Autologous Transplantation for Newly Diagnosed Multiple Myeloma in the Era of Novel Agent Induction: A Systematic Review and Meta-analysis

Binod Dhakal, MD, MS; Aniko Szabo, PhD; Saurabh Chhabra, MD; Mehdi Hamadani, MD; Anita D’Souza, MD, MS; Saad Z. Usmani, MD; Rita Sieracki, MLS; Bishal Gyawali, MD, PhD; Jeffrey L. Jackson, MD, MPH; Fotis Asimakopoulos, MD, PhD; Parameswaran N. Hari, MD, MRCP, MS

Importance The role of high-dose therapy with melphalan followed by autologous stem cell transplant (HDT/ASCT) in patients with multiple myeloma continues to be debated in the context of novel agent induction.

Objective To perform a systematic review, conventional meta-analysis, and network meta-analysis of all phase 3 randomized clinical trials (RCTs) evaluating the role of HDT/ASCT.

Data Sources We performed a systematic literature search of Cochrane Central, MEDLINE, and Scopus from January 2000 through April 2017 and relevant annual meeting abstracts from January 2014 to December 2016. The following search terms were used: “myeloma” combined with “autologous,” “transplant,” “myeloablative,” or “stem cell.”

Study Selection Phase 3 RCTs comparing HDT/ASCT with standard-dose therapy (SDT) using novel agents were assessed. Studies comparing single HDT/ASCT with bortezomib, lenalidomide, and dexamethasone consolidation and tandem transplantation were included for network meta-analysis.

Data Extraction and Synthesis For the random effects meta-analysis, we used hazard ratios (HRs) and corresponding 95% CIs.

Main Outcomes and Measures The primary outcome was progression-free survival (PFS). Overall survival (OS), complete response, and treatment-related mortality were secondary outcomes.

Results A total of 4 RCTs (2421 patients) for conventional meta-analysis and 5 RCTs (3171 patients) for network meta-analysis were selected. The combined odds for complete response were 1.27 (95% CI, 0.97-1.65; P = .07) with HDT/ASCT when compared with SDT. The combined HR for PFS was 0.55 (95% CI, 0.41-0.74; P < .001) and 0.76 for OS (95% CI, 0.42-1.36; P = .20) in favor of HDT. Meta-regression showed that longer follow-up was associated with superior PFS (HR/mo, 0.98; 95% CI, 0.96-0.99; P = .03) and OS (HR/mo, 0.90; 95% CI, 0.84-0.96; P = .002). For PFS, tandem HDT/ASCT had the most favorable HR (0.49; 95% CI, 0.37-0.65) followed by single HDT/ASCT with bortezomib, lenalidomide, and dexamethasone consolidation and single HDT/ASCT alone (HR, 0.68; 95% CI, 0.53-0.87) compared with SDT. For OS, none of the HDT/ASCT-based approaches had a significant effect on survival. Treatment-related mortality with HDT/ASCT was minimal (<1%).

Conclusions and Relevance The results of the conventional meta-analysis and network meta-analysis of all the phase 3 RCTs showed that HDT/ASCT was associated with superior PFS with minimal toxic effects compared with SDT. Both tandem HDT/ASCT and single HDT/ASCT with bortezomib, lenalidomide, and dexamethasone were superior to single HDT/ASCT alone and SDT for PFS, but OS was similar across the 4 approaches. Longer follow-up may better delineate any OS benefit; however, is likely to be affected by effective postrelapse therapy.
High-dose therapy with melphalan followed by autologous stem cell transplant—a combination henceforth referred to as HDT/ASCT—has been the standard treatment for newly diagnosed patients with multiple myeloma (MM) for the past 20 years. Several phase 3 studies conducted before the advent of modern induction therapy with immunomodulatory drugs and proteasome inhibitors (also called “novel agents”)1-4 confirmed that HDT/ASCT was associated with improved response rates (RR), progression-free survival (PFS), and even overall survival (OS) in some studies.2,4 Given the unprecedented efficacy of novel agents, investigators have sought to reevaluate the role of HDT/ASCT. All prospective studies performed in the recent era have consistently shown a PFS benefit,2-6 but their effect on RR and OS compared with the standard-dose therapy (SDT) has been variable.5,6 Some of these discrepancies have been attributed to the use of suboptimal induction regimens, single HDT/ASCT (HDT1) vs tandem HDT/ASCT (HDT2) in the study arm, and inadequate follow-up across studies. The role of HDT2 compared with HDT1 remains unclear, especially after recent results of 2 large randomized trials that had divergent results.3,10 Furthermore, 2 studies2,6 that compared HDT2 with SDT showed OS benefit, but the study that compared HDT1 with SDT did not.5 There are no randomized trials directly comparing HDT1 vs HDT2 and SDT in patients with newly diagnosed MM. Moreover, indirect comparisons of these approaches are not available as well. There is a need to clarify the relative benefits of HDT1 or HDT2 and posttransplant consolidation in the context of modern novel agent induction therapy.

To address these issues, we performed a systematic review and conventional meta-analysis of all phase 3 randomized controlled trials (RCTs) in the era of modern induction to establish the role of HDT/ASCT compared with SDT in the context of novel agents. To better delineate the role of HDT2 compared with HDT1 and SDT; we also performed a network meta-analysis of all the phase 3 RCTs that evaluated the role of HDT/ASCT.

**Key Points**

**Question** What is the role of autologous stem cell transplantation in patients with multiple myeloma in the context of use of novel agents?

**Findings** In this systematic review and meta-analysis, this modality (including tandem transplantation or single-transplant followed by consolidation with bortezomib, lenalidomide, and dexamethasone) when compared with standard-dose therapy was associated with superior progression-free survival. None of the transplant-based approaches were associated with improved overall survival.

**Meaning** Autologous stem cell transplantation remains the preferred therapy in transplant-eligible patients with multiple myeloma.

**Methods**

**Data Sources**

We searched MEDLINE (PubMed), Scopus, and Cochrane Collection of Controlled Trial databases using the term “myeloma” combined with “autologous,” “transplant,” “myeloblastic,” or “stem cell” after January 1, 2000. We conducted a hand search of conference abstracts from the last 4 annual meetings (ie, 2014-2016) of the American Society of Clinical Oncology, American Society of Hematology, and European Hematology Association and also searched Clinicaltrials.gov and the Metaregister of clinical trials. Only studies published in English were included.

**Study Selection**

Studies meeting the following criteria were included: (1) use of phase 3 RCT design; (2) enrolled and reported outcomes for patients with newly diagnosed MM undergoing HDT/ASCT; (3) directly compared combination chemotherapy with novel agents followed by consolidation with HDT/ASCT vs SDT alone; and (4) directly compared HDT1 vs HDT2 (for network meta-analysis only). Small-scale studies (sample size <100 patients) were excluded. Eligible studies had a minimum of 2 years follow-up and reported PFS and/or OS as their end points using an intention-to-treat analysis.

**Data Extraction**

Two reviewers (B.D. and S.C.) independently abstracted the data. For each study, the data collected included date of publication, first author, number of patients enrolled and randomized in each arm, age (years), proportion of patients with International Staging System (ISS) stage III classification, and high-risk cytogenetics. For the interventions, we abstracted the types of standard chemotherapy regimen used in the control arms, as well as HDT/ASCT and their doses. In each arm, we also calculated the complete response (CR) rates and the treatment-related mortality (TRM) and the between-arm hazard ratios (HRs) for PFS and OS if available. Any disagreement between the 2 reviewers was resolved by a third reviewer (P.H.) or contacting the study authors when necessary.

For one of trials selected for network meta-analysis (the STaMINA trial),10 HRs were not reported, and thus were extracted based on the Kaplan-Meier curves using the method of Parmar et al.11 The images of the curves were saved in PNG format, and their values at 4-month increments were extracted using the automatic point-finding method of the WebPlotDigitizer 3.11 software (Ankit Rohatgi [https://automeris.io/WebPlotDigitizer/]). The data were entered into an HR calculation spreadsheet template developed by Sydnes and Tierney,12 and the estimated HR and 95% CI, under the assumption of uniform within-interval censoring, were used in the analysis.

The risk of bias in the included RCTs was assessed using the Cochrane Risk of Bias Tool.13

**Data Synthesis**

Statistical analysis was performed using R 3.2.3 (R Foundation for Statistical Computing) with the metafor package.14 The effect size was quantified as the HRs for the survival outcomes and odds ratio (OR) for CRs. Heterogeneity was
assessed by the Q statistic and quantified using $I^2$. Overall survival, PFS, and CR were analyzed both separately in a univariate analysis and jointly in a multivariate analysis that used the correlation between the effects of a treatment on the related outcomes to impute results for unreported outcomes. Inference was based on a random-effects analysis, with an unstructured within-comparison covariance matrix for the multivariate analysis. A forest plot with combined HR (95% CI) for OS and PFS benefit of up-front HDT/ASCT vs SDT was constructed showing the results of both the univariate and multivariate models. We explored heterogeneity of the effects by meta-regression. Specifically, the proportions of patients receiving a tandem HDT/ASCT and median follow-up (for survival outcomes) were explored as potential effect modifiers.

A network meta-analysis exploring the differential effects of variations of the HDT treatment group was conducted using a mixed-effects model as described by Law et al. Inconsistency was evaluated by fitting an extended model including design-by-treatment interaction via a random effect and comparing the models by a likelihood-ratio test. Both univariate and multivariate analysis were conducted as described. The model-based estimates of the effect of each treatment compared with SDT were visualized on a forest plot with 95% CIs with the treatments ordered from largest to smallest effect. This work was performed in accordance with PRISMA guidelines.

Results

A total of 2480 articles were identified as outlined in Figure 1 of which 2474 articles were excluded after title and abstract review for not meeting the inclusion criteria. A total of 6 studies were found to be potentially relevant. Overall, 4 RCTs that compared HDT/ASCT vs SDT involving 2421 patients were eligible for inclusion for conventional meta-analysis. For network meta-analysis, we included 1 additional study (total 5 studies) that compared HDT2 with HDT1 alone vs HDT1 followed by consolidation with bortezomib, lenalidomide, and dexamethasone (VRD).

Conventional Meta-analysis

Study Characteristics

The summary of the 4 randomized trials is shown in Table 1. The median follow-up ranged from 26 to 52 months. The number of patients allocated to each treatment arm in these trials ranged from 127 to 695. Palumbo et al. evaluated the efficacy of low-dose melphalan, lenalidomide, and prednisone vs HDT/ASCT after initial induction. In this study of 402 patients, 273 were randomized to HDT2 with melphalan 200 mg/m² or six 28-day cycles of melphalan, lenalidomide, and prednisone after initial induction therapy with four 28-day cycles with lenalidomide and dexamethasone. Following this, the patients underwent the second randomization to lenalidomide maintenance therapy or no maintenance. Gay et al. conducted a similar study in which patients after initial induction with 4 cycles of lenalidomide and dexamethasone underwent randomization to HDT2 with melphalan 200 mg/m² or 6 cycles of cyclophosphamide, lenalidomide, and dexamethasone. The second randomization was for maintenance with lenalidomide vs lenalidomide with prednisone. Of 389 patients, 256 were eligible for randomization to the consolidation phase. Attal et al. evaluated the role of early vs delayed HDT/ASCT after induction with triplet combination including bortezomib, lenalidomide, and dexamethasone (VRD) for 3 cycles and subsequent stem cell collection. Of total 700 patients, 350 were randomized to early HDT/ASCT where they received HDT1 until disease progression. Another European study by Cavo et al. compared early HDT/ASCT (either HDT1 or HDT2 depending on the center) or four 42-day cycles of bortezomib, melphalan, and prednisone after 4 cycles of induction with cyclophosphamide, bortezomib, and dexamethasone. The patients underwent the second randomization to VRD vs no consolidation. All patients received maintenance with lenalidomide. Of 1500 patients, 1192 were randomized to HDT/ASCT or bortezomib, melphalan, and prednisone consolidation, out of which 207 patients received HDT2. As shown in Table 1, ISS stage III and high-risk cytogenetics were comparable across these studies.

Quality of the Studies and Risk of Bias

The Cochane Risk of Bias assessment is provided in eFigure 3 in the Supplement. In addition, Table 2 summarizes some important design quality characteristics of these RCTs. The risk of bias could not be assessed completely for Cavo et al.
because the study has not been published yet. Two trials7,8 described adequate methods of random sequence generation and allocation concealment, while the third trial5 did not clearly describe adequate methods of random sequence generation and stratification across studies as demonstrated by $I^2$ of 75.2% for PFS (P = .01). The forest plot with the individual and the combined studies is shown in Figure 2B. The combined HR for all 4 studies was 0.55 (95% CI, 0.41-0.74; $P = .004$) indicating statistically significant PFS benefit with HDT/ASCT. Meta-regression showed that longer median follow-up (HR/mo 0.98; 95% CI 0.96-0.99; $P = .03$) and the use of HDT2 (HR for all HDT2 vs none, 0.61; 95% CI, 0.39-0.93; $P = .02$) was associated with a larger beneficial effect of HDT on PFS (eTable 2 in the Supplement).

### OS

Only 3 studies5,7,8 included in the analysis reported OS. There was significant heterogeneity in the estimates across studies as demonstrated by $I^2$ 78.7% for OS (P = .01). The forest plot of the individual and combined studies is shown in Figure 2C. The combined HR for all 3 studies was 0.76 (95% CI, 0.42-1.36; $P = .20$). The overall estimate did not indicate a statistically significant reduction in hazard of death with up-front HDT/ASCT. Meta-regression analysis, however, showed that longer median follow-up (HR/mo 0.90; 95% CI, 0.84-0.96; $P = .002$) and the use of HDT2 (HR for all HDT2 vs none, 0.41; 95% CI, 0.23-0.71; $P = .002$) were

### Table 1. Baseline Demographics of Relevant Randomized Clinical Trials

<table>
<thead>
<tr>
<th>Source</th>
<th>Multicenter</th>
<th>Randomization</th>
<th>Assignment</th>
<th>Drop Out After Randomization</th>
<th>Salvage HDT at Progression</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palumbo et al,8 2014</td>
<td>Yes</td>
<td>Stratified by age, ISS*</td>
<td>Central</td>
<td>HDT, 4.2%; SDT, 12.1%</td>
<td>HDT, 6.0%; SDT, 70%</td>
<td>HDT, 85% for 2-y PFS of 63%; SDT, 50%</td>
</tr>
<tr>
<td>Gay et al,7 2015</td>
<td>Yes</td>
<td>Stratified by age, ISS*</td>
<td>Central</td>
<td>HDT, 7.8%; SDT, 20.0%</td>
<td>HDT, 21.0%; SDT, 43.0%</td>
<td>80% for 2-y PFS of 65% for both arms</td>
</tr>
<tr>
<td>Attal et al,5 2015</td>
<td>Yes</td>
<td>Stratified by ISS, FISH* (after 1 VRD induction)</td>
<td>Central</td>
<td>None (both arms)</td>
<td>HDT, 17.0%; SDT, 79.0%</td>
<td>80% power for 9-mo PFS benefit in HDT arm.</td>
</tr>
<tr>
<td>Cavo et al,6 2016</td>
<td>Yes</td>
<td>Stratified by ISS, after CyBord; all</td>
<td>Central</td>
<td>None (both arms)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

### Table 2. Study Quality of Randomized Clinical Trials

<table>
<thead>
<tr>
<th>Source</th>
<th>Multicenter</th>
<th>Randomization Assignment</th>
<th>Dropout Rate</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palumbo et al,8 2014</td>
<td>Yes</td>
<td>Stratified by age, ISS*</td>
<td>Central</td>
<td>HDT, 4.2%; SDT, 12.1%</td>
</tr>
<tr>
<td>Gay et al,7 2015</td>
<td>Yes</td>
<td>Stratified by age, ISS*</td>
<td>Central</td>
<td>HDT, 7.8%; SDT, 20.0%</td>
</tr>
<tr>
<td>Attal et al,5 2015</td>
<td>Yes</td>
<td>Stratified by ISS, FISH* (after 1 VRD induction)</td>
<td>Central</td>
<td>None (both arms)</td>
</tr>
<tr>
<td>Cavo et al,6 2016</td>
<td>Yes</td>
<td>Stratified by ISS, after CyBord; all</td>
<td>Central</td>
<td>None (both arms)</td>
</tr>
</tbody>
</table>

Abbreviations: CRD, cyclophosphamide, revlimid, and dexamethasone; CyBorD, cyclophosphamide, bortezomib, and dexamethasone; HDT, high-dose therapy; ISS, International Staging System; LEN, lenalidomide; LEN+P, lenalidomide plus prednisone; MEL 200, melphalan 200 mg/m2; MPR, melphalan, prednisone, and revlimid; OS, overall survival; PFS, progression-free survival; RD, revlimid and dexamethasone; RVD, lenalidomide plus prednisone; VMP, bortezomib, melphalan, and prednisone. * High-risk cytogenetics include t(4:14), t(14:16), t(14:20), 17p deletion, 1q gain, and 1p deletion.

Abbreviations: CRD, cyclophosphamide, revlimid, and dexamethasone; CyBorD, cyclophosphamide, bortezomib, and dexamethasone; HDT, high-dose therapy; ISS, International Staging System; LEN, lenalidomide; LEN+P, lenalidomide plus prednisone; MEL 200, melphalan 200 mg/m2; MPR, melphalan, prednisone, and revlimid; OS, overall survival; PFS, progression-free survival; RD, revlimid and dexamethasone; RVD, lenalidomide plus prednisone; VMP, bortezomib, melphalan, and prednisone. * High-risk cytogenetics include t(4:14), t(14:16), t(14:20), 17p deletion, 1q gain, and 1p deletion.

**Complete Response**

Overall response rates including the CR rates were reported in all studies.5-8 As shown in (eTable 1 in the Supplement), higher proportions of patients receiving HDT/ASCT achieved CR when compared with SDT arm. The forest plot with individual and combined OR is shown in Figure 2A. The combined OR for CR was 1.27 (95% CI, 0.97-1.65; $P = .07$) with HDT/ASCT when compared with SDT showing a trend toward deeper responses achieved with up-front HDT/ASCT. Meta-regression analysis showed no association with HDT2 and additional increase in the proportion of patients achieving CR (HR, 0.93; 95% CI, 0.45-1.89; $P = .84$).

**Treatment-Related Mortality**

Information on treatment-related mortality (TRM) was variably reported (eTable 1 in the Supplement). Only two studies5,8 reported TRM with HDT/ASCT. In both these studies, TRM was very minimal (<1%) and comparable with the SDT arm.

**PFS**

All 4 studies5-8 reported PFS. Significant heterogeneity was present across studies as demonstrated by $I^2$ of 75.2% for PFS (P = .01). The forest plot with the individual and the combined studies is shown in Figure 2B. The combined HR for all 4 studies was 0.55 (95% CI, 0.41-0.74; $P = .004$) indicating statistically significant PFS benefit with HDT/ASCT. Meta-regression showed that longer median follow-up (HR/mo 0.98; 95% CI 0.96-0.99; $P = .03$) and the use of HDT2 (HR for all HDT2 vs none, 0.61; 95% CI, 0.39-0.93; $P = .02$) was associated with a larger beneficial effect of HDT on PFS (eTable 2 in the Supplement).
associated with a larger beneficial effect of HDT on OS (eTable 2 in the Supplement).

The multivariate analysis accounting for correlation between the effect of treatment on PFS, OS, and CR did not substantially alter the estimates for PFS and CR for which data from all 4 studies5-8 was available. However, the estimated effect was reduced (moved closer to no effect) for OS.

Network Meta-analysis
To better delineate the role of HDT2 compared with both HDT1 and SDT, we performed a network meta-analysis of all phase 3 randomized trials that met the criteria outlined in the study selection. eFigure 1 in the Supplement represents the complex network of the role of HDT/ASCT in MM. In addition to the 4 studies included in the conventional meta-analysis, we included the results of the recent study from the Blood and Marrow Transplant Clinical Trials Network (BMTCTN 0702) or STaMiNa study.10 In this study, after receiving HDT1, the patients were randomized into 3 different arms: (1) HDT2 (n = 247); (2) HDT1 plus 4 cycles of VRD (n = 254); and (3) none (N = 257). All 3 arms received lenalidomide maintenance until progression. More than 50% of the patients in all 3 arms received prior induction with VRD; however, 32% of patients in HDT2 arm and 11% of patients in HDT1 plus VRD arm did not receive the assigned post-HDT1 treatment. The study showed no difference in the OS (HDT2, 85%; HDT1 plus VRD, 85.7%; and HDT1, 83.4%) and PFS (HDT2, 56.5%; HDT1 plus VRD, 56.7%; and HDT1, 52.2%) at 38 months follow-up.

Results vs SDT
eFigure 2 in the Supplement represents the network meta-analysis results in which SDT was used as the comparator: the solid lines show the results of univariate network meta-analysis run separately for PFS and OS, and the dashed lines (and estimates in italic) show the results of the multivariate network meta-analysis that incorporates the correlation between PFS and OS “inferring” the OS results of trials that did not report OS. Treatments based on HDT/ASCT were associ-
ated with superior PFS compared with SDT. Furthermore, HDT2 had the most favorable results for PFS compared with SDT (HR, 0.49; 95% CI, 0.37-0.65) followed by HDT1 plus VRD (HR, 0.53; 95% CI, 0.37-0.76). For OS, none of the HDT/ASCT-based approaches had a significant effect on survival compared with SDT. No significant inconsistency was found; thus, the results of the consistency model are presented. The results of the inconsistency model were not qualitatively different.

The pairwise comparisons for all these groups are shown in Table 3 in the Supplement for PFS and OS. Among the results shown, the comparison of HDT2 vs HDT1 is worth mentioning. Our results showed that HDT2 (HR, 0.79; 95% CI, 0.55-0.92; P < .001) and HDT1 plus VRD (HR, 0.78; 95% CI, 0.54-1.00; P = .02) were associated with superior PFS compared with HDT1, but no difference in OS was observed.

Discussion

This meta-analysis incorporating both conventional meta-analysis and network meta-analysis of all the large phase 3 RCTs from January 2000 to April 2017 showed that HDT/ASCT was associated with superior PFS compared with SDT. Furthermore, it showed that HDT2 and HDT1 plus VRD were associated with superior PFS compared with HDT1 alone. The results did not demonstrate any OS benefit with HDT/ASCT approaches. The toxic effects and the response rates of both HDT/ASCT and SDT were comparable demonstrating the safety of HDT/ASCT while also establishing the unprecedented response rates associated with novel agents. Using a meta-regression, we demonstrated that longer follow-up was associated with an increase in the observed beneficial effect of HDT/ASCT on both PFS and OS. A possible explanation of this finding is that the HR increases over time (ie, the proportional hazards assumption is not valid). Thus, future studies should plan for nonproportional hazards and not rely on Cox regression for analyses, as well as allow for longer follow-up for OS.

There was a trend for higher CR rates with HDT/ASCT in our analysis. Several retrospective studies have suggested the link between the achievement of CR and prolonged survival. However, a pooled analysis of 3 prospective clinical trials showed that regardless of the type of treatment or patient risk group; persistent minimal residual disease (MRD)-negative status abrogates the prognostic benefits of CR on both PFS and OS. This observation has been bolstered by a recently published meta-analysis that showed that the achievement of MRD negativity following any treatment was associated with an increase in the observed beneficial effect of HDT/ASCT on both PFS and OS. A possible explanation of this finding is that the HR increases over time (ie, the proportional hazards assumption is not valid). Thus, future studies should plan for nonproportional hazards and not rely on Cox regression for analyses, as well as allow for longer follow-up for OS.

There was a trend for higher CR rates with HDT/ASCT in our analysis. Several retrospective studies have suggested the link between the achievement of CR and prolonged survival. However, a pooled analysis of 3 prospective clinical trials showed that regardless of the type of treatment or patient risk group; persistent minimal residual disease (MRD)-negative status abrogates the prognostic benefits of CR on both PFS and OS. This observation has been bolstered by a recently published meta-analysis that showed that the achievement of MRD negativity following any treatment was associated with an increase in the observed beneficial effect of HDT/ASCT on both PFS and OS. A possible explanation of this finding is that the HR increases over time (ie, the proportional hazards assumption is not valid). Thus, future studies should plan for nonproportional hazards and not rely on Cox regression for analyses, as well as allow for longer follow-up for OS.

Discussion

This meta-analysis incorporating both conventional meta-analysis and network meta-analysis of all the large phase 3 RCTs from January 2000 to April 2017 showed that HDT/ASCT was associated with superior PFS compared with SDT. Furthermore, it showed that HDT2 and HDT1 plus VRD were associated with superior PFS compared with HDT1 alone. The results did not demonstrate any OS benefit with HDT/ASCT approaches. The toxic effects and the response rates of both HDT/ASCT and SDT were comparable demonstrating the safety of HDT/ASCT while also establishing the unprecedented response rates associated with novel agents. Using a meta-regression, we demonstrated that longer follow-up was associated with an increase in the observed beneficial effect of HDT/ASCT on both PFS and OS. A possible explanation of this finding is that the HR increases over time (ie, the proportional hazards assumption is not valid). Thus, future studies should plan for nonproportional hazards and not rely on Cox regression for analyses, as well as allow for longer follow-up for OS.

There was a trend for higher CR rates with HDT/ASCT in our analysis. Several retrospective studies have suggested the link between the achievement of CR and prolonged survival. However, a pooled analysis of 3 prospective clinical trials showed that regardless of the type of treatment or patient risk group; persistent minimal residual disease (MRD)-negative status abrogates the prognostic benefits of CR on both PFS and OS. This observation has been bolstered by a recently published meta-analysis that showed that the achievement of MRD negativity following any treatment was associated with an increase in the observed beneficial effect of HDT/ASCT on both PFS and OS. A possible explanation of this finding is that the HR increases over time (ie, the proportional hazards assumption is not valid). Thus, future studies should plan for nonproportional hazards and not rely on Cox regression for analyses, as well as allow for longer follow-up for OS.

Discussion

This meta-analysis incorporating both conventional meta-analysis and network meta-analysis of all the large phase 3 RCTs from January 2000 to April 2017 showed that HDT/ASCT was associated with superior PFS compared with SDT. Furthermore, it showed that HDT2 and HDT1 plus VRD were associated with superior PFS compared with HDT1 alone. The results did not demonstrate any OS benefit with HDT/ASCT approaches. The toxic effects and the response rates of both HDT/ASCT and SDT were comparable demonstrating the safety of HDT/ASCT while also establishing the unprecedented response rates associated with novel agents. Using a meta-regression, we demonstrated that longer follow-up was associated with an increase in the observed beneficial effect of HDT/ASCT on both PFS and OS. A possible explanation of this finding is that the HR increases over time (ie, the proportional hazards assumption is not valid). Thus, future studies should plan for nonproportional hazards and not rely on Cox regression for analyses, as well as allow for longer follow-up for OS.

There was a trend for higher CR rates with HDT/ASCT in our analysis. Several retrospective studies have suggested the link between the achievement of CR and prolonged survival. However, a pooled analysis of 3 prospective clinical trials showed that regardless of the type of treatment or patient risk group; persistent minimal residual disease (MRD)-negative status abrogates the prognostic benefits of CR on both PFS and OS. This observation has been bolstered by a recently published meta-analysis that showed that the achievement of MRD negativity following any treatment was associated with an increase in the observed beneficial effect of HDT/ASCT on both PFS and OS. A possible explanation of this finding is that the HR increases over time (ie, the proportional hazards assumption is not valid). Thus, future studies should plan for nonproportional hazards and not rely on Cox regression for analyses, as well as allow for longer follow-up for OS.

Discussion

This meta-analysis incorporating both conventional meta-analysis and network meta-analysis of all the large phase 3 RCTs from January 2000 to April 2017 showed that HDT/ASCT was associated with superior PFS compared with SDT. Furthermore, it showed that HDT2 and HDT1 plus VRD were associated with superior PFS compared with HDT1 alone. The results did not demonstrate any OS benefit with HDT/ASCT approaches. The toxic effects and the response rates of both HDT/ASCT and SDT were comparable demonstrating the safety of HDT/ASCT while also establishing the unprecedented response rates associated with novel agents. Using a meta-regression, we demonstrated that longer follow-up was associated with an increase in the observed beneficial effect of HDT/ASCT on both PFS and OS. A possible explanation of this finding is that the HR increases over time (ie, the proportional hazards assumption is not valid). Thus, future studies should plan for nonproportional hazards and not rely on Cox regression for analyses, as well as allow for longer follow-up for OS.

Discussion

This meta-analysis incorporating both conventional meta-analysis and network meta-analysis of all the large phase 3 RCTs from January 2000 to April 2017 showed that HDT/ASCT was associated with superior PFS compared with SDT. Furthermore, it showed that HDT2 and HDT1 plus VRD were associated with superior PFS compared with HDT1 alone. The results did not demonstrate any OS benefit with HDT/ASCT approaches. The toxic effects and the response rates of both HDT/ASCT and SDT were comparable demonstrating the safety of HDT/ASCT while also establishing the unprecedented response rates associated with novel agents. Using a meta-regression, we demonstrated that longer follow-up was associated with an increase in the observed beneficial effect of HDT/ASCT on both PFS and OS. A possible explanation of this finding is that the HR increases over time (ie, the proportional hazards assumption is not valid). Thus, future studies should plan for nonproportional hazards and not rely on Cox regression for analyses, as well as allow for longer follow-up for OS.

Discussion

This meta-analysis incorporating both conventional meta-analysis and network meta-analysis of all the large phase 3 RCTs from January 2000 to April 2017 showed that HDT/ASCT was associated with superior PFS compared with SDT. Furthermore, it showed that HDT2 and HDT1 plus VRD were associated with superior PFS compared with HDT1 alone. The results did not demonstrate any OS benefit with HDT/ASCT approaches. The toxic effects and the response rates of both HDT/ASCT and SDT were comparable demonstrating the safety of HDT/ASCT while also establishing the unprecedented response rates associated with novel agents. Using a meta-regression, we demonstrated that longer follow-up was associated with an increase in the observed beneficial effect of HDT/ASCT on both PFS and OS. A possible explanation of this finding is that the HR increases over time (ie, the proportional hazards assumption is not valid). Thus, future studies should plan for nonproportional hazards and not rely on Cox regression for analyses, as well as allow for longer follow-up for OS.
study, the reason for transplant in the SDT arm was disease progression and/or relapse in all these studies. Given the major improvements in treatments of relapsed MM, it is difficult to predict whether an OS difference would emerge even with longer follow-up. The use of effective induction regimens, as in the study by Attal et al., as well as the use of lenalidomide maintenance, are both highly effective survival-prolonging strategies in MM. The extensive use of lenalidomide maintenance resulting in longer survival in the SDT arm and the lack of longer-term follow-up might lead to underestimation of longer-term survival effects as our analysis showed.

Despite the lack of demonstrable OS benefit, we conclude that HDT/ASCT remains the preferred up-front treatment option. A significant PFS benefit, low TRM, and potential high MRD-negative rates conferred by HDT/ASCT in the context of best available nontransplant therapies are enough to justify this approach for patients with newly diagnosed MM. The achievement of high MRD rates with HDT/ASCT may render this approach the ideal platform for testing novel approaches (eg, immunotherapy) aiming at disease eradication and cures. Previous studies have demonstrated that HDT was associated with improved quality of life in the pre-agent era. No such quality-of-life data have been reported for the studies in the current era. Further studies looking at quality of life, patient-reported outcomes, and pharmacoeconomics are recommended because maintenance and post-transplant therapy are now standard.

LIMITATIONS
Some of the limitations of the analysis include the following: (1) a limited number of studies; (2) heterogeneous treatments delivered; and (3) unreported outcomes (eg, OS in Cavo et al.6 and HRs in STaMINA14). The heterogeneity present across studies was incorporated in the analysis in several ways: random effects approach, evaluating effect modifiers, and finally exploring the effect of HDT1 vs HDT2 using network meta-analysis. While we found that the trial characteristics explained some of the heterogeneity, we were not able to explore the functional form of the effect of modifiers or fully adjust for them owing to the low number of trials. The effect of secondary randomizations also complicates the interpretation of long-term results, especially OS. Because omitting a balanced covariate in a randomized study biases the estimated HR toward no effect, the beneficial effect of HDT/ASCT might be underestimated. However, to our knowledge, this is the first meta-analysis to consider the totality of the available evidence of RCTs evaluating the role of HDT/ASCT in the setting of novel agents and comparing the differential role of HDT2 vs HDT1 and SDT.

CONCLUSIONS
Up-front HDT/ASCT remains an effective treatment strategy for patients with newly diagnosed MM and has an acceptable profile of toxic effects and costs.


