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EDITORIAL

Optimal mobilization method and CD34+ dose calculation for autologous PBSC transplant in myeloma patients: two important unresolved questions

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Multiple myeloma (MM) is one of the more frequent indications for autologous hematopoietic SCT as intensification therapy after induction.[1–4] This procedure is included in the standard treatment for younger patients with symptomatic MM. However, several topics remain unresolved regarding the optimal methodology to collect autologous stem cells in these patients.[5–11] MM usually presents osteopenia or bone lytic lesions and this deserves the classical BM harvesting by iliac aspiration. In some patients, residual plasmacytic infiltration remains after induction treatment before collection and others also have received earlier local or extensive radiotherapy that could affect stem cell collection. For these reasons, MM was one of the first diseases in which PBSC mobilization and collection by leukapheresis was initially applied and then adapted to other oncohematological diseases for autologous transplantation.[1–4] Several clinical variables have been found as factors influencing a successful collection.[5–9] In spite of the extensive use of this strategy for intensification therapy in MM, several topics remain without a clear answer or are controversial. The optimal method of mobilizing stem cells is not established. Chemotherapy alone and chemotherapy followed by growth factors are the more frequent methods used.[10–15] However, neither the dose and type of chemotherapy nor the type and dose of growth factor are well defined. Myeloma usually affects elderly patients, and age is an unfavorable variable for stem cell mobilization. The number of earlier lines of therapies and their duration, including regimen with alkylator agents or with radiotherapy, have been related with poor mobilization. Other technical questions as the volume of blood processed and the number of leukapheresis performed, cryopreservation methods, enumeration and the target dose of CD34+ and so on are also important and need to be revised to simplify the procedure and warrant an appropriate engraftment after high-dose chemotherapy.[5–13]

This issue of *Bone Marrow Transplantation* includes two interesting papers that evaluate some of these unanswered questions regarding the methodology of mobilization and the collection of PBSC in MM patients.[15,16]

The group of the Mayo Clinic, Rochester, coordinated by Dr MA Gertz,[15] compares the use of filgrastim alone (G-CSF) with filgrastim after a high dose of CY. In this study, CY was associated with several clinically significant concerns after transplantation. In particular, time to engraftment of neutrophils and platelets was delayed when compared with that of patients mobilized with growth factor alone. Although this delay did not increase the duration of hospitalization, this group observed an association between treatment method and incidence of non-staphylococcal bacteremia (13 and 7% for patients treated with CY and growth factor, respectively, ($P=0.01$)). Owing to the delayed neutrophil engraftment, an additional growth factor was administered until engraftment was achieved, and also increased antibiotic therapy was necessary to treat higher bacteremia rates. The author hypothesizes that CY could transiently damage the BM microenvironment and that this damage delays recovery. Earlier reports support this hypothesis. They compare those who received their stem cells within 30 days of the first apheresis session with those who received stem cells longer than 30 days after the first apheresis and they observe a relation between time to transplantation and the deleterious effects of a high dose of CY as a mobilizer agent. It is difficult to consider timing as the sole explanation for the difference in engraftment; however, 75% of the CY-mobilized patients who were infused less than 30 days after collection did not achieve the platelet count of 50×10^9/l until day 39, whereas those who underwent transplantation more than 30 days after the first apheresis achieved this value at day 29. For patients with no exposure to CY, the platelet count was achieved by day 18. In this study, CY appears to produce some degree of microenvironmental damage that impedes the recovery of healthy infused CD34 cells. However, there are other variables that could explain this engraftment differences: earlier alkylator regimens, advanced age, marrow involvement, post-collection processing of cells (cryopreservation, storage, re-infusion techniques and so on) and also stem cell sub-population study as CD34+CD33− that could be a more accurate predictor of the engraftment capacity. Owing to the retrospective characteristic of this study, a prospective research of this phenomenon is needed.

The comparison of CY+growth factor:GM-CSF or G-CSF has also been evaluated by other authors.[9–15] In most studies, mobilization with chemotherapy plus growth factors has shown to be more effective than mobilization with growth factors alone. This aspect has been recently evaluated by the Spanish Myeloma Group comparing mobilization results with G-CSF alone vs G-CSF plus CY.[14] In this series, the median number of CD34+ cells collected after mobilization with CY plus G-CSF was slightly higher than that obtained with G-CSF alone, but the difference was not statistically significant, probably because we administered a lower dose (2 g/m^2) of CY than that generally used. CY is the chemotherapeutic agent most

commonly used for PBSC mobilization, but the optimal dose has not yet been established and doses used range from 2 to 7 g/m^2 Although higher doses of CY may yield higher CD34+ cell numbers, several studies have observed an increased toxicity and morbidity. Several studies show that mobilization with G-CSF alone at the steady state is a valid alternative for PBSC collection in MM patients. The deleterious effects of CY for engraftment observed by Gertz and co-workers[16] were not observed by these groups. Although other factors could explain this finding in most patients, the transplant was performed more than 30 years after the first apheresis and not very close to the high dose of CY, and patients even receive some induction chemotherapy schemes after mobilization to improve clinical response and to reduce the disease burden before transplant.

This aspect should be evaluated with more details, considering other factors that could influence engraftment. Regarding CD34+ target for collection, there is great heterogeneity between groups. Some groups consider that $>5\times10^6$/kg is correlated with a consistent rapid platelet engraftment.[6] However, other groups observe no differences between 2 and 5×10^6. Most groups suggest that 2×10^6 kg CD34+ cells should be the minimum target although a higher dose could be better for a more rapid recovery and useful for tandem transplant.[5,7–14] Owing to the heterogeneity of MM patients and different induction regimens, it is difficult to make meaningful comparisons. On the other hand, it should be noted that interlaboratory differences in CD34+ cell enumeration may have contributed to these findings.

This issue includes other interesting publications related to PBSC collection in MM patients.[16] Singh *et al.*,[16] from the Northwestern University Medical School of Chicago, coordinated by Dr J Mehta, evaluate the relevant question of the use of actual body weight (ABW) vs the ideal body weight (IBW) to calculate the CD34+ cell dose to infuse for PBSCT in MM patients. Although it is virtually universal to express cell doses for hematopoietic SCT in terms of ABW, there are data suggesting that IBW may be a better basis for calculating cell dose.[16,17] This was studied further in 514 MM autografts in this study. IBW-based cell doses correlated slightly better with engraftment than ABW. They conclude that CD34+ cell doses based on IBW as well as ABW significantly affected engraftment when analyzed separately as continuous variables. However, when analyzed together, only the dose based upon IBW retained significance. They conclude that a CD34+ cell dose based on IBW is a better predictor of engraftment speed than that based on ABW, and that IBW should be used as the basis for cell-dose calculations in autologous hematopoietic SCT. This is the standard and recommended practice for this group. The authors indicate that weigh loss, which is especially frequent in MM patients, due to osteopenia, should be taken into account while calculating IBW for this purpose. This observation has been described by other groups, and it is a relevant aspect because it could simplify the collection.[16]

There are recent advances for MM treatment that could influence these aspects. Lenalidomide originates myelosuppression and some authors have recommended the use of CY before growth factor to ensure collection, although this needs further research.[17] Other new drugs for MM should be evaluated regarding their influence on mobilization. On the other hand, some groups have observed best mobilization results with pegylated G-CSF (pegfilgrastim) compared with standard G-CSF not pegylated.[18,19] Recently, this method has been evaluated by Tricot *et al.*[19] This study showed that PBSC post-chemotherapy is feasible and similarly effective with pegfilgrastim and filgrastim, with the advantages of greater ease and cost-effectiveness with pegfilgrastim. For these authors, pegfilgrastim may become the standard growth factor to be used for stem cell mobilization with or without chemotherapy. Different CD34+ and progenitor cells subsets with potential distinct functional properties when mobilized with pegfilgrastim should been evaluated in comparison with those mobilized with filgrastim non-pegilated.

In relation with poor mobilizers in MM patients, recently, a phase III study has been performed with a new drug that mobilizes PBSC inhibiting XCR4 receptor on marrow stroma that originates CD34+ liberation to PBSC for collection. This new drug, AMD3100, combined with G-CSF, is useful for MM patients with a mobilization failure with standard methods.[20]

In summary, the optimal method to mobilize MM patients is not well defined, but there are several efficacious methods and, although G-CSF alone is useful in most patients, probably the method selected needs to be adapted to each patient according to its clinical characteristics. Pegylated G-CSF could become the standard growth factor in this context, with or without chemotherapy. The minimum CD34+ cell dose infused should be superior to 2×10^6, and calculation based on IBW is a better predictor of engraftment than that based on ABW. Finally, the analysis of these and other aspects deserves further research due to the recent approval of new drugs for MM patients and the availability of new mobilizer agents.

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