be preemptively administered in patients undergoing mobilization with G-CSF and  $<10$  CD34 + cells per  $\text{mm}^3$  at day +5, between 6 and 11 hours before apheresis. Patients showing failure mobilization with chemotherapy and G-CSF are also candidates for rescue with plerixafor and G-CSF. There are no conclusive data for the use of chemotherapy in combination with plerixafor.*

## MOBILIZATION FAILURE APPROACHES

G-CSF, alone or in combination with chemotherapy is still the most common approach to mobilize hematopoietic progenitor cells for autologous transplantation candidates. Considering that a proportion of patients have insufficient mobilization and are therefore deprived of the transplantation benefit, at least at a first moment, the costs associated with failure are many, including the inconvenience and the psychological impact of mobilization failure on the patient, in addition to the costs of morbidity and mortality associated with subsequent attempts at mobilization. Therefore, strategies are crucial to minimize the risks of failure at the second or third mobilization. Options for

remobilization include dividing the G-CSF dose, remobilization with chemotherapy and G-CSF, remobilization with the same previous regimen, the combination of plerixafor and G-CSF and bone marrow collection.<sup>10,42,59</sup>

Mobilization failures are generally defined as  $<2 \times 10^6$  CD34+ cells collected per kg in a single mobilization or more than 4 sessions of apheresis to collect this minimum number of cells.<sup>10</sup> The division of the G-CSF dose seems to be effective in approximately 1/3 of the patients; however, confirmatory data regarding the effectiveness of this strategy are scarce.<sup>60</sup> Evidence from different centers suggest that remobilization with the combination of intensive chemotherapy and growth factor may result in an increase in the number of progenitor cells in patients with poor pre-mobilization; however, the benefit of this strategy must be weighed against its toxicity and cost. For cases in which the mobilization has been performed earlier – before complete recovery from the previous chemotherapy – and mobilization is poor, a second mobilization with the same regimen may be useful. Regarding the combination of plerixafor and G-CSF, this strategy is more likely to be successful than other rescue strategies<sup>0</sup>, allowing obtaining the target CD34+ cell count in  $>70\%$  of cases. Finally, isolated reports seem to indicate that the addition of bone marrow cells to peripheral blood progenitor cells may benefit patients with poor mobilization.<sup>10,42,59</sup>

*Recommendation: in cases of mobilization failure, it is recommended to allow at least 3 weeks for recovery before a new attempt, particularly in cases of unsuccessful chemomobilization. In cases of failure with G-CSF alone, it is recommended to carry out the remobilization by dividing the G-CSF dose, or chemomobilization. In case of chemomobilization failure, it is recommended to carry out the remobilization with plerixafor and G-CSF, or with the growth factor alone. In case of failure using plerixafor and G-CSF, remobilization is recommended using the same strategy, or to perform bone marrow collection.*

## CONCLUSIONS

The presence of risk factors for poor mobilization should be carefully investigated and it may have an impact on the selection of the most appropriate mobilization regimen. The counting of the number of CD34+ cells in peripheral blood should be performed prior to apheresis in all patients submitted to autologous hematopoietic stem cell transplantation through an accurate and reliable laboratory test, of which quality is controlled. Patients with cell count  $<10$  CD34+ cells per  $\text{mm}^3$  on day +5 are candidates for the preemptive use of plerixafor in combination with G-CSF. The selection of other mobilization regimens



should take into account efficacy, safety, convenience and cost-effectiveness. Algorithms to minimize mobilization failure risks should be used to reduce complications and additional costs associated with treatment failure.

In cases of poor mobilization (collection resulting in  $<2 \times 10^6$  CD34+ cells per kg, in a single mobilization or  $>4$  apheresis sessions), remobilization strategies should also take into account the previously used system. Pharmacoeconomic evaluations should include not only the cost of drugs, but also resource savings associated with the reduction in the number of apheresis sessions, complications of treatment, need for hospitalization, mobilization failure risks, as well as morbidity and mortality associated to remobilization.

## RESUMO

Mobilização de células progenitoras hematopoéticas para transplante autólogo: recomendações de consenso

Pacientes selecionados com certas neoplasias hematológicas e tumores sólidos têm o potencial de alcançar sobrevida de longo prazo com o transplante autólogo de células progenitoras hematopoéticas. A coleta dessas células no sangue periférico evita múltiplas aspirações de medula óssea, resulta em enxertia mais rápida, e permite o tratamento de pacientes com infiltração, fibrose ou hipocelularidade medular. Contudo, para o sucesso desse procedimento, é essencial mobilizar um número suficiente de células progenitoras da medula óssea para a circulação sanguínea. Por isso, um painel de especialistas brasileiros se reuniu com o objetivo de desenvolver recomendações para estratégias de mobilização adaptadas à realidade do sistema de saúde nacional, que pudessem contribuir para minimizar os riscos de falha, reduzir a toxicidade e melhorar a alocação de recursos financeiros.

**Palavras-chave:** Mobilização de células-tronco hematopoéticas; Transplante autólogo; Plerixafor; G-CSF.

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