

Autologous Hematopoietic Stem Cell Transplantation for Multiple Myeloma: Frequently Asked Questions

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When caring for patients with multiple myeloma, questions often arise about the role and timing of autologous hematopoietic stem cell transplantation. As a complement to the other articles in this supplement, as well as to ensure that readers are provided with the insight needed to feel comfortable speaking to patients and other practitioners about this topic, the authors address eight frequently asked questions about common decision points in the process of autologous hematopoietic stem cell transplantation as a treatment for patients with multiple myeloma.

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Who are the best candidates for transplantation?

Multiple myeloma is the leading indication for autologous hematopoietic stem cell transplantation (AHST) in North America, which has become the standard of care for patients aged 65 years and younger (Gertz, Ghobrial, & Luc-Harousseau, 2009; Giralt et al., 2009; Moreau, Avet-Loiseau, Harousseau, & Attal, 2011; Palumbo & Anderson, 2011; Palumbo, Attal, & Roussel, 2011; Pasquini & Wang, 2012). Several randomized clinical trials demonstrated a superior survival outcome for patients who underwent high-dose melphalan and AHST when compared to those who received standard-dose chemotherapeutic agents (Attal et al., 1996; Matsui, Borrello, & Mitsiades, 2012; Palumbo, Attal, et al., 2011). Although most of those trials were conducted before newer agents such as lenalidomide, bortezomib, and thalidomide were available, more recent comparative trials using lenalidomide-containing initial regimens, with or without AHST, continue to demonstrate superiority of survival. One study stated that progression-free survival (PFS) at two years is 73% with transplantation compared to 43% without transplantation (Palumbo, Cavallo, et al., 2011). With that in mind, AHST

should at least be considered for all patients with active multiple myeloma who have adequate organ function and performance status (Palumbo & Rajkumar, 2010).

AHST is not without risk and results in morbidity and mortality for 1%–2% of patients, usually from infection, bleeding, or organ toxicity (Hari & McCarthy, 2013). Patients with poor performance status are at a higher risk for these complications. Organ dysfunction, including compromised cardiac or liver function, as well as renal insufficiency, also predict a higher risk of toxicity and may lead to poor outcomes (Cavo et al., 2011; Palumbo & Anderson, 2011). Patients older than 70 years can undergo transplantation, but the incremental benefit of transplantation in this age group has not been demonstrated in randomized, prospective clinical trials. In addition, the standard dose of melphalan (200 mg/m²) has been shown to be of increased toxicity in patients older than 70 years with poor performance status and other comorbidities. A risk-adapted dosing of melphalan for patients older than aged 70 years (e.g., 140 mg/m²) and patients with renal insufficiency (100 mg/m²) has allowed patients to successfully undergo transplantation with acceptable toxicities (Gertz et al., 2009). Therefore, the use of AHST in these populations should be conducted cautiously and with risk-adapted dose modification of melphalan.

Patients with poor risk biology, defined by cytogenetic abnormalities such as t(4;14), del (17p), as well as high β_2 microglobulin, have shorter remission duration after AHST. Although this varies widely, median overall survival in the poor risk group can range from 18–36 months (Chang et al., 2004; Neben et al., 2010). This group of patients is the subject of clinical trials incorporating newer agents, including next-generation immunomodulatory medications and proteasome inhibitors that may improve overall results (Bladé, Rosiñol, Cibeira, Rovira, & Carreras, 2010; Palumbo & Rajkumar, 2010). Participation in clinical trials should be encouraged whenever possible.

What is the optimal timing for transplantation?

The role of initial therapy for patients with symptomatic myeloma is to stabilize the patient, improve any organ dysfunction, and obtain a tumor response prior to transplantation. Patients who attain deep remissions and reversal of organ dysfunction have the best success following AHST. Whether attempting to deepen the response by extending induction therapy is beneficial prior to stem cell transplantation is unclear. In fact, continued initial therapy for months after attaining a response may cause toxicity as well as decrease the stem cell yield, particularly if the initial therapy includes alkylating agents or prolonged use of immunomodulatory agents (Giralt et al., 2009). Although a complete remission is obviously favorable, treatment beyond six cycles of therapy in an attempt to achieve a deeper remission does not definitively improve outcome (Cavo et al., 2011).

Data comparing the benefit of induction therapy followed by high-dose melphalan and AHST to up-front chemotherapy alone as initial therapy for active myeloma demonstrate improvement in PFS, response rates, and overall survival (OS) (Attal et al., 1996; Child et al., 2003). High-dose chemotherapy and stem cell transplantation as part of first-line therapy after initial response has resulted in median survival of more than five years compared to response without AHST (Attal et al., 1996; Child et al., 2003). Patients undergoing transplantation as part of their initial line of therapy have experienced longer event-free survival and better quality of life than patients who undergo stem cell transplantation as a late therapy, but early transplantation has not been shown to improve overall survival (Cavo et al., 2011; Fermand et al., 1998; Palumbo & Anderson, 2011; Palumbo, Attal, et al., 2011). On the other hand, retrospective analyses of series of patients treated with AHST during their first line of therapy have reported similar outcomes as patients treated with transplantation as part of second-line therapy (Gertz et al., 2009; Palumbo, Attal, et al., 2011). The optimal timing for transplantation continues to be an area of investigation. An international, prospective comparison of transplantation as first-line therapy versus second-line therapy is underway to help clarify this issue (ClinicalTrials.gov, n.d.a.; Moreau et al., 2011).

Despite the success of high-dose melphalan and AHST, the regimen is not a curative treatment, and the majority of patients will relapse. Many strategies have been used to improve survival for patients with multiple myeloma who have undergone AHST, such as tandem transplantation, second transplanta-

tion, and using newer agents (e.g., lenalidomide, bortezomib, thalidomide) as consolidation therapy or maintenance therapy after stem cell transplantation.

What is the role of tandem transplantation?

Tandem autologous transplantation occurs when two autologous transplantations are performed within a period of no more than six months. For more than two decades, patients with multiple myeloma have successfully been treated with tandem stem cell transplantation using high-dose melphalan. One trial showed improved PFS and OS with tandem transplantation compared to single transplantation (Attal et al., 2003). That study suggests that patients who either progress after the first transplantation or are in complete remission are less likely to benefit from the second transplantation. Patients who achieve less than a very good partial response (VGPR) but are responding and have tolerated the first transplantation well may be the best candidates for a second transplantation (Bladé et al., 2010; Cavo et al., 2011; Moreau et al., 2011). A large national trial is underway to prospectively compare single AHST with tandem AHST, which should help clarify this issue (ClinicalTrials.gov, n.d.b.).

What is the role of salvage transplantation?

Mobilization techniques have improved and stem cells now can be stored for more than a decade. Salvage AHST has been used for patients who have relapsed after a prior stem cell transplantation, or who had stem cells harvested and did not initially proceed to stem cell transplantation. Response rates in the setting of relapsed and refractory myeloma are high, although the toxicity is increased (as high as 10% mortality versus 1%–2% mortality when AHST is conducted in the initial line of therapy) (Olin et al., 2009). Response durations also tend to be shorter (measured in months rather than years) with a second stem cell transplantation, or one conducted in the setting of refractory disease (Cook et al., 2011; Olin et al., 2009). Frequently, the remission induced by a stem cell transplantation acts as a bridge to another therapy for which the patient was not eligible because of rapid progression of disease or organ dysfunction. An intermediate dose of melphalan (100–140 mg/m²) usually is used in this setting, keeping in mind the patient's performance status and organ function and implementing the same risk-adapted approaches used for initial therapy.

What is the role of consolidation therapy after stem cell transplantation?

Despite the improvement in survival after AHST, a high likelihood of disease progression remains. Interest is increasing in the role of post-transplantation consolidation using lenalidomide, bortezomib, and alkylating agents as consolidation therapy. A number

of trials (Cavo et al., 2011; Hari & McCarthy, 2013) have demonstrated the feasibility of this approach, and regimens such as bortezomib, lenalidomide, and dexamethasone and bortezomib, thalidomide, and dexamethasone for two to four cycles following AHST and prior to initiation of maintenance therapy have been well tolerated with suggestion of improved duration of response. Preliminary results show increasing rates of complete remission following consolidation therapy. Once again, a number of clinical trials are prospectively analyzing the incorporation of these regimens after stem cell transplantation.

What is the role of maintenance therapy after autologous hematopoietic stem cell transplantation?

Although AHST is associated with improved remission rates and PFS, relapse is inevitable for almost all patients. The goal of maintenance therapy is to prolong the duration of remission, extend OS, maintain quality of life, and reduce toxicities (Matsui et al., 2012; Moreau et al., 2011). Maintenance therapy has been investigated since the 1990s, and a number of approaches have been used. Alpha interferon given subcutaneously initially showed benefit, but prospective randomized trials demonstrated increased toxicity without a clear survival advantage (Attal et al., 1996; Cunningham et al., 1998). Oral thalidomide also has been used in the maintenance setting, with several randomized trials demonstrating improved remission rates, PFS, and OS. However, the use of thalidomide in this setting is limited because of cumulative toxicities including neurotoxicity and the development of resistance with prolonged exposure (Cavo et al., 2011; Gertz et al., 2009). Pulse doses of corticosteroids (prednisone or dexamethasone) also have been used after stem cell transplantation, showing improved PFS and tolerability with intermittent administration (Berenson et al., 2002).

A number of prospective trials have assessed low-dose lenalidomide as a maintenance therapy after AHST. McCarthy et al. (2012) showed significant PFS benefit in patients who received low-dose lenalidomide (86%) versus those who did not (58%), in addition to an OS advantage at three years of 88% versus 80%, respectively. Attal et al. (2012) showed a PFS benefit for the lenalidomide maintenance group at four years of 43% compared to 22% for those who did not receive lenalidomide. In those trials, lenalidomide was given until either progression or toxicity precluded additional use. Maintenance lenalidomide was well tolerated with a low incidence of neurotoxicity. However, the risk of second cancers, including solid tumor and hematologic malignancies, increased (Attal et al., 2012; McCarthy et al., 2012). Second cancers have been observed in patients with multiple myeloma; however, the risk has been less than 5% in previous studies (McCarthy et al., 2012). Most recent analyses report that the incidence of second cancers increases to 8% for patients on lenalidomide (McCarthy et al., 2012). When compared to the risks of progressive myeloma, the consensus remains supportive of the use of lenalidomide as maintenance therapy. However, research is ongoing. Efforts are now underway to identify the mechanisms for secondary malignancies and to determine risk factors that might reduce the likelihood of carcinogenesis (Cavo et al., 2011).

Bortezomib as part of initial and maintenance therapy has been shown to improve outcomes when compared to a similar regimen containing thalidomide instead of bortezomib (PFS median survival = 13 months versus 30 months; median OS = 21 months versus 54 months, respectively) (Sonneveld et al., 2012). When given on a weekly or biweekly schedule, bortezomib is well tolerated, although neurotoxicity remains a potential side effect. The relative benefit of proteasome inhibitors to immunomodulatory agents as single-agent maintenance therapy as well as in combination continues to be an area of active investigation (Palumbo & Anderson, 2011; Sonneveld et al., 2012). The combination of thalidomide and bortezomib, for instance, has been shown to be well tolerated and may result in improved disease-free outcomes (Mateos et al., 2012).

Maintenance therapy prolongs duration of remission, particularly for those who have achieved less than a VGPR. The ultimate benefit of maintenance therapy for those who have achieved complete remission after transplantation remains to be determined. However, increasing knowledge suggests that continued exposure may be advantageous even for patients in complete remission by preventing proliferation of malignant plasma cells and by maintaining a hostile bone marrow microenvironment (Giralt, Landau, & Palumbo, 2012; Matsui et al., 2012; McCarthy et al., 2012). Additional evaluation may clarify the use of maintenance in the post-transplantation setting (ClinicalTrials.gov, n.d.b).

Is there a role for transplantation in the era of novel therapies?

Since 2000, the survival of patients with multiple myeloma has substantially improved. The median OS for patients with multiple myeloma in 1996 was three years; in 2012, patients had a median OS of eight years (McCarthy et al., 2012). That is a result of the incorporation of newer agents (e.g., thalidomide, lenalidomide, bortezomib) and the use of high-dose melphalan and AHST. Given that information, the timing of high-dose melphalan and stem cell transplantation should be considered. As noted earlier, despite the use of lenalidomide and dexamethasone in both groups of patients, the incorporation of high-dose therapy and AHST continues to improve the survival of patients compared to those who did not receive transplantation (Bladé et al., 2010). That finding may be explained by the heterogeneous nature of myeloma cells and the complementary nature of the use of high-dose alkylating agents, such as melphalan, to overcome the resistance mechanisms in cells that are otherwise resistant to immunomodulatory agents and bortezomib. In particular, melphalan may have a greater effect against the myeloma stem cell. Additional studies investigating high-dose melphalan and autologous transplantation in the era of newer agents are ongoing.

What needs to be considered when choosing a transplantation center?

Healthcare insurance coverage should be considered when choosing a transplantation center. The cost of transplantation

can be prohibitive and requires insurance approval. Patients without insurance will require assistance from resourceful social workers and financial counselors to successfully undergo transplantation. Insurance carriers frequently contract with a select group of “centers of excellence” or other transplantation networks that they direct their patients to for evaluation; these may or may not be geographically close to where the patient lives. If the third-party payer does not direct the patient to a particular transplantation center, the primary hematologist may refer the patient to a center with which he or she has had prior success. Geographic location and resources available within that community also are important factors in choice of centers. Fortunately, most regions of the country have one or more experienced centers within close proximity of the patient in need. Ultimately, patients and their primary oncologists need to feel comfortable with the treatment philosophy and care approach of their transplantation team. A listing of available transplantation centers by location, disease, and statistical review can be found at www.CIBMTR.org or www.HRSA.gov.

Summary

Since 1998, high-dose melphalan and AHSCT have been a standard of care for patients with multiple myeloma, particularly when administered early in the course of disease. The willingness of patients to participate in the randomized comparative trials has been essential to the development of successful treatment approaches. The current practice of combining an initial (or induction) course of chemotherapy to autologous stem cell harvest and one or two cycles of high-dose melphalan and AHSCT followed by maintenance therapy with lenalidomide or bortezomib has resulted in unprecedented survival for this disease. A number of questions concerning the optimal timing, best initial therapy, post-transplantation consolidation, and maintenance therapy still remain. Ongoing clinical trials of innovative approaches hold great promise that these questions will be answered soon. The ultimate result will be improved survival and quality of life for patients with multiple myeloma.

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