Review

Role of Hematopoietic Stem Cell Transplantation in Multiple Myeloma

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Abstract

High-dose therapy followed by autologous stem cell transplantation (ASCT) has been the standard frontline consolidative therapy for patients with newly diagnosed multiple myeloma (MM) for > 2 decades. This approach has resulted in higher complete response (CR) rates and increased event-free survival and overall survival (OS) compared with conventional chemotherapy. The emergence of novel agent-based therapy combined with ASCT has revolutionized MM therapy by improving the CR rates and OS, raising questions concerning the role of hematopoietic stem cell transplantation in this setting.

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Introduction

During the past 30 years, patients with multiple myeloma (MM) have experienced advancements in therapy. Since the early 1990s, high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) have remained the standard treatment for patients < 65 years old with newly diagnosed MM.[1] Notwithstanding recent improvements in therapy, MM remains incurable, with an annual mortality rate of 3.4/100,000.[2] Treatment of MM remains difficult, and, regrettably, most patients ultimately develop drug resistance and relapse with refractory disease.[3] Improving survival remains the primary goal of treatment. Uncontrolled studies have shown that, for patients responding to the initial induction chemotherapy, ASCT is a safe (< 5% toxic deaths) and effective consolidation therapy. Most importantly, some of these studies have suggested that complete response (CR) levels of 30% to 50% can be achieved, leading to prolonged remission and overall survival (OS).[4]

During the past decade, novel therapeutic agents, such as thalidomide, bortezomib, lenalidomide, and, more recently, carfilzomib and pomalidomide, have expanded the therapeutic options for patients with MM. Combinations of these agents have improved the overall response rate (ORR), CR, progression-free survival (PFS), and OS in patients considered not suitable candidates for transplantation, raising questions regarding the role of HDT and ASCT in the treatment of patients with MM.[5] However, the use of HDT and ASCT combined with these novel agents for transplant-eligible patients has resulted in substantial and profound improvements in the median survival time, from 3 years in the 1960s to mid-1990s to approximately 5 years from the late 1990s to 2008.[6] Ongoing clinical trials are now addressing this controversial issue of whether HDT followed by ASCT should remain the standard therapy in the era of novel agents.[7,8]

Evolution of HDT for MM

MM was first described in the 19th century as "mollities ossium" accompanied by Bence Jones protein in the urine. The prognosis was fatal, and the OS was 7 to 10 months owing to lack of successful treatment at that time. By the early 1960s, the first effective treatment of MM was established using alkylating agent-based therapy, which improved the OS to 36 months from the diagnosis for the approximately 50% of patients who responded to therapy. However, it was associated with an 18% mortality rate in those without a response.[9] During the past 15 years, many advances in MM therapy have further improved the OS, and HDT plus ASCT has established itself as an accepted therapy for patients with MM. This approach has been supported by the results from a number of randomized trials, showing an advantage compared with conventional chemotherapy (CC) regarding the response rate and event-free survival (EFS). Some trials have also shown an advantage for OS.[10,11] The preeminence of HDT/ASCT equated with CC was largely attributed to the superior quality of response, with an increased CR or very good partial response (VGPR). Generally with HDT/ASCT, the CR plus VGPR rates have been 40% to 50%, with a median PFS of 24 to 36 months and median OS of 5 to 6 years.[10-12]

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To further increase the cytotoxic dose intensity, the value of an even more assertive approach, with tandem ASCT, was explored in several studies. After demonstration that such a procedure was feasible and effective, randomized trials were conducted to investigate the question of single versus tandem ASCT as upfront therapy for MM. The results of these trials were contradictory, most likely because of the heterogeneity across the different trials with respect to their methodologic characteristics. To date, 2 published randomized controlled trials have shown tandem ASCT improved the CR and PFS rates compared with single ASCT; however, improvement in OS was not consistently shown.[13-15] Furthermore, only patients who had not had at least a VGPR after the first ASCT appeared to benefit from the second ASCT.[14,15] A first systematic review related to this topic was conducted and published in 2009. It included an analysis of 5 studies and showed no PFS or OS benefit in the tandem ASCT arm.[16] However, the method of this systematic review was highly criticized for errors, and critics dismissed the validity of their conclusions.[17-19] A second systematic review was published by Naumann-Winter et al[20] in 2012. They concluded that the quality of studies related to this topic was poor owing to weak sample size calculations (eg, lack of consideration of a potentially steep decrease in compliance with the second ASCT).[20] Furthermore, Naumann-Winter et al.[20] cautioned readers that no evidence has shown that the published studies of single versus tandem ASCT are still relevant in the current treatment decision-making context. This is largely because these published studies of single versus tandem ASCT were mostly conducted before the era of novel agents.

In summary, it is unclear whether tandem ASCT is better than single ASCT. In particular, patients with high-risk cytogenetics features [eg, patients with del 17p, t(4;14), t(14;16), or t(14;20) by fluorescence in situ hybridization (FISH) study or del 13 by conventional cytogenetics] did not show improvement in OS, despite the use of a more intensive approach such as tandem HDT/ASCT. With the recent integration of novel agents into the transplantation paradigm, the value of single versus tandem transplants continues to be uncertain, and prospective randomized clinical trials are warranted.[20] Two such studies are currently in progress in Europe and the United States.[21,22]

Novel Agents as First-Line Therapy in Transplant Eligible Patients

Before the development of novel therapies, the prospect of attaining a CR for transplant-eligible patients with MM who had predominately been treated with conventional induction regimens was < 5%.[12] The aim of induction therapy before ASCT has been (1) reduction of the tumor burden and increased post-ASCT CR or VGPR rate; (2) reversal of organ damage; and (3) diminution of plasma cell bone marrow infiltration (in vivo purging).[11,13]

Before the introduction of the proteasome inhibitor (PI) bortezomib and immunomodulatory agents (IMiDs) thalidomide and lenalidomide, the standard induction was dexamethasone-based, either as a single agent or combined with vincristine and doxorubicin (VAD). Although high-dose dexamethasone provoked adverse events, these regimens were chosen instead of melphalan- or prednisone-based regimens because of the better quality of stem cell collection. Nonetheless, the CR and VGPR rates after 3 to 4 cycles remained low (CR < 10% and CR plus VGPR < 20%).[10,11] In the current era of novel agents, management will differ, contingent on whether the patient is ASCT eligible. Age > 65 years, poor performance status (Eastern Cooperative Oncology Group performance status 3-4), and organ dysfunction (significant liver disease, renal disease with creatinine > 220 μmol/L unless receiving stable chronic dialysis, and/or New York Heart Association class III-IV) renders patients inappropriate for such intensive therapy.[13]

A meta-analysis of 9 randomized trials established a PFS advantage with upfront ASCT compared with CC combinations. Three randomized studies revealed that OS was comparable whether ASCT was performed early or as salvage therapy at relapse. Remarkably, in 1 trial, early ASCT improved the median EFS (39 vs. 13 months), along with the average period without symptoms (27.8 vs. 22.3 months) compared with late ASCT, but OS survival was unchanged (64.6 vs. 64 months). The early approach also correlated with a lower relapse rate, decreased treatment-related toxicities, and termination. An additional trial identified no significant PFS improvement with early ASCT (42 vs. 33 months; $P = .57$) and proposed that the largest benefit from early ASCT was among patients with disease refractory to induction therapy.[21]

The novel agents, thalidomide, bortezomib, and lenalidomide, have been effectively intermixed with one another and/or with cytotoxic drugs to form various doublet, triplet, and quadruplet combinations. These have been extensively studied as induction therapy before ASCT. All trials evaluating combinations of dexamethasone and thalidomide or bortezomib compared with high-dose dexamethasone alone or VAD as induction regimens have shown a superiority of the novel agents in terms of an increased ORR, including CR, emphasizing that VAD no longer has a role as standard induction therapy before HDT and ASCT.[12,22]

With thalidomide-dexamethasone (TD), the postinduction ORR was superior to that with dexamethasone alone or VAD. However, the postinduction CR and the post-HDT plus ASCT CR plus VGPR rates were not significantly increased. In contrast, with bortezomib-dexamethasone (VD), the CR plus VGPR rate improved significantly compared with that after VAD, both before and after HDT plus ASCT. One randomized study has investigated the response rate after 4 cycles of lenalidomide-dexamethasone as induction therapy. The CR plus VGPR rate improved with lenalidomide plus high-dose dexamethasone compared with low-dose dexamethasone. Lenalidomide-dexamethasone has yet to be compared with other induction regimens in the setting of HDT plus ASCT.[11]

The inclusion of cytotoxic drugs such as doxorubicin or cyclophosphamide with either thalidomide (TAD [thalidomide, doxorubicin, dexamethasone], CTD [cyclophosphamide, thalidomide, dexamethasone]) or bortezomib (PAD [bortezomib, doxorubicin, dexamethasone], CyBorD [bortezomib, cyclophosphamide, dexamethasone]) improved the response rates. The TAD regimen extended PFS compared with VAD (34 vs. 22 months; $P < .001$), and the PFS generated by CTD was comparable to that with cyclophosphamide-VAD (median, 27 vs. 25 months; $P = .59$). The CyBorD regimen led to 70% CR/near CR (nCR) rates after ASCT. The grouping of PAD significantly enhanced PFS compared with VAD (35 vs. 28 months; $P = .002$). The combination of bortezomib and IMiDs has resulted in similar outcomes. BTD