THE CURRENT ROLE OF TRANSPLANTATION IN MULTIPLE MYELOMA

Myeloma Today in conversation with Dr. Cristina Gasparetto

Please tell us about your medical background and how you came to work in myeloma.

I received my medical training at the Sapienza University of Rome, Italy. My residency in Internal Medicine was at Duke University Medical Center, followed by residency in Hematology and Bone Marrow Transplant, also at Duke. During my first year at Duke, I was called to a consultation with a young woman who had just been diagnosed with multiple myeloma. At that time, the treatment options available to myeloma patients were very limited. She was a candidate for a transplant and, as she struggled with the decision, I wanted to help her with the best recommendations I could give. This led me to do a lot of reading about myeloma. I knew at that point that I wanted to make myeloma the focus of my medical career. I spent the last two years of my fellowship doing myeloma research in the laboratory.

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Do you currently work both in the lab and in the clinic?

Before my work at Duke University Medical Center, when I first came to the US from Italy, it was on a scholarship. I worked in the lab at Memorial Sloan-Kettering Cancer Center, where I focused my research on stem cells and growth factors for stem cell mobilization. I was involved with a lot of pre-clinical studies. At that time, the dendritic cell vaccine was introduced for other cancers, and I thought it would be interesting to explore this avenue in myeloma. When I joined the faculty, I kept my laboratory work going, even though it was difficult to do both clinical and lab work simultaneously. I love my clinical work because I really love working with patients and participating directly in their care, which was why I became involved with translational research and clinical trial development.

Currently, what is your primary focus?

I have always been interested in transplantation, both in terms of my laboratory research and in terms of working with patients with hematologic malignancies who could be candidates for high-dose chemotherapy and stem-cell transplantation. I am involved both with laboratory and clinical research, following my interest in developing immunotherapy approaches to treating myeloma, particularly in conjunction with stem cell transplantation. My current lab research projects include the development of dendritic cell vaccines and antibody therapies. Clinical studies include a recently approved trial involving vaccination with autologous dendritic cells pulsed with idiotypic protein following high-dose chemotherapy and autologous stem cell transplant (ASCT). Upcoming trials include novel antibody therapies. I am also an investigator on several other clinical trials for myeloma, including non-myeloablative allogeneic transplantation, high-dose sequential chemotherapy and ASCT, and transplantation of partially HLA-matched unrelated cord blood.

How would you assess the current role of transplantation in myeloma?

For now, myeloma remains an incurable disease, and we have only three options to offer our patients – chemotherapy, transplantation, and novel agents. Since we have not yet cured anybody, I don't think that any one option has clearly surpassed the other treatment approaches.

Some doctors see the novel agents – thalidomide, lenalidomide (Revlimid®), and bortezomib (Velcade®) – as substitutes for a transplant, while I see novel agents as a way to improve upon transplant. In my opinion, the real question is, "What is the best sequential way to tackle myeloma?"

Our goal must be not to simply achieve complete remissions (CR), but to achieve a CR with good depth and durability. As with other approaches to myeloma therapy, the major failure of transplant is relapse, but transplant patients usually experience longer periods of progression-free survival (PFS) and often have longer periods of time off therapy. This also helps them avoid developing significant toxicity-related issues and/or drug resistance.

Over the past decade, I have acquired a lot of experience with transplants in myeloma. ASCT is not a perfect solution to myeloma, but I think it remains a valid option, particularly for younger patients. In transplant, one approach is a short course of powerful induction therapy; the other approach is to continue therapy with consolidation and maintenance. The second choice requires us to continue therapy longer – we cannot stop after just a few cycles. Younger patients may not wish to spend much of the rest of their lives receiving anti-cancer therapy, so a more aggressive transplant approach may be the right choice for these individuals. Others may not be able to tolerate the toxicity of therapy that goes on for a prolonged period of time.

This is why I tailor therapy to each individual patient. Some patients prefer to "go for the cure" while others decide that it is more appropriate to control the disease without attempting to cure it. Plus, given the heterogeneity of myeloma, what is a reasonable goal for one patient may not be for another.

You are a member of the IMWG, which recently published a paper on allogeneic transplantation. Please tell us about that consensus statement.

The IMF's International Myeloma Working Group (IMWG) consensus statement regarding the current status of allogeneic stem-cell transplantation (allo-SCT) as a treatment option for myeloma was published in October by the Journal of Clinical Oncology. The IMWG reviewed the results from prospective and retrospective studies of allo-SCT in myeloma. Allo-SCT, which uses cells from a compatible donor, is a treatment with a potential to cure myeloma due to the graft-versus-myeloma (GVM) effect, and because the donor cells are free from myeloma contamination. However, given the high treatment-related mortality rates with allo-SCT, and the increasing survival rates being achieved with other anti-myeloma therapies and supportive care, allo-SCT should only be recommended in the context of clinical trials until it is made safer and more effective for patients with myeloma. The promising results of reduced-intensity conditioning (RIC) transplantation in low-grade lympho-proliferative disorders

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renewed the interest in allo-SCT as a treatment option for myeloma. However, no definite conclusions could be drawn as to whether allo-RIC was even of benefit. Future studies of allo-SCT in myeloma should aim at improving the graft-versus-myeloma (GVM) effect while reducing the morbidity and mortality of allo-SCT.

Any closing comments?

The survival of patients with myeloma has improved significantly over the past decade. Not only are many patients living longer, but many also have good quality of life. The overall outlook is encouraging, and it continues to improve. **MT**

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phonate dosing and decreased dosing frequency will further decrease the incidence of ONJ.

What about denosumab, a bisphosphonate currently in clinical trials?

Denosumab is a potent new osteoclast inhibitor. It targets the same cells but uses a completely different mechanism of action than the bisphosphonates Zometa® (zoledronic acid) and Aredia® (pamidronate). It has a much shorter duration of action, staying in the bones approximately 3-6 months, not 5-10 years like we believe some other bisphosphonates do. Also, it does not seem to have an adverse effect on renal function. In a recent study of 1776 patients with solid tumors or myeloma who had not previously received intravenous bisphosphonates, those who were randomized to receive 120 mg of subcutaneous denosumab attained results similar to the patients who received intravenous zoledronic acid every 4 weeks. Denosumab also reduced urinary NTX levels by more than 80% within the first month. However, in the subgroup of patients with myeloma (approximately 10% of the total study population), denosumab was associated with significantly worse survival. As a result, the FDA did not approve the drug for treatment in myeloma. Further studies are needed to evaluate the safety and efficacy of denosumab in myeloma.

What is the effect of novel anti-myeloma agents on bone markers?

The effect of novel drugs – thalidomide (Thalomid®), lenalidomide (Revlimid®), and bortezomib (Velcade®) – on bone metabolism in myeloma has been evaluated in several studies. The available data indicate that immunomodulatory drugs have more effect on osteoclast activity than on osteoblast activity. Two clinical phase II trials have studied the effect of thalidomide on bone metabolism in myeloma. One study of relapsed/refractory patients showed that after six months of therapy with thalidomide plus dexamethasone (TD) there was a significant reduction of serum levels of some bone markers. The other study of newly diagnosed myeloma patients showed that the combination of TD and zoledronic acid (Zometa®) for four months produced a significant reduction of urinary NTX and serum CTX in patients who responded to therapy. There is limited data on the effects of lenalidomide on myeloma bone disease. Studies have shown that bortezomib may decrease bone resorption and increase bone formation, but data suggest that the beneficial effect of bortezomib may be reduced when it is combined with other anti-myeloma agents.

What do you anticipate in your field in the near future?

Better understanding bone disease and the bone marrow microenvironment, the area within the bone where myeloma cells grow, is crucial to controlling and/or curing myeloma. Clinical trials are needed before biochemical markers of bone remodeling become part of the routine clinical care of myeloma patients. There are ongoing studies with breast cancer patients and in patients with other forms of cancer and bone metastases, and trials in myeloma are anticipated in the future. **MT**

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Also, it is important to remember that we are not looking for one silver bullet. We are learning to combine drugs, old and new, to increase efficacy and lessen toxicity. This approach also helps us counter drug resistance. There is such a complex nature to the growth and development of myeloma that we have not been able to shut it down with a single drug. One patient might have more than one type of myeloma growing in them simultaneously, and a strategic combination approach appears to be most successful at limiting the disease. Some of these therapies are only available in the context of a clinical trial.

So who is the best candidate for entering a clinical trial?

Clinical trials are available to patients at all stages of myeloma, and we encourage all patients to consider participating if there is one available to them. There is no down side. Clinical trials are not using people as guinea pigs. Clinical trials are providing patients an opportunity to be treated with either a validated therapy or a therapy that's undergoing validation. Patients always have the option to opt for standard therapy later on. Of course, as with all other important decisions, it is very important to have clear and honest discussions with the healthcare provider and the team running the trial.

Any closing comments?

Our management of myeloma – the ability to diagnose, treat, and monitor this disease – has improved tremendously. We can now detect the disease at a much lower lever than ever before, both at initial diagnosis and at relapse, and we can run tests that help us stratify the patients. The use of newer drugs and drug combinations is resulting in longer and deeper remissions for many patients. Another important point is that supportive care continues to get better. We don't just treat the myeloma, we are continuing to get better at treating the whole patient.

I consider myself an optimistic realist and, overall, the future looks very optimistic. Although myeloma is still not curable, we have seen a tripling in the average patient survival rates. Dramatic progress has been made in the field in the last decade, and our understanding of myeloma has improved significantly in the last three years. But our successes notwithstanding, we all share a very strong drive to find better and longer-lasting therapies.

In the meantime, I would stress the importance of myeloma patient education. This is a very complex disease, and knowledge IS power. While scientists and clinicians seek to better understand the disease and to develop better treatments, I would encourage all patients to take a participatory role in their own care in partnership with their healthcare providers. **MT**