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Reviews

Augmenting Autologous Stem Cell Transplantation to Improve Outcomes in Myeloma

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A B S T R A C T

Consolidation with high-dose chemotherapy and autologous stem cell transplantation (ASCT) is the standard of care for transplantation-eligible patients with multiple myeloma, based on randomized trials showing improved progression-free survival with autologous transplantation after combination chemotherapy induction. These trials were performed before novel agents were introduced; subsequently, combinations of immunomodulatory drugs and proteasome inhibitors as induction therapy have significantly improved rates and depth of response. Ongoing randomized trials are testing whether conventional autologous transplantation continues to improve responses after novel agent induction. Although these results are awaited, it is important to review strategies for improving outcomes after ASCT. Conditioning before ASCT with higher doses of melphalan and combinations of melphalan with other agents, including radiopharmaceuticals, has been explored. Tandem ASCT, consolidation, and maintenance therapy after ASCT have been investigated in phase III trials. Experimental cellular therapies using ex vivo–primed dendritic cells, ex vivo–expanded autologous lymphocytes, Killer Immunoglobulin Receptor (KIR)-mismatched allogeneic natural killer cells, and genetically modified T cells to augment ASCT are also in phase I trials. This review summarizes these strategies and highlights the importance of exploring strategies to augment ASCT, even in the era of novel agent induction.

INTRODUCTION

Myeloma represents just over 1% of all cancers and despite a recent increase in available therapeutics, the disease remains incurable with an estimated 5-year survival just over 50% [1]. Randomized controlled trial (RCT) evidence from France and the United Kingdom demonstrated improved disease response and overall survival (OS) after autologous hematopoietic stem cell transplantation (ASCT) compared with after conventional chemotherapy [2,3]. However, subsequent trials from France, the United States, and Spain did not show an OS benefit, although Fermand et al. [4] did show an improvement in progression-free survival (PFS) [4-6]. The differences in outcomes between groups may be accounted for by prolonged use of conventional chemotherapy in the study by Fermand et al. and a high rate of ASCT salvage therapy at relapse in the study by Barlogie et al. [6]. A Dutch trial demonstrated that after treatment with intermediate-dose melphalan, further treatment with ASCT did not improve outcomes [7]. These trials support the use of high-dose alkylating agents in myeloma treatment. For patients who are fit for high-dose therapy (approximately one-third of newly diagnosed patients), treatment with chemotherapy conditioning followed by ASCT has been the standard of care, and the standard conditioning regimen has been a single dose of intravenous melphalan at 200 mg/m^2 [8]. There has been much interest in augmenting conditioning but no single regimen has been shown to improve outcomes in a randomized trial. Adjunctive strategies have also been explored: second tandem ASCT; consolidation and maintenance chemotherapy; attempts to augment immune responses after transplantation; and new drugs, particularly monoclonal antibodies. This review will evaluate the strategies employed and make recommendations for further research in this area.

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METHODS

We searched Pubmed using the terms myeloma, autograft, ASCT, autologous, transplant, graft, transplantation, conditioning, preparative regimen, treatment, RCT, randomized, trial, and induction in various permutations, yielding 1393 results and abstracts from the American Society of Haematology and American Society of Clinical Oncology annual meetings. Reference lists from these search results were used to identify other relevant publications. In the tables, overall response rate (ORR) is the proportion of patients achieving a partial response (>50% reduction in paraprotein) or better.

NOVEL AGENT INDUCTION

Induction for transplantation-eligible patients with immunomodulatory drugs (IMiD) (thalidomide and lenalidomide) and proteasome inhibitors (bortezomib) has improved response rates before ASCT. The HOVON50 trial demonstrated that substituting thalidomide for vincristine in the vincristine, doxorubicin, and dexamethasone (VAD) regimen could increase pre-ASCT ORR from 54% to 72% [9]. The benefit conferred by thalidomide combinations in induction was confirmed by the Myeloma IX and Total Therapy 2 trials [10,11]. The Intergroupe Francophone Myélome (IFM) 2005-01 trial demonstrated that bortezomib and dexamethasone was also superior to VAD, increasing the pre-ASCT response rate to 79% from 63% [12], and a similar improvement with bortezomib-based induction was observed in the HOVON65/GMMGHD4 trial [13]. Cavo et al. tested the addition of bortezomib to thalidomide plus dexamethasone (VTD), and this combination of both IMiD and proteasome inhibitor significantly improved both pre-ASCT ORR (93% versus 79%) and PFS [14]. This combination, VTD, is also superior to bortezomib, cyclophosphamide, and dexamethasone, producing pre-ASCT ORR of 92% versus 83% in a phase III trial [15]. Combining lenalidomide with bortezomib plus dexamethasone (VRD) produced an ORR of 94% in a phase II IFM study [16]. An ongoing phase II study of carfilzomib, lenalidomide, and dexamethasone for both induction and maintenance obtained an ORR pre-ASCT of 98% and demonstrated no unexpected toxicity [17].

The improvement in responses seen with newer induction programs has prompted further trials after induction comparing upfront ASCT with a nontransplantation option of novel agent consolidation followed by maintenance. Recently published phase III trials comparing ASCT with lenalidomide-containing regimens found ASCT confers superior PFS, although at a median follow up of 52 months, no differences in OS were observed [18,19]. An ongoing French/American RCT (the IFM/DFCI 2009 study) compares ASCT plus 2 cycles of VRD with 5 cycles of VRD alone, and results from the French cohort show superior complete response (CR) rate (58% versus 46%) and 3-year PFS (61% versus 48%) in the ASCT arm [20]. EMN02/HO95 is a European 2×2 factorial RCT, currently recruiting patients to compare ASCT versus bortezomib, melphalan and prednisolone (VMP) intensification and then consolidation with VRD versus no consolidation [21]. The possible merits of a delayed transplantation strategy are being evaluated in the PADIMAC phase II study for patients achieving very good partial response (VGPR) or CR after bortezomib, doxorubicin, and dexamethasone: up to 20% of patients had negative minimal residual disease (MRD) after induction, and survival outcomes are awaited [22].

CONDITIONING FOR ASCT

High-dose melphalan 200 mg/m^2 (mel200) delivered as a single dose for conditioning has been shown in a randomized trial to be less toxic and at least as effective as melphalan 140 mg/m^2 (mel140) plus 8 Gy total body irradiation (TBI) [8], and mel200 has since remained the gold standard for single ASCT in patients with normal renal function. Escalating the dose of melphalan above 200 mg/m^2 is prohibitively toxic to the gastrointestinal tract. Minimizing oral mucositis with protective agents amifostine [23] and palifermin, a keratinocyte growth factor, may facilitate dose increases to 280 mg/m^2 for a proportion of patients [24]. However, wide variability in melphalan exposure due to pharmacokinetic differences has been reported. In a pharmacokinetic study of high-dose melphalan in 100 patients, higher mucositis rates and improved disease response were seen in patients with higher exposure to melphalan, as measured by increased area under the curve of both total and unbound melphalan [25].

Melphalan and Chemotherapeutic Agent Combinations

A number of chemotherapeutic agents and combinations with mel200 have been tested in clinical studies, but the majority of these studies enrolled fewer than 100 patients and were nonrandomized studies, so it is difficult to draw significant conclusions (Table 1).

Regarding alkylating agents in combination with melphalan, oral busulfan is demonstrably too toxic, as 8% of patients in a Spanish study developed veno-occlusive disease, with a case fatality rate of 25% [26]. The intravenous busulfan formulation introduced in 2003 reduces hepatic exposure via the portal circulation, and a nonrandomized study (n = 153) comparing mel140 plus busulfan 9.6 mg/kg i.v. with mel200 suggested a small benefit in terms of PFS but increased treatment-related mortality, with neither difference reaching statistical significance [27]. Adding cyclophosphamide 120 mg/kg to mel200 worsens outcomes [28], and further addition of idarubicin progressively increases treatment-related mortality to 20% [29]. An RCT of cyclophosphamide, oral busulfan, and total marrow irradiation versus 2 consecutive ASCT with mel200 found the chemoradiotherapy regimen to be more toxic with no significant improvement in efficacy [30]. Reports from MD Anderson Cancer Centre using mel140 plus topotecan and cyclophosphamide in combination show outcomes comparable to mel200 but a controlled comparison is required [31,32]. The addition of carmustine to mel200 was found to be safe in single-arm studies, with comparable PFS and OS to previously published mel200 studies [33,34]. More recently, bendamustine, which has shown single agent activity in relapsed myeloma, was combined with mel200 at escalated doses reaching 225 mg/m^2 with only 1 dose-limiting toxicity in the first 100 days after transplantation [35].

Melflufen is a dipeptide prodrug of melphalan, which by virtue of increased intracellular hydrolysis is concentrated in myeloma cells. Melflufen induces apoptosis in melphalan-resistant cells and is highly effective in mouse models [36]. A phase I/II trial of melflufen and dexamethasone in relapsed-refractory myeloma is ongoing, but initial results are encouraging with an ORR of 60% [37]. Based on these encouraging results, melflufen as a conditioning regimen before ASCT should be explored in future trials.

Topoisomerase inhibitors (doxorubicin, idarubicin, mitoxantrone, topotecan) have been tested in combination with melphalan as conditioning, although in vitro data on the combination are limited. The addition of cyclophosphamide and idarubicin to mel200 was shown in an RCT to markedly increase treatment-related mortality [29], but adding cyclophosphamide and topotecan to mel140 produced promising outcomes in an uncontrolled series [32]. Two small phase II studies of mitoxantrone combined with