

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

New Drugs in Multiple Myeloma and the Significance of Autologous Stem Cell Transplants

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H&O What are the challenges of autologous stem cell transplants (ASCTs) in multiple myeloma (MM) today?

SJ First, the actual ASCT is no longer a challenge. Collecting stem cells, determining the quality of stem cells and the quantity of stem cells to give back—all of this have become very precise. Safety has also improved; the chances of a patient dying from high-dose chemotherapy plus SCT, which were approximately 15% in the 80s and early 90s, are now usually under 5%.

However, the biggest challenge remaining is that high-dose chemotherapy plus SCT is still not a cure for MM. Whereas a proportion of patients with non-Hodgkin lymphoma or Hodgkin lymphoma have a chance to be cured, patients with MM unfortunately do not have that option. Physicians can only inform MM patients that their cancer will be controlled for a longer period of time.

H&O With newer and more effective agents available, is there still a role for ASCT?

SJ This is where the situation currently stands: with the availability of newer agents such as thalidomide (Thalomid, Celgene), bortezomib (Velcade, Millennium Pharmaceuticals), lenalidomide (Revlimid, Celgene), etc. that have shown improved efficacy in MM, some

may think that ASCT is no longer relevant. However, my belief is that there is still a need for ASCT because none of these new drugs is a cure for MM.

Additionally, Dr. Jean-Luc Harousseau and colleagues presented an interesting study at the 2008 American Society of Hematology (ASH) annual meeting, suggesting synergy with one of these new drugs and transplant.¹ In this open-label, multicenter, phase II study of 57 patients, the primary endpoint was the complete response (CR) plus very good partial response (VGPR) rate at 3 months after ASCT with bortezomib and high-dose melphalan as the conditioning regimen. The secondary endpoint was the safety profile of this regimen. The choice of induction therapy was not specified. In the group that received standard VAD (vincristine, doxorubicin, dexamethasone) for induction therapy, 43% of the patients achieved CR and 25% achieved VGPR after SCT. Similarly, in those who received a bortezomib-dexamethasone-based induction therapy, 39% achieved CR and 33% achieved VGPR. Bortezomib did not increase hematologic toxicity when combined with high-dose melphalan. When compared to results from the IFM 2005/01 trial (comparing bortezomib and dexamethasone to VAD as induction prior to SCT) the results were improved. Previous CR rates were 20% after VAD and 34% after bortezomib/dexamethasone.

This study showed the safety and high efficacy of bortezomib and high-dose melphalan as a conditioning

regimen in frontline MM patients, and also found that in newly diagnosed patients, bortezomib plus dexamethasone produced superior response rates and CR rates and longer progression-free survival following transplant, compared with the standard VAD.

Additionally, if a new drug is given to a patient with MM and the patient does not respond, very few options are left, ASCT being one of them. Therefore, ASCT remains relevant. Even in patients with renal failure, a patient population that had previously been turned down for ASCT because of the risk, ASCT can be performed safely by a team with experience and expertise. It should be noted that a team of experts is necessary for this procedure; otherwise, the mortality will be higher. Institutions such as University of Arkansas and M.D. Anderson Cancer Center are places that can handle this.

H&O What are some new drugs of interest in the treatment of MM?

SJ *Carfilzomib*: First, there is the proteasome inhibitor carfilzomib, which selectively inhibits a single subunit of the proteasome, allowing it to have minimal activity against off-target proteases. Carfilzomib forms an irreversible adduct when it binds to its target proteasome subunit, which leads to a more sustained proteasome inhibition than the reversible activity of bortezomib. Dr. Ravi Vij and colleagues reported the PX-171-004 study at the recent ASH meeting, showing the efficacy of carfilzomib in patients failing 1 to 3 prior regimens, including bortezomib-naïve patients.² This phase II, open-label, single-arm study included 31 patients with relapsed/refractory MM who failed 3 or fewer prior treatments. Over half of the patients had prior bortezomib exposure. After given carfilzomib, approximately one-third of patients had a response; the rate of response was higher in patients who were bortezomib-naïve compared with patients with a prior history of bortezomib (57% versus 18%, respectively). Bortezomib-naïve patients also had a longer median duration of carfilzomib therapy compared to those patients with prior bortezomib exposure (271 vs 99 days, respectively), suggesting that carfilzomib was well tolerated.

Also at ASH, my colleagues and I presented similar data in the relapsed/refractory setting.³ The open-label, multicenter PX-171-003 study investigated patients with MM who had relapsed after at least 2 prior therapies, including bortezomib, and were therefore given carfilzomib. We found that in this heavily pretreated

MM population, carfilzomib as a single agent was able to induce clinical benefit response (including CR, VGPR and minimal response) in 26% of the patients. Carfilzomib was generally well-tolerated, and the pre-existing peripheral neuropathy in these patients was seldom exacerbated.

Pomalidomide: Secondly, there is a thalidomide-like drug, pomalidomide. Pomalidomide is structurally similar to thalidomide and lenalinomide, but it is associated with more potent immunosuppression and fewer adverse events. In a phase II single-arm study presented at ASH by Dr. Martha Lacy, 60 patients with relapsed/refractory MM received oral pomalidomide and oral dexamethasone. After a median follow-up of 4 months, a 58% overall response rate (ORR) was observed, and 29% of lenalinomide-refractory patients achieved a response. Pomalidomide dose reductions occurred in 13% of patients, mainly due to neutropenia and neuropathy, while dexamethasone dose reductions occurred in 32%.

Dr. Lacy and colleagues concluded that pomalidomide, when combined with low-dose dexamethasone, had a relatively safe profile and was highly active in patients with relapsed/refractory MM.

Other agents that are of interest are antibodies such as elotuzumab, a humanized monoclonal antibody directed against a cell surface glycoprotein that is highly and uniformly expressed in MM, and anti-CD138 antibodies with immunotoxins attached.

I think myeloma is a changing field with more new drugs to come. More progress in this area can be expected, and I believe a cure should be on its way in the next 5–10 years.

References

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