Scientific & Clinical

PLERIXAFOR AND TRANSPLANTATION IN MULTIPLE MYELOMA

Myeloma Today in conversation with Dr. Sergio Giralt

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Please give us a brief overview of transplantation in multiple myeloma.

In the early 1980s, Tim McElwain (Professor of Medical Oncology at the Royal Marsden Hospital in the UK) made a seminal observation that by giving myeloma patients high doses of melphalan, we could overcome the resistance of their disease to standard doses of melphalan therapy and regain control of their myeloma, albeit for a short period of time. The other thing he demonstrated was that the toxicity of melphalan primarily affected the bone marrow, the organ in the bone that produces the red and white blood cells and the platelets, which carry oxygen to the body, protect us from infection, and prevent bleeding. Some patients who received very high doses of melphalan died from complications due to the marrow toxicity. It was Bart Barlogie's concept to take out the patients' marrow and freeze it before giving them high doses of melphalan, then re-infuse the marrow to help patients recover more quickly from the melphalan therapy. That's how the whole field of bone marrow transplantation (BMT) for myeloma began.

Initially, BMTs were performed on patients who had exhausted their other options. Later, transplantation became a frontline therapy option. There was much controversy in this arena, but most studies showed that patients who underwent transplantation had a higher complete remission (CR) rate and lived longer without disease than those who did not.

In the late 1980s, it was discovered that bone marrow stem cells, which give birth to all mature cells, circulate in the blood after the patient undergoes chemotherapy. The stem cells could be collected from the bloodstream after patients received high doses of Cytoxan® (cyclophosphamide). At the same time, white cell growth factors such as Neupogen® (filgrastim), Neulasta® (pegfilgrastim), and Leukine®(sargramostim) were becoming commercially available to help patients receive chemotherapy with less marrow toxicity than before. Investigators in Europe demonstrated that the combination of chemotherapy and these granulocyte-colony stimulating factors (G-CSF) “mobilized” the release of stem cells from the bone marrow into the bloodstream. It was no longer necessary to put patients under general anesthesia to harvest cells by direct penetration and aspiration of the marrow

from the bones. We could collect large numbers of patients' stem cells directly from the blood, as if it were a blood donation. This is how autologous bone marrow transplantation (BMT) was replaced by autologous stem cell transplantation (ASCT).

What is the current place of ASCT in myeloma?

As with other forms of therapy, the goals of ASCT are to achieve the maximum depth and duration of response leading to the best overall survival. Myeloma is the most common indication for high-dose chemotherapy with ASCT in North America today. It remains the treatment associated with the highest CR rate in myeloma and, when compared to conventional chemotherapy regiments, ASCT is associated with improved survival.

Is this likely to remain the case in the context of available novel agents?

We have seen a continued increase in the number of ASCTs performed for myeloma, even after the approval of thalidomide, Velcade® (bortezomib) and Revlimid® (lenalidomide). The role of high-dose therapy in the context of these novel anti-myeloma therapies and combinations is being re-explored, but it is likely that high-dose therapy will remain an important component of frontline and relapsed myeloma therapy. Discussions continue regarding ASCT and stem cell mobilization in myeloma in the context of new therapies.

What about single versus double ASCT?

It is interesting that you ask this. The Italian and French studies have shown that if you respond well to the first transplant, you do not benefit from the second. But that conclusion was made based on a very small number of patients in an analysis that was not really planned so, in my opinion, this assertion is not statistically valid.

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN), a cooperative group funded by two divisions of the U.S. National Institutes of Health -- the National Cancer Institute (NCI) and the National Heart, Lung, and Blood Institute (NHLBI) -- is conducting a randomized clinical trial of 750 patients who will all receive one transplant with high-dose melphalan, followed by either four cycles of novel therapy or a second transplant, or maintenance alone. We encourage all patients and physicians to consider participating in this study. The results of this study should show us, in the context of novel therapies, if one transplant is as good as two.

Let's return to the topic of stem cell mobilization.

Mobilization is the process by which we get the stem cells from the marrow into the bloodstream. Stem cell procurement for ASCT has most commonly been performed with stem cell mobilization

using G-CSF with or without prior chemotherapy.

What are the determining factors in whether a myeloma patient is mobilized with or without chemotherapy?

This often depends on whether the patient has active myeloma, the extent (and type) of prior therapy, and disease duration. Sometimes the determination is based upon the program in which the patient's physician is participating. Modern technology allows for about 95% of myeloma patients to be successfully mobilized with enough cells for one or two transplants. Most clinical trials suggest that more cells can be collected after chemo-mobilization, but chemo-mobilization has not demonstrated superior outcomes while being associated with more toxicity, and the failure rate with chemo-mobilization is similar to the failure rate with G-CSF alone.

What are the options for the myeloma patients who are not mobilized successfully?

Years ago, the patients who were poor mobilizers, who failed to mobilize despite multiple attempts, were never able to proceed to transplant. Most retrospective studies addressing mobilization have identified patient age, method of mobilization, time to stem cell mobilization, number of prior regimens, and prior melphalan and/or radiation exposure as predictors of patients failing to achieve a minimal dose. Parallel to this, other studies have been exploring the biology of myeloma and the mechanism of how cells move out of the bone marrow. The science is very elegant, with parallels between how stem cells find their home in the bone marrow. Stem cells are designed to live as long as we live, and they are there to produce all the blood cells and platelets that we need for our lifespan. The stem cells “stick” with what are called adhesion molecules, the glue that holds the stem cells against the walls of the bone marrow to prevent them from being released. Today, novel mobilization strategies are disrupting the “glue” so the stem cells can separate themselves and circulate in the blood to improve collection yield and efficiency.

This is where plerixafor steps into the picture?

Plerixafor (also known as Mozobil®) is a drug that was originally developed for AIDS. During the clinical trials conducted with plerixafor for AIDS, an observation was made that patients taking this drug had very high white blood cell counts. Further studies showed that plerixafor breaks the bond between stem cells and the walls of the marrow cells, thereby releasing more stem cells into the bloodstream.

In myeloma and lymphoma, two important clinical trials have shown that plerixafor is safe and effective in combination with G-CSF and results in increased stem cell mobilization in fewer apheresis days compared to G-CSF alone.

Also, plerixafor showed to be effective in mobilizing adequate stem cells in two thirds of the patients who had failed traditional mobilization techniques as demonstrated in the compassionate use protocol. In patients with myeloma, plerixafor in combination with G-CSF has also been shown to be more effective as an initial mobilizing regimen than G-CSF alone. More studies need to be done with this agent to better define its role in the treatment of myeloma, but we have found the use of plerixafor to be both safe and predictable (in terms of cell yields) as a mobilization agent.

Plerixafor is a major advance in ASCT in myeloma. It has a very manageable toxicity profile, with the most common adverse events being injection-site reaction and mild GI upset. It allows us to more efficiently collect larger numbers of cells from good responders, to mobilize patients who have failed mobilization, to help save patient resources, and to study if transplanting very high numbers of stem cells can improve outcome for patients.

Any closing comments?

High-dose melphalan is still recommended for eligible patients, and stem cell collection early in the course of therapy should be considered in all patients eligible for ASCT. The decision of whether or not to pursue ASCT must be made by the patient in consultation with their treating physician. If a patient chooses to undergo ASCT, they don't necessarily need to incorporate plerixafor into their mobilization regimen but it can be very helpful if they fail to mobilize without it.

In closing, I would recommend that patients discuss with their doctors the benefits of plerixafor in combination with G-CSF, as opposed to using G-CSF alone, especially since plerixafor does not add the significant toxicities associated with stem cell mobilization using chemotherapy.
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