Transfusion and Apheresis Science xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Review

Current status of art mobilization in Myeloma

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
Hematopoietic cell transplantation
Hematopoietic progenitor cell mobilization
Multiple myeloma

ABSTRACT

Multiple myeloma is the leading indication of autologous hematopoietic cell transplantation (AHCT) worldwide. Hematopoietic progenitor cell mobilization (HPCM) is the first step of a successful AHCT. A minimum of 2×10^6 $CD34^+$ cells/kg are needed for successful engraftment. Growth factors have been used both alone or in combination with chemotherapy for HPCM of patients with myeloma. Mobilization failures result in delays in AHCT and increased cost and resource utility. Strategies to mobilize progenitor cells were mainly chemotherapy and growth factor or growth factor-only mobilization until the advent of plerixafor. Plerixafor is successfully integrated into both growth factor-only and cyclophosphamide and growth factor mobilization strategies with significantly reducing the mobilization failure rate in myeloma patients. The best strategy to mobilize progenitor cells with the highest yield and lowest toxicity and cost in patients with multiple myeloma has not yet been determined. This review aims to summarize the current status of art mobilization in myeloma comparing the pros and cons of different mobilization strategies.

Contents

1. Introduction

Multiple myeloma (MM) accounts for 1% of all cancers and 10% of all hematological malignancies. Annual incidence is approximately 4 per 100000 and median age of patients at the time of diagnosis is about 65 years [1]. The median survival is about 6–7 years and is getting longer with the integration of newer novel agents like carfilzomib, pomalidomide, elotuzumab and daratumumab, which are recently approved. However, depending on host factors, cytogenetic abnormalities, tumor burden and response to therapy there is a major variation among survival. Patients with higher risk cytogenetic abnormalities can only achieve a median of 3 years overall survival despite novel agents [2–5].

Autologous hematopoietic cell transplantation (AHCT) improves median OS in multiple myeloma approximately 12 months. Considering the standard approach of the treatment of multiple myeloma, AHCT remains as a mainstay of the therapy despite the advent of novel drugs. One should consider

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https://doi.org/10.1016/j.transci.2017.11.028
1473-0502/

AHCT in all patients who are eligible for high dose therapy. Multiple myeloma is the leading indication of AHCT worldwide [6,7].

Aim of this manuscript is to review the recent literature among hematopoietic progenitor cell mobilization in myeloma, and to conclude the evidence based state of art in mobilization.

1.1. Historical Progress of Hematopoietic Progenitor Cell Mobilization in Multiple Myeloma

Early stem cell transplants were applied with a bone marrow harvest until the discovery of growth factor induced mobilization. GM-CSF was the first colony stimulating factor that had been used to mobilize hematopoietic progenitor cells from the bone marrow niche to peripheral blood. This approach gained a rapid reputation over bone marrow harvesting, with an easy applicability, lower cost and lower complication rate.

Today, one can only consider bone marrow harvesting after a definite mobilization failure with available growth factor, chemotherapy and growth factor or plerixafor induced mobilization, which accounts for a small amount of all myeloma patients [8].

1.2. Modern Era of Mobilization in Multiple Myeloma

After the discovery of growth factor induced mobilization of hematopoietic progenitor cells, the major questions to be answered were the ideal amount of yield, ideal way of mobilization, factors that predict the yield and definition of poor mobilization, strategies to overcome and manage poor mobilization and the effect of tumor contamination in the yield. This review will try to cover these issues with an evidence based approach.

1.3. Ideal amount of yield

Correlation of number of progenitor cells infused and engraftment kinetics is well established in AHCT. Administration of $CD34^+$ cell doses less than $1.5–2.5 \times 10^6$/kg leads to delayed neutrophil and platelet recovery. Administration of doses less than 1×10^6/kg has been associated with increased erythrocyte and platelet support and even permanent loss of engraftment, whereas infusion of more than $3–5 \times 10^6$ $CD34^+$ cells/kg is associated with earlier neutrophil and platelet engraftment [9–12].

Over 6×10^6 $CD34^+$ cells/kg has also further decreased the need for platelet support, although there was no significant difference in the time to platelet recovery [13]. Some, less well controlled trials, have investigated the role of higher $CD34^+$ cell doses had documented that the time to engraftment shortened with 1 to 2 days with eliminating platelet support [14–16]. But more research is needed to suggest a mega dose infusion. Besides, literature lacks randomized trials that document a better outcome of transplant with a higher infusion dose of $CD34^+$ cells.

Today, one can target at least 2×106 CD34 + cells/kg for a minimum cut-off of a successful mobilization. Ideal target should be more than 3×106 CD34 + cells/kg for one transplant. Higher targets ($6–8 \times 106$ CD34 + cells/kg) are necessary if more than one transplant is planned. Over 5×106 CD34 + cells/kg should be considered to be the optimal dose and mobilization failure can be defined as a yield less than 2×106 CD34 + cells/kg for patients planned to undergo AHCT for myeloma

1.4. Ideal way of mobilization

After the introduction of growth factors in the field of transplant, first option was to add them to chemotherapy and mobilize progenitor cells at count recovery, which is called chemo-mobilization, with a hesitation of tumor contamination of the progenitor cell yield, and with an aim of in-vivo purging. Trials that document the pros and cons of chemo-mobilization or growth factor-only mobilization will be covered at this section.

1.4.1. Chemo-mobilization vs growth factor-only mobilization

Considering chemo-mobilization, cyclophosphamide was the main therapeutic agent used for this approach. Being widely used, the optimal dose of cyclophosphamide, which results with the best yield outcome and least toxicity, has not yet been determined. Fitoussi et. al., have compared two different doses of cyclophosphamide as $4\,g/m^2$ vs $7\,g/m^2$ retrospectively in 116 multiple myeloma patients combined with growth factors and found that $4\,g/m^2$ decreased hematological and extrahematological toxicity with the same amount of progenitor cell yield [17]. Cyclophosphomide doses less than $3–4\,g/m^2$ with G-CSF (Cy + GCSF) were also tried with varying degrees of mobilization success and less toxicity compared to intermediate ($3–4\,g/m^2$) dose Cy + GCSF mobilization [18,19]. In the age of novel induction regimens, Hamadani et. al., have reported that intermediate dose (ID) cyclophosphamide ($3–4\,g/m^2$) with G-CSF have significantly resulted with a lower rate of mobilization failure and produced a more robust peripheral blood progenitor cell mobilization when compared with low dose (LD, $1.5\,g/m^2$) cyclophosphamide with G-CSF mobilization [20]. Shimura et al. have also compared ID ($4\,g/m^2$) vs LD Cy + GCSF ($1.5\,g/m^2$) mobilization in a smaller cohort and have shown that LD-Cy + GCSF mobilization is as effective as ID-Cy + GCSF mobilization while the former is clearly more practicable and convenient for patients with MM [21].

Despite conflicting data, one should consider intermediate dose (3–4 g/m2) cyclophosphamide plus GCSF mobilization as the standard of care in patients who are planned to be mobilized with this combination approach

GM-CSF was the first growth factor which was shown to mobilize progenitor cells from bone marrow niche to peripheral blood. For a long period of time it was used to mobilize patients with myeloma both as a single agent and a conjunct to chemotherapy. After the availability of G-CSF, GM-CSF has been shown to be inferior to G-CSF in terms of number of progenitor cells collected and in post-transplantation outcomes of hematopoietic recovery, transfusion and antibiotic support, febrile episodes and hospitalization [22,23].

Hence, if G-CSF is available GM-CSF is not a reasonable option in mobilization of patients with MM, both as a single agent or as a conjunct to chemotherapy.

Chemo-mobilization was believed to be associated with a better progenitor cell yield, with a lesser tumor contamination and with a possible better transplant outcome when compared with growth factor only mobilization. Multiple groups have demonstrated that chemotherapy mobilization yields significantly more progenitor cells than growth factor only mobilization, with an increased risk of neutropenic fever, hospitalization and transfusion support [24–26]. High dose cyclophosphamide (3 g/m2) with growth factor mobilization was associated with a higher incidence of post-transplant non-stapyhlococcal bacteremia and a prolonged engraftment if progenitor cell reinfusion occurred before 30 days after first apheresis session, suggesting a potential bone marrow microenvironment damage with cyclophosphomide [26]. Despite being associated with a higher yield, effect of chemo-mobilization on disease control was also not well established. In this manner, Dingli et al. have tried to determine the potential impact of addition of cyclophosphamide to improve CR rates after ASCT and TTP in patients undergoing HDT for myeloma, excluding patients who

Please cite this article in press as: Sevindik OG, et al. Current status of art mobilization in Myeloma. Transfus Apheresis Sci (2017), https://doi.org/10.1016/j.transci.2017.11.028