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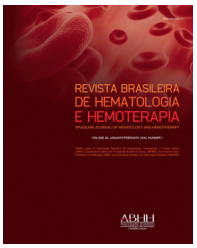

Original article

Is it feasible to use granulocyte-colony stimulating factor alone to mobilize progenitor cells in multiple myeloma patients induced with a cyclophosphamide, thalidomide and dexamethasone regimen?

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ABSTRACT

Background: Cyclophosphamide plus thalidomide as induction for multiple myeloma patients eligible for autologous stem cell transplantation may be a limiting factor for cell mobilization. The minimum acceptable mobilized peripheral blood stem cell count to prevent deleterious effects during transplantation is 2.0×10^6 CD34$^+$ cells/kg. Combining other treatments to granulocyte-colony stimulating factor, such as cyclophosphamide, could overcome the mobilization limitation. The objective of this study was to assess the number of CD34$^+$ cells mobilized using granulocyte-colony stimulating factor with and without cyclophosphamide after induction with cyclophosphamide, thalidomide and dexamethasone.

Methods: A retrospective study was performed of a cohort of multiple myeloma patients submitted to autologous stem cell transplantations at two Brazilian centers between May 2009 and July 2013. The oral cyclophosphamide and thalidomide induction doses used were 1500 mg/month and 100–200 mg/day, respectively. Mobilization doses were 10–15 mcg/kg granulocyte-colony stimulating factor with 2–4 g/m^2 cyclophosphamide, or 15–20 mcg/kg granulocyte-colony stimulating factor alone for 5 days. Collection of $>2.0 \times 10^6$ CD34$^+$ cells/kg was considered sufficient.

Results: Eighty-eight patients were analyzed; only 18 received cyclophosphamide. The median age was 58 years old (range: 51–62) for the granulocyte-colony stimulating factor group and 56.5 years old (range: 54–60) for granulocyte-colony stimulating factor plus

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cyclophosphamide group. Fifty-two patients were male. Eighty cases (90.9%) were Durie-Salmon Staging System III-A/B and 38 (44.7%) and 20 cases (23.5%) were International Staging System 2 and 3, respectively. The group that received cyclophosphamide collected a higher median number of progenitor cells [3.8 (range: 3.1–4.4) vs. 3.2 (range: 2.3–3.8)] (p-value = 0.008). No correlation was observed between better responses or number of induction cycles and the number of cells collected.

Conclusion: The number of cells mobilized with granulocyte-colony stimulating factor plus cyclophosphamide was higher. However, in both groups, the median number of $CD34^+$ cells was sufficient to perform a single autologous stem cell transplantation; no deleterious effects were reported during harvesting.

Introduction

The use of high-dose chemotherapy plus autologous stem cell transplantation (ASCT) as consolidation after chemotherapy induction has been the first line of treatment for eligible multiple myeloma patients for over three decades.[1] Currently, the most commonly employed induction strategy is to use a number of cycles (4–6) with three drugs.[1] The introduction of triple combinations of novel agents for induction, such as the immunomodulators thalidomide and lenalidomide or the proteasome inhibitor bortezomib, has significantly changed as these drugs resulted in better outcomes and tolerability compared to classic regimens such as vincristine, doxorubicin and dexamethasone (VAD).[1] However, the induction regimens should not affect hematopoietic progenitors in the mobilization process.[2–6] Recently, this influence on mobilization has been gaining increased attention due to the use of chemotherapy combinations involving novel agents such as immunomodulators (lenalidomide) and, in particular, alkylating agents (cyclophosphamide) which can increase hematologic toxicity.[2,6] Auner et al.[2] found that the combination of cyclophosphamide, thalidomide and dexamethasone (CTD) in the induction of patients with multiple myeloma significantly reduced mobilization of progenitor cells compared to the classic VAD or VAD-like regimens, even when using cyclophosphamide in association with granulocyte colony-stimulating factor (G-CSF) during mobilization. In an effort to overcome this mobilization problem, other agents have been associated with G-CSF, most notably plerixafor.[7] However, the high cost of plerixafor limits its use in many centers. Chemotherapy associated with G-CSF can significantly increase the mobilization of progenitor cells. One of the most used chemotherapy drugs in mobilization based on a combination with G-CSF is cyclophosphamide, administered at a typical dose of 2–4 g/m^2.[8] However, this treatment has some drawbacks given that it raises the cost of the procedure owing to the need for hospitalization of patients and can lead to slower bone marrow engraftment, greater toxicity with pancytopenia, neutropenia, infections and death.[9–12] The number of $CD34^+$ collected for ASCT depends on several factors the most important of which are the number of transplantations planned and the least impact in terms of time on the mobilized peripheral blood stem cells. Traditionally, the target for $CD34^+$ cell collection for single ASCT has been 4–6 $\times 10^6$ cells/kg, with the value also hinging on the deleterious impact of harvesting at counts of below 2×10^6 $CD34^+$ cells/kg, defined as the lowest acceptable level.[3] Greater numbers of $CD34^+$ cells have not been associated with any significant benefit in the parameters studied.[6] Another objective in the quantity of cells mobilized is to allow for a cell reserve for a second ASCT as rescue in the event of future disease relapse, rendering the target cell count in the first mobilization $\geq 4 \times 10^6$ $CD34^+$ cells/kg.[8,13] Some peculiarities exist in Brazil which hamper the use of ASCT such as low number of beds for transplantations and the shortage of frozen cell storage for second transplants within the Brazilian National Health System (SUS). The three-drug induction regimen widely used in Brazil for multiple myeloma patients is cyclophosphamide, thalidomide and dexamethasone (CTD).[14] The primary objective of this study was to determine whether the collection of progenitor cells using G-CSF alone is sufficient to perform at least one ASCT, compared with a group undergoing mobilization with G-CSF associated with cyclophosphamide, in patients submitted to the CTD chemotherapy regimen for induction.

Methods

A retrospective, sequential analysis of 88 multiple myeloma patients who had been mobilized for peripheral blood stem cell harvest and submitted to ASCT at two Brazilian centers between May 2009 and June 2013 was conducted. All patients were induced using the CTD regimen. Center 1, Hospital da Irmandade da Santa Casa de Misericórdia de São Paulo, used a continuous infusion of cyclophosphamide (50 mg/day), a continuous infusion of thalidomide (100–200 mg/day) and dexamethasone (160 mg/month). Center 2, Hospital das Clinicas of the Faculdade de Medicina da Universidade de SP (HC-FMUSP), used cyclophosphamide (500 mg) on Days 1, 8 and 15, thalidomide (100 mg/day) and dexamethasone (200–400 mg/month). All the agents were administered orally with four to six planned induction cycles. The protocol used for mobilization differed between the centers giving two groups for comparison: Group 1 received cyclophosphamide

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