Hematological Oncology
Hematol Oncol 2013; **31** (Suppl. 1): 42–46
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hon.2066

Supplement Article

VI. Autologous stem cell transplantation and maintenance therapy

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Keywords: **multiple myeloma; autologous stem cell transplantation; consolidation; maintenance; novel agents**

Introduction

High-dose therapy (HDT) with autologous stem cell transplantation (ASCT) for multiple myeloma (MM) was developed in the 1980s and has been considered the standard frontline treatment for younger patients with normal renal function since the mid-1990s [1,2]. The recent introduction of the novel agents, thalidomide, bortezomib and lenalidomide, is now changing the transplantation scenario in several ways. Indeed, these agents are being incorporated into the pretransplantation setting as part of induction regimens with the objective of increasing the response rate prior to ASCT, as well as following the transplantation as consolidation and maintenance treatments. Consolidation is aimed at increasing the quantity and the depth of the response achieved with high-dose melphalan, whereas maintenance therapy has the goal of prolonging duration of the first response and the delaying relapse. The goals of applying treatments in the post-ASCT setting is the extension of progression-free survival (PFS) and hopefully, overall survival (OS).

Novel agents incorporated into induction treatments prior to autologous stem cell transplantation

Until recently, combination vincristine, doxorubicin and dexamethasone (VAD) was the induction regimen most widely used prior to ASCT [1,2].

Thalidomide was the first novel agent to be compared with VAD either in combination with dexamethasone (TD) or with doxorubicin plus dexamethasone (TAD). Overall, the benefit of TD or TAD compared with VAD remained modest [1].

Bortezomib, the second novel agent to become available, was investigated in combination with dexamethasone in a large trial by the Intergroupe Francophone du Myélome (IFM 2005–01) and prospectively compared with VAD [3]. Post-induction complete remission CR or near-CR (nCR; 15% versus 6%), with at least very good partial response (VGPR) (38% versus 15%), and overall response rates (79% versus 63%) were significantly higher with bortezomib plus dexamethasone (VD) versus VAD. These superior response rates translated into better response rates after HDT (CR/nCR: 35% versus 18%; at least VGPR: 54% versus 37%). This improvement also had an impact on the outcome of the disease (median PFS 36 versus 30 months with VD versus VAD, respectively). Survival was not superior in the VD arms of the study, possibly due to effective salvage regimens at the time of relapse.

The addition of a third agent to the VD regimen, such as thalidomide (VTD), doxorubicin (DVD or PAD), lenalidomide (RVD) or cyclophosphamide (CVD), has been tested in several small phase II studies with improved outcomes showing response rates of around 90% and CR rates up to 24% [1,2].

Three prospective studies have already shown that VTD is superior to TD or VD. An Italian group prospectively compared TD with VTD prior to tandem ASCT [4]. They found that VTD resulted in higher CR/nCR rates compared with TD (31% versus 11%), which translated into better 3-year PFS rates after HDT (68% versus 56%). A Spanish group also compared TD with VTD versus a more complex chemotherapy regimen including bortezomib prior to ASCT [5]. They confirmed that, compared with TD, VTD was associated with a higher CR rate before ASCT (35% versus 14%) and after ASCT (46% versus 24%). In the IFM 2007–02 trial, 4 cycles of VD induction regimen were prospectively compared with 4 cycles of VTD [6]. VTD was again found to result in superior response rates (VGPR or better) both before ASCT (49% versus 36%) and after ASCT (74% versus 58%). The results of a phase III randomized prospective trial comparing VAD with PAD as induction prior to HDT have also been reported [7]. This study confirmed the

superiority of the bortezomib-based three-drug induction regimen over VAD; OS was also superior in the bortezomib arm of the trial.

On the basis of the available data from phase II and III studies as described previously, three-drug combination regimens are considered the standard of care for use as induction therapy prior to ASCT.

Novel agents incorporated into consolidation treatments following autologous stem cell transplantation

Prior to the availability of novel agents, the main approach to consolidating a response achieved following the initial ASCT procedure was the use of a second ASCT, in a tandem fashion [1,2]. Currently, novel agents are being assessed as consolidation treatment following ASCT to further improve the quantity and quality of the responses.

The first report involving novel agents in this setting was provided by an Italian group. Ladetto recruited 39 patients who had achieved at least a VGPR after ASCT [8]. These patients were treated with four courses of VTD. Immunofixation CRs increased from 15% after ASCT to 49% after VTD. Molecular remissions (MRs), assessed by PCR analysis, were observed in 3% of patients after ASCT and in 18% after VTD. Treatment with VTD was associated with additional reduction in disease burden (median estimated depletion of tumour burden as evaluated by PCR: four logarithms. Patients with a tumour load lower than the median value were found to have a superior outcome, compared with those who had tumour loads above the median value following VTD treatment: the PFS at 42 months for patients with a low tumour load was 100% versus 57% for patients with a higher tumour load after VTD. This study was the first to document MR in a proportion of MM patients treated with ASCT followed by a novel agent-based consolidation therapy.

Results of another prospective randomized Italian trial of TD or VTD during induction and as consolidation therapy after a tandem ASCT procedure confirmed these findings [9]. Two cycles of consolidation therapy were started 3 months after the second transplantation procedure and comprised either TD or VTD. In the TD arm, consolidation improved the CR rate from 40% to 47%. In the VTD arm, the CR rate was increased from 49% to 61%. Samples were available from a subgroup of patients for PCR analysis, and this demonstrated that patients who received VTD consolidation had a greater reduction in residual tumour burden compared with TD (5 log versus 1 log reduction, respectively). This partly explains the PFS benefit observed for the VTD arm of the trial.

Another three-drug combination, comprising RVD, has been examined as consolidation treatment following ASCT in a pilot study conducted by the IFM (IFM 2008) [10]. Two cycles, administered after high-dose melphalan to 31 patients, were found to increase the CR plus stringent CR rate from 35% after HDT to 52% after consolidation.

Lenalidomide and bortezomib have also been investigated as single-agent consolidation treatments. In the IFM 2005–02 study, 2 cycles of lenalidomide (25 mg/day on days 1–21 of each 28-day cycle) were administered and then 614 patients were randomized to lenalidomide or placebo maintenance [11]. Following lenalidomide consolidation, the rate of VGPR or better increased significantly from 58% to 69%.

Single-agent bortezomib as consolidation treatment following ASCT was investigated in a phase III trial conducted by the Nordic Myeloma Group [12]. Patients were randomized post-ASCT to receive no treatment or bortezomib, for a total of 20 injections over 21 weeks. The proportions of patients achieving at least a VGPR were 70% in the bortezomib group versus 58% in the control group. Importantly, this improvement in response translated to a better outcome with a 7-month gain in PFS following ASCT (median 27 versus 20 months).

Overall, several studies are now supporting the use of novel agent-based consolidation therapy following ASCT. Nevertheless, the optimal consolidation treatment remains to be determined and a number of important trials examining this question are ongoing. In one key trial in the USA, the BMT CTN 0702 study, patients will be randomized after a single ASCT step to either no consolidation, 4 cycles of RVD, or a second ASCT procedure. Another important prospective trial has been designed to assess the RVD regimen with or without ASCT (IFM/DFCI2009 trial). This trial will examine the impact of 2 cycles of RVD given as consolidation after ASCT. The effect of 2 cycles of RVD versus no consolidation will also be examined in the prospective European EMN02 study.

Novel agents incorporated into maintenance strategies

In most countries, thalidomide was the first novel agent to become available. This oral drug was soon examined post-ASCT in the maintenance setting, with the objective of prolonging the duration of response. Six randomized phase III studies have since been published.

The Arkansas group performed a large randomized trial to assess the impact of thalidomide within a complex protocol consisting of induction treatment, double ASCT, consolidation therapy and α-interferon plus dexamethasone maintenance (Total Therapy 2) [13]. In this trial, thalidomide was administered from the outset until disease progression or undue toxicity. Thalidomide therapy was associated with superior response rate (62% versus 43%), 5-year event-free survival (EFS) (56% versus 44%) compared with the control arm and after a follow-up of

DOI: 10.1002/hon

72 months, a trend of increased 5-year OS with thalidomide emerged (68% versus 65%).

A similar phase III trial, the HOVON-50 study, was designed to evaluate the effect of thalidomide during induction treatment and as maintenance in transplantation-eligible patients [14]. A total of 556 patients were randomly assigned to VAD or TAD induction, followed by high-dose melphalan, 200 mg/m^2, and ASCT. This was followed by maintenance therapy with α-interferon (VAD patients) or thalidomide 50 mg/daily (TAD patients). Thalidomide therapy significantly improved the overall response rate and the median EFS (34 versus 22 months), but median OS did not differ significantly between the two treatment groups.

In the IFM99-02 trial, 597 patients were randomly assigned to receive no further treatment (Arm A), pamidronate alone (Arm B) or thalidomide plus pamidronate (Arm C) after tandem ASCT [15]. A CR or VGPR was achieved in 55% of patients in Arm A, 57% in Arm B and 67% in Arm C ($p = 0.03$). The 3-year post-randomization probability of EFS was 36% in Arm A, 37% in Arm B and 52% in Arm C ($p < 0.009$). The 4-year post-diagnosis probability of survival was 77% in Arm A, 74% in Arm B and 87% in Arm C ($p < 0.04$); recently updated results did not confirm the survival advantage of the thalidomide-containing arm [16]. In the Australian trial, 269 patients were randomized post-ASCT to receive prednisone maintenance therapy indefinitely and 114 to receive prednisolone treatment with the addition of 12 months of thalidomide consolidation therapy [17]. After a median follow-up of 3 years, the post-randomization 3-year PFS rates were 42% and 23% and the OS rates were 86% and 75% ($p = 0.004$) in the thalidomide and control groups, respectively.

The Medical Research Council study in the UK also confirmed that low-dose thalidomide maintenance (50 mg/day) significantly prolongs PFS compared with no maintenance therapy (median 23 versus 15 months), although no significant difference in OS was observed [18]. There was evidence of a late OS benefit in the subgroup of patients with favourable interphase FISH characteristics. In contrast, patients with adverse cytogenetics receiving thalidomide showed no PFS benefit (9 versus 12 months) and significantly worse OS.

Finally, the recent Canadian NCIC CTG MY.10 trial compared prospectively thalidomide–prednisone as maintenance therapy with observation following ASCT, and confirmed the improvement in PFS in the thalidomide arm, without any survival benefit [19].

Taken together, six separate phase III studies have shown a significant benefit for thalidomide in terms of response and PFS, whereas OS was improved in two of these trials. The safety profile of thalidomide may hinder its use as long-term maintenance therapy. Notably, peripheral neuropathy (PN) observed with thalidomide is cumulative and related to treatment duration. The incidence of peripheral neuropathy was high across all trials, and was the main cause of discontinuation of maintenance therapy. In the Canadian study, patients allocated to thalidomide–prednisone reported worse quality of life with respect to cognitive function, dyspnea, constipation, thirst, leg swelling, numbness, dry mouth and balance problems. The possible emergence of tumour-resistant clones in patients with prolonged exposure to thalidomide has also led to concerns about its lack of efficacy in patients with adverse cytogenetic abnormalities.

Lenalidomide is currently considered the best candidate for use as maintenance therapy. Results from two randomized trials evaluating lenalidomide maintenance following ASCT have recently been published.

In the IFM 2005–02 study, 614 patients received lenalidomide consolidation treatment after ASCT and were then randomized to receive either placebo (Arm A) or lenalidomide maintenance (10–15 mg/day until relapse; Arm B) [11]. After a median follow-up of 30 months, patients who received lenalidomide maintenance had improved median PFS by 18 months (median 23 months in Arm A versus 41 months in Arm B). A benefit in terms of OS has not yet been demonstrated. Second primary malignancies (SPMs) were observed in 26 patients treated with lenalidomide and 11 treated with placebo; the incidence of SPMs was 3.1 per 100 patient-years with lenalidomide and 1.2 per 100 patient-years with placebo.

The Cancer and Leukemia Group B reported the results of a similar phase III randomized trial of lenalidomide or placebo following HDT and ASCT (The Cancer and Leukemia Group B 100104 study) [20]. Patients ($n = 460$) aged <70 years with nonprogressive MM were randomized post-ASCT to receive placebo ($n = 229$) or lenalidomide 10 mg/day ($n = 231$) until progression. The study was stopped prematurely because of the significant superiority observed with lenalidomide maintenance, which resulted in a 63% reduction in the risk of progression compared with placebo. The median time-to-progression was 46 months for the lenalidomide arm versus 27 months for the placebo arm at a median follow-up of 34 months. Interestingly, despite a crossover of patients with disease progression from the placebo arm to the lenalidomide arm, an improvement in OS was observed favouring the lenalidomide arm (3-year OS rate: 88% versus 80%; $p = 0.03$). Of the 231 patients treated with lenalidomide, 18 developed SPMs (7.8%), whereas 6 of the 229 patients (2.6%) treated with placebo developed SPMs.

The benefits observed with lenalidomide maintenance therapy in terms of delaying disease progression and prolonging survival have to be balanced with an increased incidence of SPMs. This finding highlights the importance of defining the optimal duration of therapy, elucidating the underlying mechanisms, and identifying risk factors for this complication.

Bortezomib has also been investigated as maintenance treatment after HDT in a large phase III trial (HOVON-

DOI: 10.1002/hon

65/GMMG-HD4) comparing VAD with PAD prior to ASCT, and as maintenance including thalidomide (50 mg/day) on the VAD arm, or bortezomib (1.3 mg/m^2 twice a month) on the PAD arm, for 2 years [7]. Overall results favour the PAD plus HDT-ASCT-bortezomib maintenance arm in terms of response, PFS (median 28 versus 35 months) and OS (5-year: 55% versus 61%). This phase III study was the first to demonstrate a survival advantage with the use of a novel agent-containing treatment. In the bortezomib arm, maintenance was discontinued because of toxicity in 9% of cases (versus 31% in the thalidomide arm), progression in 29% (versus 31%) or other causes in 9% (versus 2%). Maintenance was continued for the entire 2-year period in 47% of the patients in the bortezomib arm compared with 27% of patients in the thalidomide maintenance arm.

Summary

Recent studies examining novel agents as induction treatment prior to ASCT have shown that three-drug combinations are the standard of care. Consolidation treatments following ASCT have clearly shown improvements in the depth of response, with the achievement of molecular CRs. However, the optimal consolidation therapy, if any, is still to be defined, as well as the duration of such treatment. The results of ongoing studies are eagerly awaited.

Although maintenance trials have demonstrated a PFS advantage for prolonged treatment, the OS benefit of such a strategy is less clear, and longer follow-up of ongoing trials is needed. Evidently, several open questions remain, such as the optimal duration of treatment, and, in addition, the observed PFS benefit has to be balanced with the potential risk of toxicities associated with long-term treatment, together with cost.

Conflict of interest

The author is on the advisory board for Janssen, Millenium, and Celgene.

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DOI: 10.1002/hon

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