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EDITORIAL

Stem-cell collection before high-dose therapy for multiple myeloma: time has come to raise the standards!

The introduction of high-dose melphalan therapy supported by autologous transplantation of peripheral hematopoietic stem cells (ASCT) was the first improvement in multiple myeloma (MM) treatment after several years of stagnation. At present, MM is the most common indication for high-dose chemotherapy with ASCT worldwide. Indeed, ASCT has now become the standard-of-care in patients with MM under the age of 65–70 years and without significant comorbidities. The latter is the consequence of two large and well-designed randomized trials demonstrating the superiority of ASCT over conventional chemotherapy in terms of response rate, progression-free survival and overall survival.[1] The benefit from high-dose therapy and ASCT is related to an improved and more sustained effective disease control, and is likely to have a significant relationship with complete remission achievement.[2] Although the role of ASCT in MM in the context of novel anti-MM combination therapies, such as thalidomide, bortezomib and lenalidomide, is currently under considerable debate,[3] it is likely that ASCT will remain a major therapeutic tool for frontline and relapsed MM therapy for the next decade.

In the setting of ASCT, since the mid-1990s, the use of bone marrow as a hematopoietic stem cell source has largely been supplanted by the use of peripheral blood stem cells (PBSCs). Compared with marrow infusion, transplantation with PBSCs leads to faster engraftment and hematological reconstitution, and as a result patients may benefit from improved outcomes.[4] Mobilization of PBSCs is accomplished by treatment with cytokine (usually granulocyte-colony stimulating factor (G-CSF)) alone or in combination with chemotherapy. With the current PBSCs mobilization techniques, a significant proportion of MM patients may not be able to mobilize a sufficient or target number of cells to proceed to ASCT. The failure rate with the current techniques is estimated to be between 5 and 40%.[4] This wide range of reported failure rates stems at least partly from different definitions of what constitutes a failure.

In this issue of the journal, the International Myeloma Working Group (IMWG) provides a comprehensive consensus statement and guidelines regarding the current status of stem-cell collection and high-dose therapy for MM. Indeed, with the advent of Plerixafor (AMD3100, Genzyme Corporation, Cambridge, MA, USA) as well as novel MM induction regimens, it was very desirable to review the current status of PBSC mobilization for ASCT in MM and draw some perspectives for the future. A major conclusion from this consensus statement was that optimizing stem-cell collection either early or later during the course of the disease should continue to be an integral component of MM treatment planning, and should be incorporated in the design of future prospective trials, as the advent of Plerixafor as well as novel induction regimens will likely change the current standards for stem-cell transplant and PBSCs mobilization.

At present, advances in mobilization techniques to improve patient outcomes are considered as important because current mobilization regimens have a relatively high rate of mobilization failures, make it impossible for most patients to reach an optimal target cell dose of >4–5×10^6 CD34 + cells/kg, require more than one aphaeresis session and a need for long (that is, often up to 6 days) treatment with G-CSF or other mobilization agents, and are associated with the occurrence of side effects. In December 2008, the Food and Drug Administration (FDA) approved Plerixafor for use in combination with G-CSF for the mobilization of autologous PBSCs in adult patients with non-Hodgkin's lymphoma and MM. Plerixafor is a small-molecule bicyclam derivative with a novel mechanism of action. It reversibly and selectively antagonizes the CXCR4 chemokine receptor and blocks binding of its cognate ligand, stromal cell-derived factor-1α (SDF-1α, also known as CXCL12). The interruption of the CXCR4/SDF-1α interaction results in mobilization of CD34 + cells to the peripheral blood, where they can be collected for ASCT.[5] Peak mobilization of CD34 + cells occurred for 4–6 h in healthy donors after s.c. dosing with 240 µg/kg Plerixafor alone.[6] Although Plerixafor mobilizes CD34 + cells adequately on its own,[7] it significantly improves the mobilization capacity of G-CSF when used in combination with G-CSF.[8] Peak mobilization in healthy volunteers occurs 10–14 h after the administration of Plerixafor (when used in combination with G-CSF). The approval of Plerixafor is broadening the therapeutic options for mobilization of PBSCs for patients in need of high-dose chemotherapy, thereby increasing the pool of patients for whom ASCT is an option.

Usually, PBSC mobilization regimens differ with respect to PBSC yield, predictability of the time-to-peak mobilization, resource utilization, and general safety and tolerability considerations. There may also be differences between treatments in aphaeresis content (in terms of cell composition and as well as tumor contamination). Also, clinical practice depends to an extent not only on clinical or medical factors, but also on certain logistical factors, such as the relationship of the aphaeresis unit to the transplant team, and distance of the patient's home from treatment centers. The elements that are generally recognized to be key factors for successful mobilization of autologous PBSCs are as follows: (i) number of PBSCs collected and reinfused, (ii) predictability of peak mobilization time, (iii) number of required aphaeresis days and (iv) the burden on the patient and medical team. In addition, if daily blood tests are required to monitor whether mobilization is occurring and when aphaeresis should take place (as happens with chemo-mobilization), this is an additional strain, as are the side effects of chemotherapy, G-CSF and aphaeresis. With this background, an optimal PBSC mobilization regimen should have a high mobilization efficiency that translates into a reliable and optimal yield of PBSCs with as few aphaeresis collections as possible, ideally allowing collection within a single aphaeresis procedure, to increase the proportion of patients achieving a target optimal number of cells to proceed to potentially curative high-dose chemotherapy followed by ASCT, with successful, prompt and durable engraftment of neutrophils and platelets, improved survival rates with minimal toxicity, and as little burden as possible for

the patient. Also, an optimum regimen should have predictable mobilization kinetics, so that the day of initial apheresis can be planned in advance, resulting in a more efficient use of apheresis equipment and related resources, including health-care personnel. The 'quality' of the apheresis product (e.g., the number of lymphocytes in the graft and the absence of tumor-cell contamination), and the possibility of collecting enough PBSCs for tandem, salvage or back-up autologous transplant are additional factors to take into account. Finally, pharmaco-economic factors (for example, resource utilization, hospital admission rates, need for transfusions and antibiotic therapy, and so on) and the resulting overall financial outcome may be of less importance to the individual patient, but does have an impact on the national healthcare systems and should therefore be considered as well.

If Plerixafor is used with G-CSF, the patient and their family benefit from (i) reduced risk of mobilization failure (and so reduced risk of disease progression while waiting for remobi-lization), (ii) no need for daily blood tests, (iii) no need to wait for the results of CD34 + count before commencing apheresis, (iv) fewer days of G-CSF, and so fewer days of side effects, (v) no risk of febrile neutropenia and potential infection, or thrombo-cytopenia and potential bleeds due to chemotherapy used for mobilization and (vi) fewer days of unpleasant apheresis.

Scientifically, we have never been in a better position to advance MM treatment. Basic scientific research, fueled in recent years by the tools of molecular biology and genomics, has generated unprecedented knowledge of MM pathophysio-logy. We now understand many of the cellular pathways that can lead to MM. We have learned how to develop drugs that block those pathways.[9] And increasingly, we know how to personalize therapy to the unique genetics of the tumor, and the patient.[9] The advent of Plerixafor will indirectly enrich the therapeutic armamentarium of MM, as it represents a great opportunity to rejuvenate clinical research in the field of stem-cell collection for ASCT. The safety and *efficacy* ('estimate of effect under ideal circumstances') of this agent are already established, and its post-regulatory appraisal will likely demon-strate its clinical *effectiveness* (the 'real-life' effect).[11]

Conflict of interest

The author declares no conflict of interest.

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