To Transplant or Not To Transplant in Multiple Myeloma

High-dose therapy in combination with autologous stem cell transplantation (ASCT) has become the standard of care for younger multiple myeloma patients. Is ASCT still the best treatment for these patients in the era of new antimyeloma agents, and should its use be expanded? Or has the introduction of novel agents rendered ASCT an obsolete treatment for multiple myeloma? This month, James R. Berenson, MD, and Claudia Andreu-Vieyra, PhD, make the case against ASCT, while Sergio Giralt, MD, argues that the approach should be used more often.

More Treatment Is Not Always Better

James R. Berenson, MD, is the medical and scientific director of the Institute for Myeloma & Bone Cancer Research and the chief executive officer of Oncotherapeutics in West Hollywood, California.

Claudia Andreu-Vieyra, PhD, is a medical writer for Oncotherapeutics in West Hollywood, California.

Transplantation Remains Significantly Underused

Sergio Giralt, MD, is the chief of the Adult Bone Marrow Transplantation Service in the Division of Hematologic Oncology in the Department of Medicine at Memorial Sloan Kettering Cancer Center in New York, New York.

The use of autologous stem cell transplantation (ASCT) as first-line therapy for multiple myeloma (MM) has clearly led to improved survival. We have good data from a review of more than 20,000 patients in the United States and Canada who underwent ASCT for MM and were registered at the Center for International Blood and Marrow Transplant Research (CIBMTR). In both the 2000 to 2004 cohort and the 2005 to 2010 cohort of the CIBMTR study, ASCT was associated with a reduction in death. The survival rate 60 months after ASCT improved from 47% in 1995 to 1999 to 55% in 2000 to 2004 and to 57% in 2005 to 2010.1

Although ASCT is increasing in popularity in the United States as a treatment for MM, it remains significantly underused. What the researchers in the CIBMTR study found is that ASCT was used in just 1 out of 3 patients younger than 55 years, 1 out of 5 patients between the ages of 55 and 65 years, and 1 out of 10 patients older than 65 years.1

One unfortunate barrier to the adoption of ASCT is the fact that many clinicians confuse autologous transplantation, which is the safe procedure that we generally
More Treatment Is Not Always Better (cont)

take advantage of the plethora of choices that are presently available and will become available during their disease course. This means that administering the regimen associated with the highest proportion of complete responses (CRs) is not necessarily best for the patient in the long run. In fact, little difference exists in tumor burden between patients showing stable disease and those exhibiting CRs. Until recently, high-dose chemotherapy (HDT) followed by autologous stem cell transplantation (ASCT) was associated with the highest CR rates for MM patients, and this procedure has been the standard frontline treatment for younger MM patients with normal renal function. Three main arguments have been used in support of ASCT: (1) high CR rates; (2) improved progression-free survival (PFS) and, in some trials, overall survival (OS); and (3) the lack of a need for additional therapies following ASCT.

The higher CR rates resulting from ASCT compared with conventional therapy have been consistently associated with both a delay in time to progression and prolongation of PFS. It is important to recognize that CR is based on the absence of measurable paraprotein, which unfortunately does not translate into the absence of tumor cells in the vast majority of MM patients. Thus, patients with a CR may show progressive disease at a time when their paraprotein remains immeasurable, whereas patients with less than a CR will have a marker that can be measured as they progress. Thus, it is obvious that patients with a CR will show a longer PFS than patients who do not obtain a CR and continue to have a measurable protein marker.

Most importantly, the advantage of ASCT in terms of OS has proven to be inconsistently demonstrated in randomized trials, despite the consistent PFS advantage. This applies even to randomized trials completed prior to the advent of many new, more effective therapies. Furthermore, trials comparing early ASCT vs ASCT at the time of disease progression have shown no differences in OS. Notably, the recent introduction of proteasome inhibitors and IMiDs into induction regimens administered prior to ASCT has greatly improved response rates, especially CRs—even prior to these patients undergoing the HDT procedure. Even when patients underwent induction treatment with IMiDs, followed by early (within 12 months of diagnosis) or late (more than 12 months after diagnosis) ASCT, the timing of ASCT did not affect OS in a recently published retrospective study.

More recently, a phase 3 trial of 402 MM patients ages 65 years and younger evaluated PFS and OS for the combination of melphalan, prednisone, and lenalidomide (Revlimid, Celgene) (MPR) compared with high-dose melphalan followed by ASCT (MEL200-ASCT). After a median follow-up of 45 months, the results showed that MEL200-ASCT significantly prolonged PFS compared with MPR, whereas OS was similar between both arms. Interestingly, a previous study comparing MPR with melphalan and prednisone (MP) showed no OS advantage among MM patients who were not transplant candidates, suggesting that the ASCT procedure provided no OS advantage, even compared with conventional chemotherapy. An ongoing phase 3 trial (ClinicalTrials.gov identifier: NCT01208662) is currently evaluating whether HDT is still necessary for the management of MM in younger patients (<65 years) in the era of new anti-MM drugs. This study is exploring the lenalidomide/bortezomib/dexamethasone combination with or without ASCT, followed by maintenance therapy with lenalidomide.

Newer drug combinations may offer superior outcomes without high-dose therapy.

Regarding the need for additional therapies after ASCT (or lack thereof), both consolidation (short-term) and maintenance (long-term) therapies following ASCT have been used to improve outcomes for MM patients over the past several years. Before novel agents became available, the consolidation treatment consisted of a second, tandem ASCT. More recently, bortezomib, thalidomide, dexamethasone, and lenalidomide—either as single agents or in combination therapy—have been evaluated as consolidation therapy. The recent introduction of proteasome inhibitors and IMiDs into induction regimens administered prior to ASCT has greatly improved response rates, especially CRs—even prior to these patients undergoing the HDT procedure. Even when patients underwent induction treatment with IMiDs, followed by early (within 12 months of diagnosis) or late (more than 12 months after diagnosis) ASCT, the timing of ASCT did not affect OS in a recently published retrospective study.

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Newer drug combinations may offer superior outcomes without high-dose therapy.
time to progression and improved OS. This finding likely makes obsolete the argument that MM patients could have a treatment-free interval following ASCT.

In the past, HDT and newer induction regimens followed by ASCT were far better at achieving a CR than any other treatment regimen for MM patients. Times have changed, however, and recently the combination of carfilzomib, lenalidomide, and dexamethasone without ASCT for previously untreated MM patients demonstrated the highest CR rates and superior PFS. The studies mentioned earlier clearly show that no recent trials have demonstrated an OS advantage associated with ASCT, and this recent 3-drug combination trial suggests that newer drug combinations may offer superior outcomes without HDT.

As more treatment options become available, it is important to consider that the toxicity associated with HDT, especially when combined with aggressive multidrug induction regimens, may compromise the ability of MM patients to receive the ever evolving panoply of new therapeutic options that are continually becoming available to them. Using these multidrug combinations in induction therapy may have an additional disadvantage: being exposed to these newer antmyeloma agents may make obsolete the eligibility of patients for clinical trials that might be of significant benefit to them.

MM patients are living much longer than they once did. Therefore, finding the treatment that best fits their overall needs in the long run, as well as optimizing their quality of life during their disease course, is becoming increasingly important. In this case, more is not necessarily better, and transplants are all about “more”—although they are not more specific or better at targeting the myeloma tumor cells. Thus, this type of therapy is fraught with off-target negative effects on other organs, which need to be kept in optimal condition as patients face a future of multiple treatment regimens to treat this largely incurable disease.

As the medical community moves toward personalized medicine in other oncology areas, it is time to focus on and develop anti-MM therapies that are tailored to the patient’s disease, age, comorbidities, lifestyle, and work. Ultimately, therapies that only affect the myeloma tumor cells need to be made available. Advances in biology have led to the recent identification of targets on myeloma cells that can be exploited to allow the specific delivery of toxic therapy that eliminates only the tumor cell population. These approaches are now showing high efficacy in the laboratory. Not only are they efficacious in vitro, they are able to cure mice harboring human myeloma without any off-target negative effects. These therapies may be available for clinical testing in the near future and will provide MM patients with treatments that will finally eliminate the cancer cells permanently without compromising their other organs. Most importantly, this new chapter in the era of targeted therapies will allow patients to lead lives that are not limited by the untoward effects of anti-MM treatments.

References

use in MM, with allogeneic transplantation, which is riskier. Autologous transplantation is what allows us to give patients with MM high-dose therapy, specifically high-dose melphalan. High-dose melphalan is one of the most effective single agents in MM, with a complete response (CR) rate of between 20% and 30%.

Our goal in treating MM is to give our patients the longest lifespan with the best quality of life, using the minimal treatment necessary. Because we do not always measure both of these endpoints, CR has become a common surrogate endpoint. Until recently, the induction chemotherapy we were using—dexamethasone, vincristine, or alkylators—had produced a CR rate of just 5% to 10%. Adding high-dose melphalan and ASCT boosted the CR rate to 40%.

Today, we are more likely to use an induction chemotherapy regimen that includes an amide, a proteasome inhibitor, and corticosteroids, or an alkylator, a proteasome inhibitor, and corticosteroids. These regimens have a CR rate of approximately 20% to 25%. The combination of carfilzomib (Kyprolis, Onyx), pomalidomide (Pomalyst, Celgene), and dexamethasone, which is one of the most intense regimens that does not include ASCT, may be able to put an even higher proportion of patients into CR.

Given the changes in chemotherapy, I think it is time for us to readdress the role of high-dose therapy and ASCT in MM. Indeed, 3 important randomized trials are now being conducted. The first, an interim analysis of which was presented at the American Society of Hematology meeting in 2013, was a trial that randomly assigned newly diagnosed MM patients to low-dose melphalan, lenalidomide (Revlimid, Celgene), and prednisone or 2 cycles of high-dose melphalan with ASCT. Although there was no statistically significant difference in overall survival, there was a significant progression-free survival difference in favor of the high dose melphalan group.

The evidence is solid for ASCT with high-dose melphalan, and I think the burden of proof needs to be on those who think it should not be used. One important meta-analysis of 9 studies, comprising 2411 patients, found that high-dose therapy with ASCT led to a statistically significant improvement in progression-free survival but not overall survival compared with standard-dose chemotherapy. Although the studies in this meta-analysis were old, they clearly showed a benefit for high-dose melphalan. The next generation of studies is now being performed. I think that clinicians should offer ASCT to all their eligible MM patients younger than 80 years, unless the patient is participating in a clinical trial. Giving patients 4 to 6 cycles of induction therapy with lenalidomide, bortezomib (Velcade, Millennium Pharmaceuticals), and dexamethasone (RVD) or bortezomib, cyclophosphamide, and dexamethasone (CyBorD) in combination with high-dose melphalan and ASCT, followed by lenalidomide maintenance, is a highly effective treatment. We have good evidence from the Cancer and Leukemia Group B trial that lenalidomide maintenance treatment after ASCT increases progression-free survival from 42% to 63% at a median follow-up of 35 months. Now that we have improved maintenance therapy to use after ASCT, we can expect even more patients to achieve CR and stay in remission for a long time.

It is possible that transplant-free regimens will be able to match this rate. One ongoing study is the BMT CTN 1304/DFCI 10-106 trial, which is a phase 3 study that is comparing RVD with high-dose therapy plus peripheral stem cell transplantation in the initial management of MM in patients up to 65 years of age (ClinicalTrials.gov identifier: NCT01208662). We will have the results of this study in 3 years. In the meantime, I think that clinicians should be recommending ASCT for most patients outside of a clinical trial.

Several factors have contributed to making ASCT an increasingly good option for patients. First, the fact that we are now using peripheral blood stem cells means that people recover quickly from the procedure. Second, the fact that we have lenalidomide for maintenance therapy means that we can provide longer-lasting control of disease. Third, the fact that ASCT is often being done as an outpatient procedure means less disruption for the patient. Many patients are able to recover quickly enough to return to their home after 2 to 3 weeks, and go back to work after 3 months. Some centers are even starting to explore the possibility of ASCT in the home for home-bound patients.

A key part of successful ASCT is early referral to a transplantation center for stem cell collection. Even if patients ultimately decide to opt against ASCT as frontline treatment, it is important to collect the highest-
quality stem cells early and store them in case they are needed later. Luciano Costa and I recently published a set of recommendations that emphasized the importance of early referral to be able to collect high-quality stem cells.5

I always tell patients that ASCT is a choice, not a necessity. The risk of dying from ASCT in the United States is less than 1.5%. It's not zero, but it is a relatively safe procedure.

Some clinicians have argued that ASCT is no longer necessary because now we have newer, better drugs. The truth is that even though melphalan is old, we know that it works. Furthermore, melphalan is the most cost-effective way of getting a major response in MM. Instead of moving to discard melphalan, we should learn how to use high-dose melphalan in the context of the availability of new drugs.

A great deal of research is being conducted in the transplantation setting to make high-dose melphalan more effective and easier to tolerate. For example, one area of inquiry concerns reducing fatigue through the use of cytokines or other agents.

In summary, although it has been more than 20 years since high-dose therapy with ASCT demonstrated therapeutic potential for MM, we continue to debate its role and value. Despite this continued controversy, we know this agent is extremely active, with 30% of patients achieving a CR. We know that the procedure is relatively safe, with more than 95% of patients achieving disease-free survival. As frontline consolidation therapy followed by maintenance, it can be associated with long-term disease control in a substantial number of patients.

Only well-designed clinical trials both in the upfront and salvage setting will demonstrate the effectiveness of high-dose therapy compared with other, nontransplant options. Until that time, it is important that this therapeutic option be offered to all potentially eligible patients. An essential part of this is encouraging early referral to a transplant program, so stem cells can be harvested for either early consolidation or late salvage therapy.

References


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