Treatment Intensification With Autologous Stem Cell Transplantation and Lenalidomide Maintenance Improves Survival Outcomes of Patients With Newly Diagnosed Multiple Myeloma in Complete Response

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Abstract

In patients with a complete response (CR), high-dose therapy with autologous stem cell transplantation (HDT-ASCT) consolidation improved progression-free survival (PFS), second PFS (PFS2), and overall survival (OS) versus R-Alk (lenalidomide, alkylator) consolidation. Also, lenalidomide maintenance therapy enhanced PFS compared with no maintenance therapy. The survival advantage with HDT-ASCT compared with R-Alk in CR patients can be attributed to the greater minimal residual disease negativity rate induced by HDT-ASCT.

Background: High-dose therapy with autologous stem cell transplantation (HDT-ASCT) and maintenance treatment with novel agents are the best options for patients with newly diagnosed multiple myeloma, increasing the rate of complete response (CR) and prolonging progression-free survival (PFS) and overall survival (OS). Indeed, the achievement of a CR is a predictor of long-term survival among transplant-eligible patients. However, it is unclear whether patients reaching a CR after induction treatment could receive less intense consolidation or avoid maintenance therapy. **Patients and Methods:** We analyzed CR patients treated in 2 phase III trials, GIMEMA-RV-MM-PI-209

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and RV-MM-EMN-441, to compare HDT-ASCT with an R-Alk (lenalidomide, alkylator) regimen as consolidation, and lenalidomide (R) maintenance with no maintenance. The primary endpoints were PFS, second PFS (PFS2), and OS from consolidation and maintenance (_m). **Results:** Overall, the data from 166 patients in CR were analyzed, 95 in the HDT-ASCT group and 71 in the R-Alk group. The CR patients who received HDT-ASCT had a better PFS (hazard ratio [HR], 0.55; $P = .01$), PFS2 (HR, 0.46; $P = .02$), and OS (HR, 0.42; $P = .03$) compared with patients randomized to R-Alk. The survival benefit with HDT-ASCT was confirmed among all the subgroups, according to age, International Staging System (ISS stage, cytogenetic profile, and receipt of maintenance therapy. CR patients who received lenalidomide maintenance had a better PFS_m (4 years: 54% vs. 19%; HR, 0.43; $P = .02$) compared with those who received no maintenance. However, no difference was observed in terms of PFS2_m (4 years: 72% vs. 58%; HR, 0.83; $P = .67$) and OS_m (4 years: 79% vs. 72%; HR, 0.82; $P = .73$) with maintenance therapy. **Conclusion:** Even in CR patients, outcomes were improved by an intensified approach with HDT-ASCT consolidation and lenalidomide-based maintenance therapy.

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Introduction

Multiple myeloma (MM) is a hematologic neoplasm accounting for ~1% of all cancers and represents the second most common hematologic malignancy.[1] The introduction of high-dose therapy (HDT) with melphalan, followed by autologous stem cell transplantation (ASCT), and novel agents, such as immunomodulators and proteasome inhibitors (PIs), have significantly extended the median overall survival (OS), from 2-3 to 7-8 years for MM patients.[2-10]

With the increasing availability of highly effective novel agents, the role of the ASCT for patients with newly diagnosed MM has been questioned, and several trials have been designed to compare consolidation therapy with HDT-ASCT to a nontransplant-based approach that includes novel agents. In 4 European phase III trials, patients with newly diagnosed MM eligible for transplantation were randomized to consolidation with either HDT-ASCT or a novel agent-containing regimen: MPR (melphalan, prednisone, lenalidomide), CRD (cyclophosphamide, lenalidomide, dexamethasone), VMP (bortezomib, melphalan, prednisone) or VRD (bortezomib, lenalidomide, dexamethasone).[11-14] In all the trials, patients in the HDT-ASCT group had a significantly better PFS compared with those who did not receive transplantation, 2 of which also reported an OS advantage in favor of the HDT-ASCT group.[11,12,15-17]

Maintenance treatment with lenalidomide has been extensively investigated among patients with newly diagnosed, transplant-eligible MM.[11,12,15-17] A meta-analysis of 1208 transplant-eligible patients enrolled in 3 randomized phase III trials comparing lenalidomide maintenance and observation/placebo showed a 25% reduction in the risk of death in favor of lenalidomide maintenance therapy.[18]

The adoption of HDT-ASCT and novel agents also dramatically increased the likelihood of obtaining a complete response (CR).[19,20] Among transplant-eligible patients, the achievement of a CR has been related to a significantly improvement in PFS and OS.[21] In a meta-analysis evaluating the correlation between the response depth and survival, patients who achieved a CR, after both induction and ASCT, had a significantly longer PFS and OS compared with patients without a CR.[22]

We report the results of a pooled analysis conducted among newly diagnosed, transplant-eligible MM patients enrolled in 2 phase III randomized clinical trials (GIMEMA [Gruppo Italiano Malattie Ematologiche dell'Adulto]-RV-MM-PI-209 and EMN [European Myeloma Network] RV-MM-EMN-441) to evaluate the role of intensification and maintenance treatment in patients who had attained a CR.

Patients and Methods

Study Design

The data from patients with newly diagnosed MM who were aged < 65 years, were eligible for ASCT, and were enrolled in 2 randomized, multicenter, phase III trials (ie, GIMEMA-RV-MM-PI-209 and RV-MM-EMN-441) were pooled and retrospectively analyzed.

Details on the treatment and results of the 2 trials have been previously reported.[11,12] The institutional review board at each participating center approved the studies in accordance with the Declaration of Helsinki. All patients provided written informed consent. Both trials were registered at ClinicalTrials.gov (ClinicalTrials.gov identifiers NCT00551928 and NCT01091831). In brief, all patients received a common induction with 4 cycles of Rd (lenalidomide, low-dose dexamethasone). At enrollment, patients were also randomized in a 1:1:1:1 ratio to receive consolidation treatment with either 2 courses of high-dose melphalan followed by ASCT in both studies or 6 cycles of chemotherapy with either MPR (melphalan, prednisone, lenalidomide) in the GIMEMA-RV-MM-PI-209 study or CRD (cyclophosphamide, lenalidomide, dexamethasone) in the RV-MM-EMN-441 study. Afterward, they could receive maintenance with R (lenalidomide) alone in both studies or no maintenance in the GIMEMA-RV-MM-PI-209 study or RP (lenalidomide, prednisone) maintenance therapy in the RV-MM-EMN-441 study.

Patients who completed induction treatment and had confirmed eligibility for consolidation, provided that they had reached a CR at any time during first-line treatment, were included in the present analysis. The patients were then stratified according to the type of consolidation treatment received (HDT-ASCT or R-Alk [lenalidomide, alkylator-based chemotherapy]), and type of maintenance treatment (R-based maintenance therapy vs. no maintenance).

We analyzed the effect of consolidation (HDT-ASCT vs. R-Alk) and maintenance treatment (R-based vs. no maintenance) on PFS, second PFS (PFS2), and OS in patients who had achieved a CR.

Assessment

In the GIMEMA-RV-MM-PI-209 and RV-MM-EMN-441 trials, the responses to treatment were assessed according to the International Myeloma Working Group criteria and were confirmed in $\geq$ 2 consecutive assessments.[23]

A CR was defined as negative serum and urine immunofixation findings, the disappearance of any soft tissue plasmacytoma, and the presence of $<$ 5% bone marrow monoclonal plasma cells. PFS was calculated from the time of eligibility for consolidation until the date of progression or relapse, death from any cause, or the date the patient was last known to be in remission. PFS2 was calculated from the time of eligibility for consolidation until the date of second progression or relapse, death from any cause, or the date the patient was last known to be in remission. OS was calculated from the time of eligibility for consolidation until the date of death or the date the patient was last known to be alive. To evaluate the effect of maintenance therapy, all survival outcomes were calculated from the date of eligibility for the maintenance phase (PFS_m, PFS2_m, OS_m). The time to a CR was calculated from the date of the start of treatment to the date of detection of the first CR. The duration of the CR was calculated from CR achievement until the date of progression, relapse, death from any cause, or the date the patient was last known to be in remission. The high-risk fluorescence in situ hybridization (FISH) results were defined by the presence of $\geq$ 1 of the following: del17p, t(4;14), or t(14;16).

Statistical Analysis

For the present retrospective, not preplanned analysis, data from the GIMEMA-RV-MM-PI-209 and RV-MM-EMN-441 studies were pooled, and only patients who had achieved a CR were included in the analysis. The baseline characteristics were compared using the Fisher exact test for discrete variables and the Kruskal-Wallis test for continuous variables.

The time-to-event data (time to CR, duration of CR, and survival data) were analyzed using the Kaplan-Meier method. The treatment groups were compared using the log-rank test. Cox proportional hazards models were used to estimate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the main comparisons and the Grambsch and Therneau test to test the proportional hazard assumption.

To account for potential confounders, the Cox models for the comparison of HDT-ASCT versus R-Alk were adjusted for age, sex, International Staging System (ISS) stage, cytogenetic profile, and trial effect. Subgroup analyses were performed to determine the consistency of the treatment effects of HDT-ASCT versus R-Alk in the different subgroups using interaction terms between treatment and age, sex, ISS stage, cytogenetic profile, and maintenance treatment. All HRs were estimated with their 95% CIs and 2-sided P values. The data were analyzed in December 2017 using R, version 3.1.1 (R Foundation).

Results

Patients

A total of 791 patients with newly diagnosed MM enrolled in the GIMEMA-RV-MM-PI-209 (n = 402) and in the RV-MM-EMN-441 (n = 389) trials were evaluated. Of the 791 patients, 166 (21%) were eligible for randomization to consolidation after completing induction treatment and had achieved a CR during the whole first-line treatment. These patients were therefore included in the present analysis: 93 from GIMEMA-RV-MM-PI-209 and 73 from RV-MM-EMN-441.

Among the patients who achieved a CR, 95 (57%) received HDT-ASCT consolidation, and 71 (43%) received R-Alk consolidation. Of the patients who achieved a CR, 122 (73%) were assigned to R-based maintenance, 40 (24%) with RP and 82 with R (49%), while 44 (27%) were randomized to no maintenance. No significant differences were found in the distribution of patients in CR who were randomized to RP, R, and no maintenance in the HDT-ASCT group (24%, 47%, and 28%, respectively) or in the R-Alk group (24%, 52%, and 24%, respectively; $P = .80$).

The patient characteristics were well balanced within the HDT-ASCT and R-Alk groups (Table 1). The median age at enrollment was 57 years (interquartile range, 51-60 years) for the entire population. Patients considered at high risk, according to the ISS (ISS stage III, 15% vs. 21%; $P = .45$), revised ISS (R-ISS III, 3% vs. 6%; $P = .60$), and FISH (14% vs. 14%; $P = 1$), were equally distributed between the 2 groups.

Time to CR and Duration of CR

In the HDT-ASCT group, 18 patients (19%) achieved a CR during induction, 33 (35%) after HDT-ASCT consolidation and 44 (46%) during maintenance. In the R-Alk group, 29 patients (41%) achieved a CR during induction, 17 (24%) after R-Alk consolidation, and 25 (35%) during maintenance. Overall, the median time to a CR was 11.9 months (95% CI, 10.2-14.5). The median time to a CR was 13.5 months in the HDT-ASCT group and 9.5 months in the R-Alk group (HR, 0.73; 95% CI, 0.53-1.01; $P = .06$). The median CR duration was 45.3 months in the HDT-ASCT group and 30.5 months in the R-Alk group (HR, 0.60; $P = .03$).

Effect of Treatment Strategy on Survival Outcomes

After a median follow-up of 48 months (interquartile range, 45-52 months), the median PFS was significantly longer for the HDT-ASCT patients than that for the R-Alk patients (not reached vs. 37 months; HR, 0.55; 95% CI, 0.35-0.88; $P = .01$). The 5-year PFS was 55% in the HDT-ASCT group and 45% in the R-Alk group (Figure 1A).

PFS2 was significantly better for the HDT-ASCT group compared with the R-Alk group (5-years: 71% vs. 62%; HR, 0.46; 95% CI, 0.24-0.87; $P = .02$; Figure 1B).

Patients who received HDT-ASCT consolidation had a 58% reduced risk of death compared with those randomized to R-Alk consolidation (5-year OS: 87% vs. 71%; HR, 0.42; 95% CI, 0.19-0.92; $P = .03$; Figure 1C). In a subgroup analysis accounting for age, sex, ISS stage, cytogenetic risk by FISH, and type of

Table 1 Patient Characteristics

Baseline Characteristic	All (n = 166)	HDT-ASCT (n = 95)	R-Alk (n = 71)
Median age, y (IQR)	56.5 (51-60)	57 (51-61.5)	56 (50.5-60)
Age group, y			
≤ 60	125 (75)	67 (71)	58 (82)
> 60	41 (25)	28 (29)	13 (18)
Sex			
Male	79 (48)	46 (48)	33 (46)
Female	87 (52)	49 (52)	38 (54)
ISS stage			
I	83 (50)	47 (49)	36 (51)
II	54 (33)	34 (36)	20 (28)
III	29 (17)	14 (15)	15 (21)
R-ISS stage			
I	44 (27)	25 (26)	19 (27)
II	79 (48)	48 (51)	31 (44)
III	7 (4)	3 (3)	4 (6)
Missing	36 (22)	19 (20)	17 (24)
Cytogenetic risk[a]			
Standard	87 (52)	51 (54)	36 (51)
High	23 (14)	13 (14)	10 (14)
Missing	56 (34)	31 (33)	25 (35)
Maintenance			
None	44 (27)	27 (28)	17 (24)
R	82 (49)	45 (47)	37 (52)
RP	40 (24)	23 (24)	17 (24)
Protocol			
RV-MM-EMN-441	73 (44)	43 (45)	30 (42)
GIMEMA-RV-MM-PI-209	93 (56)	52 (55)	41 (58)
Median follow-up, mo (IQR)	48 (45-52)	48 (44 -52)	47 (45-50)

Data presented as n (%), unless otherwise noted.
Abbreviations: HDT-ASCT = high-dose therapy with autologous stem cell transplantation; IQR, interquartile range; ISS = International Staging System; mo = months; R = lenalidomide; R-Alk = lenalidomide-alkylator based chemotherapy; RP = lenalidomide, prednisone; R-ISS = revised ISS.
[a]High-risk cytogenetics using fluorescence in situ hybridization (FISH) is defined by the presence of ≥1 of the following: del17p, t(4;14), or t(14;16).

maintenance, the advantage in terms of PFS, PFS2, and OS reported in CR patients treated with HDT-ASCT compared with R-Alk was confirmed in all subgroups (Figure 2).

To account for the different time points at which patients achieved a CR in the HDT-ASCT and R-Alk groups, we also conducted a sensitivity analysis of the entire patient population of the 2 trials examined, with CR as a time-dependent variable. The Cox model was also adjusted for age, sex, ISS stage, cytogenetic profile, and trial effect. This analysis confirmed the advantage in terms of PFS (HR, 0.52; 95% CI, 0.40-0.65; $P < .001$), PFS2 (HR, 0.54; 95% CI, 0.40-0.72; $P < .001$), and OS (HR, 0.51; 95% CI, 0.35-0.75; $P < .001$) for patients who underwent HDT-ASCT consolidation compared with those who received R-Alk consolidation.

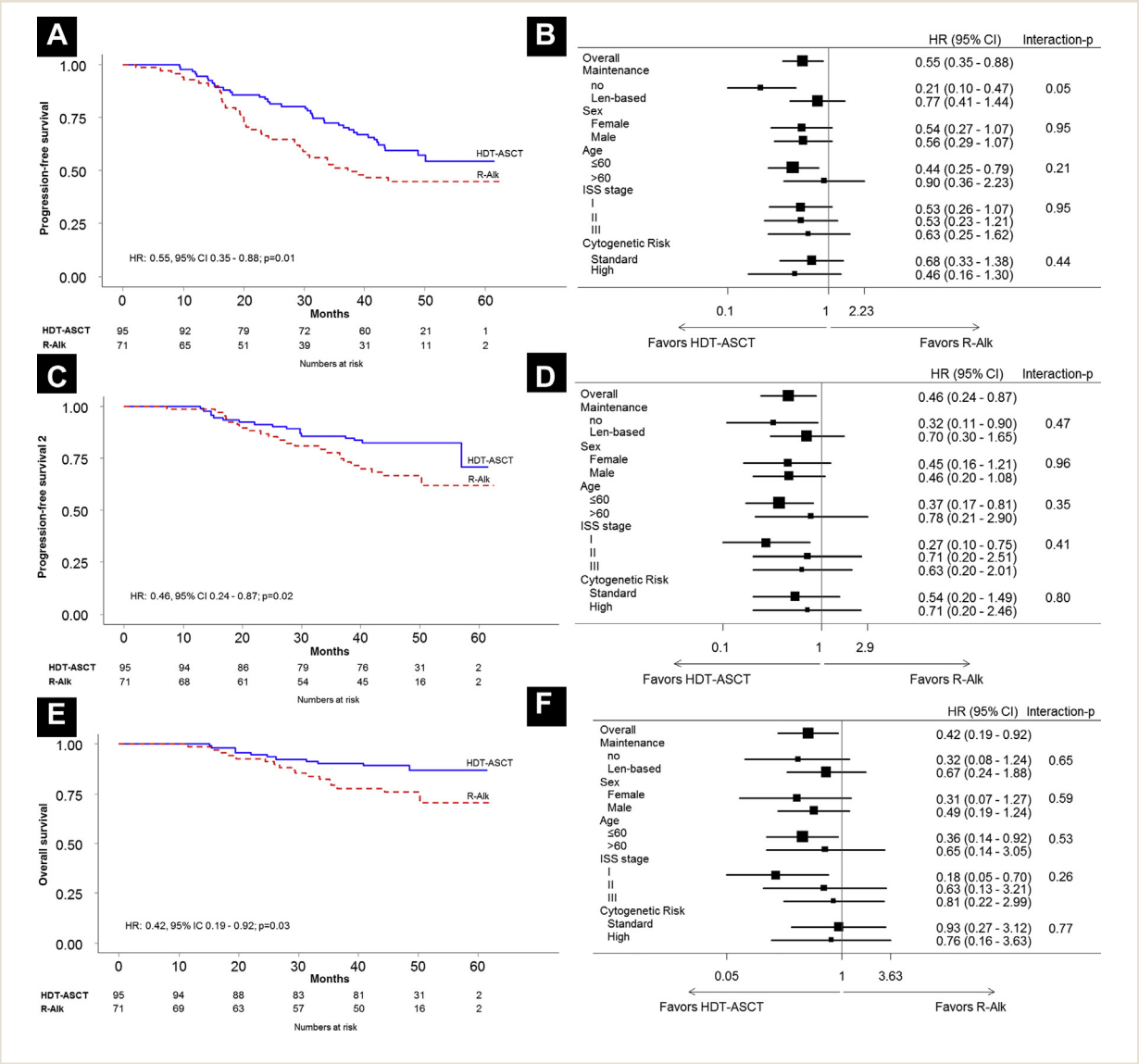
Effect of Consolidation Strategy on Survival Outcomes

To better describe the effect of consolidation treatment on the survival outcomes, we conducted an analysis that included only those patients who had reached a CR after the induction phase and before consolidation therapy (Figure 2). A total of 47 patients had attained a CR after the induction phase, 18 in the HDT-ASCT group and 29 in the R-Alk group. The patients with a CR after induction treatment who received HDT-ASCT consolidation had an improved PFS (4 years: 52% vs. 33%; HR, 0.55; 95% CI, 0.22-1.40; $P = .21$), PFS2 (4 years: 82% vs. 51%; HR, 0.42; 95% CI, 0.11-1.56; $P = .20$), and OS (4 years: 88% vs. 63%; HR, 0.50; 95% CI, 0.09-2.63; $P = .41$) compared with patients who had received R-Alk consolidation, although the difference was not statistically significant.

Effect of Maintenance on Survival Outcomes

To better define the role of maintenance treatment, we performed an analysis from the time of eligibility confirmation for maintenance that included those patients who had achieved a CR after consolidation therapy with either HDT-ASCT or R-Alk or during the first 3 months of the maintenance phase (Figure 3). Of these patients, 72 received maintenance therapy, 51 with R and 21

Figure 1 High-dose Therapy With Autologous Stem Cell Transplantation (HDT-ASCT) Versus Lenalidomide-Alkylator Based Chemotherapy (R-Alk). (A) Progression-free Survival (PFS); (B). PFS on Multivariate Analysis; (C) Second PFS (PFS2); (D) PFS2 on Multivariate Analysis; (E) Overall Survival (OS); and (F) OS on Multivariate Analysis



Abbreviations: CI = confidence interval; HR = hazard ratio; ISS = International Staging System; Len = lenalidomide.

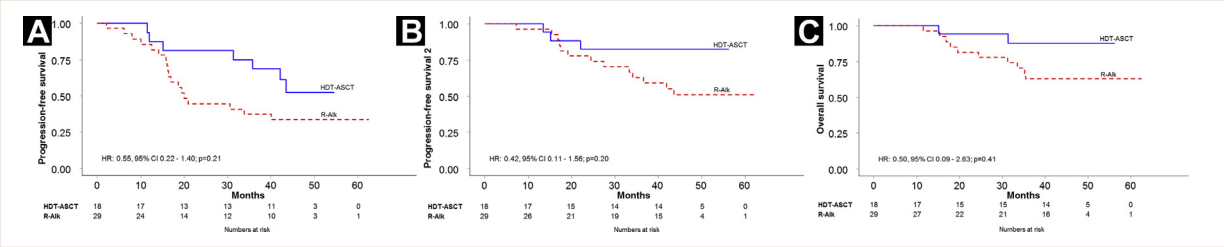
with RP; and 37 did not receive maintenance therapy. Patients in CR after the consolidation phase who received maintenance treatment displayed a better and statistically significant PFS_m (4 years: 54% vs. 19%; HR, 0.43; 95% CI, 0.21-0.86; $P = .02$) compared with those who did not receive maintenance. However, no differences were observed in terms of either PFS2_m (4 years: 72% vs. 58%; HR, 0.83; 95% CI, 0.35-1.97; $P = .67$) or OS_m (4 years: 79% vs. 72%; HR, 0.82; 95% CI, 0.26-2.56; $P = .73$).

A trend, although not statistically significant, toward better PFS_m (4 years: 71% vs. 47%; HR, 0.41; 95% CI, 0.14-1.21; $P = .11$), PFS2_m (4 years: 86% vs. 65%; HR, 0.38; 95% CI, 0.09-1.57; $P = .18$), and OS_m (4 years: 86% vs. 75%; HR, 0.41; 95% CI, 0.09-1.83; $P = .24$) was observed among patients who received RP maintenance compared with those who received R maintenance.

Discussion

ASCT and novel agents have dramatically improved the rate and quality of remissions, ultimately resulting in prolonged PFS and OS.[2-8] Several studies in the ASCT setting have confirmed the role of CR as a predictor of long-term PFS and OS.[2,3,21,24] In a meta-analysis of patients who had received HDT-ASCT, those who had obtained a CR after HDT-ASCT had a 38% reduced risk of progression or death and a 41% reduced risk of death compared with those patients without a

Figure 2 High-dose Therapy With Autologous Stem Cell Transplantation (HDT-ASCT) Versus Lenalidomide-Alkylator Based Chemotherapy (R-Alk). Analysis from Time to Eligibility Confirmation for Consolidation Phase. (A) Progression-free Survival (PFS), (B) Second PFS (PFS2), and (C) Overall Survival (OS)



Abbreviations: CI = confidence interval; HR = hazard ratio.

CR. Furthermore, a significant correlation between the achievement of CR after induction therapy and long-term PFS and OS was found.[22] Patients treated in Total-Therapy-Program (TT1, 2, and 3) who achieved a CR showed longer event-free survival and OS than those who did not, with the greatest benefit in patients with an early-onset and sustained CR (> 3 years).[25,26]

However, as previously suggested, CRs might not all be of the same quality. Among CR patients in the VISTA (Velcade as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone) study, the duration of the CR was 24 months with VMP and 12.8 with MP, suggesting deeper responses in patients who received bortezomib than in those who did not.[27]

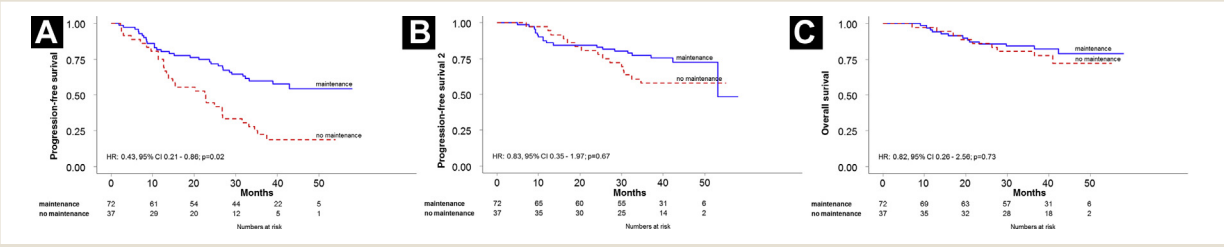
To assess the value of treatment intensification with different consolidation and maintenance strategies in CR patients, we evaluated 166 patients who achieved a CR and were randomized to either HDT-ASCT or R-Alk consolidation. Patients in the HDT-ASCT group experienced better and statistically significant PFS (5 years: 55% vs. 45%), PFS2 (5 years: 71% vs. 62%), and OS (5 years: 87% vs. 71%) compared with patients in the R-Alk group, and this benefit was independent of ISS status, cytogenetic risk, and maintenance therapy.

The incorporation of novel agents in the upfront treatment of MM patients has undoubtedly brought into question the role of HDT-ASCT consolidation. Several trials have been designed to compare HDT-ASCT with a nontransplant consolidation regimen. In the GIMEMA-RV-MM-PI-209 and RV-MM-EMN-441 trials, patients randomized to HDT-ASCT had significantly longer PFS (HR, 0.44 and 0.4, respectively) and OS (HR, 0.55 and 0.42, respectively) than those who received R-Alk consolidation.[11,12] The phase III HOVON65/EMN02 trial compared HDT-ASCT and VMP consolidation in ASCT-eligible patients.[13] The preliminary results showed that patients who underwent HDT-ASCT had a better PFS (HR, 0.76) compared with those who did not.[13] Even compared with a combination of RVD (lenalidomide, bortezomib, dexamethasone) consolidation, HDT-ASCT significantly prolonged PFS (HR, 0.65).[14]

In our analysis, although all the analyzed patients had achieved a CR, HDT-ASCT consolidation still induced superior survival outcomes compared with R-Alk consolidation. To better describe the role of HDT-ASCT, we narrowed our analysis to the subgroup of patients in CR before consolidation therapy. Again, the patients who received HDT-ASCT showed a trend toward better PFS (4 years: 52% vs. 33%), PFS2 (4 years: 82% vs. 51%), and OS (4 years: 88% vs. 63%) compared with the patients randomized to R-Alk consolidation. The lack of statistical significance likely resulted from the reduced number of patients included in this subgroup analysis and the low number of events observed.

One possible explanation for this finding could be the better depth of CR in terms of minimal residual disease (MRD) that was obtained with HDT-ASCT compared with R-Alk. Multiparameter

Figure 3 Maintenance Versus No Maintenance—Analysis From Time to Eligibility Confirmation for Maintenance Phase. (A) Progression-free Survival from maintenance (PFS_m), (B) Second PFS_m (PFS2_m), and (C) Overall Survival from Maintenance (OS_m)



Abbreviations: CI = confidence interval; HR = hazard ratio.

flow cytometry (sensitivity, 10^{-4}) analysis was performed to determine the presence of MRD in 50 patients in the RV-MM-EMN-441 study, 16 of whom had reached a CR. In that substudy, despite an equal number of patients achieving at least a very good partial response (VGPR), patients who received HDT-ASCT consolidation were more likely to reach MRD negativity (63%) than those who received R-Alk (37%). Likewise, in the IFM2009 trial comparing consolidation with HDT-ASCT versus RVD, patients in the ASCT group were more likely to obtain MRD negativity (79% vs. 65%; $P > .001$) than were the patients in the RVD arm.[14] However, for those with MRD-negative status (sensitivity, 10^{-6}), no differences in terms of outcomes were noted among the patients between the ASCT and RVD arms.[28] These data support our hypothesis that the advantage with HDT-ASCT compared with R-Alk in CR patients is likely attributable to the greater MRD negativity rate induced by HDT-ASCT. Also, the benefit of HDT-ASCT was seen in all subgroups included in the multivariate analysis, regardless of sex, ISS stage, cytogenetic risk determined by FISH, and maintenance treatment. Of note, the benefit with HDT-ASCT was greater in patients with low-risk disease by ISS (ISS stage I) than in those with high-risk disease (ISS stage II/III), possibly reflecting that a more sensitive disease benefits more from intensive treatment.

Lenalidomide has been extensively investigated as maintenance therapy for younger patients after HDT-ASCT.[11,12,15,16] In a meta-analysis of 3 phase III trials of patients with newly diagnosed MM, lenalidomide maintenance after HDT-ASCT significantly reduced the risk of progression or death by 52% and the risk of death by 25% compared with observation/placebo.[16] The PFS and OS advantage reported with lenalidomide was confirmed also in patients with a VGPR or a CR before maintenance. Moreover, as shown in the FIRST (Frontline Investigation of Revlimid and Dexamethasone Versus Standard Thalidomide) trial, continuous treatment in CR patients significantly prolonged the duration of response compared with fixed-duration treatment (median, 59 vs. 40 months).[29]

In the present analysis, we have confirmed the benefit of continuous treatment with lenalidomide even for patients in CR after HDT-ASCT. Lenalidomide maintenance resulted in a 68% reduction in the risk of progression or death compared with no maintenance. Longer follow-up is needed to detect any differences in terms of PFS2_m and OS_m between the 2 groups.

Because HDT-ASCT and novel agents have increased the chance of reaching a CR and because the achievement of a CR is associated with long-term survival, whether the achievement of a CR can be considered a reliable-enough endpoint to guide treatment selection is still under debate. However, the heterogeneity of outcomes with different MRD negativity rates in CR patients and the benefit displayed by HDT-ASCT and maintenance treatment in this population suggest that treatment intensification in patients with negative serum and urine immunofixation should be pursued with the goal of MRD negativity. Indeed, MRD is a stronger predictor of long-term outcomes compared with the standard CR and has, therefore, been incorporated into the updated International Myeloma Working Group response criteria published in 2016.[30] Whether the achievement of MRD negativity could be used to guide treatment decisions, such as intensification with HDT-ASCT or maintenance therapy, just as for other hematologic malignancies, needs to be addressed in clinical trials.[31,32]

The present study had some limitations. First, the lack of a comprehensive MRD data set of patients included in our analysis did not allow us to confirm whether the difference in survival outcomes between HDT-ASCT and R-Alk resulted from a different burden of residual disease. However, data from the MRD analysis conducted among a subset of patients in the RV-MM-EMN-441 study included in the present analysis and from the MRD study of patients in the IFM2009 study seemed to support this hypothesis. Another limitation was that patients included in the present analysis did not receive a PI as a part of their initial treatment. A 3-drug regimen combining either thalidomide or lenalidomide and a PI such as bortezomib has already been proved to be superior to a 2-drug regimen that includes thalidomide or lenalidomide as induction treatment before HDT-ASCT.[7,33] In a phase I/II trial, 20 of 22 patients (91%) in CR after upfront treatment with CRd (carfilzomib, lenalidomide, dexamethasone) had MRD-negative status. Similarly, in the relapse setting, 3-drug combinations such as DaraRd (daratumumab, lenalidomide, dexamethasone) or DaraVd (daratumumab, bortezomib, dexamethasone) resulted in greater CR and MRD negativity rates compared with 2-drug regimens.[34,35] However, as shown by the IFM2009 French study, even in patients treated with RVD, HDT-ASCT resulted in a greater CR rate and a doubling of MRD negativity compared with RVD consolidation, supporting the benefit of HDT-ASCT.

Conclusion

We have demonstrated that in patients who achieved a CR, consolidation with HDT-ASCT prolonged PFS, PFS2, and OS compared with the nontransplantation approach and that lenalidomide-based maintenance therapy induced a better PFS_m compared with no maintenance therapy. To the best of our knowledge, the present study is the first data set showing that, among CR patients, the choice of consolidation regimen continues to favor the use of HD-ASCT independently of ISS stage and cytogenetic risk. Our analysis also indirectly confirmed that the goal of MM treatment is to obtain sustained CR and MRD negativity.

Clinical Practice Points

- The role of HDT-ASCT in patients with newly diagnosed MM has been called into question by the introduction of novel agents.
- Nevertheless, ASCT remains a standard of care in this setting, as well as lenalidomide maintenance after ASCT, which has shown to prolong both PFS and OS.
- To address the role of ASCT and maintenance for patients attaining a CR, we conducted a pooled analysis among patients newly diagnosed, transplant-eligible MM patients enrolled in 2 phase III, randomized clinical trials (GIMEMA-RV-MM-PI-209 and RV-MM-EMN-441) to compare HDT-ASCT to R-Alk as consolidation therapy and R maintenance against no maintenance.
- Overall, the data from 166 patients with a CR were analyzed.
- CR patients who received HDT-ASCT had a better PFS (HR, 0.55; $P = .01$), PFS2 (HR, 0.46; $P = .02$), and OS (HR, 0.42; $P = .03$) compared with patients randomized to R-Alk.

- The survival benefit with HDT-ASCT was confirmed among all the subgroups, according to age, ISS stage, cytogenetic profile, and maintenance therapy.
- CR patients who received R-maintenance experienced a better PFS_m (4 years: 54% vs. 19%; HR, 0.43; $P = .02$) than those who received no maintenance.
- Our results have demonstrated that even in patients attaining a CR, the choice of HDT-ASCT consolidation, independently of ISS stage, cytogenetic risk, and prolonged lenalidomide-based maintenance, improves survival outcomes.

Disclosure

M.T.P. has received honoraria from and served on the advisory boards for Celgene, Janssen-Cilag, BMS, Amgen, and Takeda. F.P. has served on the advisory boards for Celgene and Janssen and has received lecturing fees from Amgen. L.D.P. has served on the advisory boards for AbbVie, Amgen, Celgene, and Janssen. R. R. has served on the speakers bureau for Janssen-Cilag, Celgene, Italfarmaco, Bristol-Myer Squibb, Amgen, and CSL Behring and on the advisory board for Janssen-Cilag and consulted for Amgen and CSL Behring. P.M. has received honoraria from Celgene, Janssen, Novartis, Bristol-Myers Squibb, Amgen, AbbVie, and Takeda. R.H. has received research grants from Celgene, Amgen, Takeda, Janssen, and Novartis and consulting fees from Janssen, Amgen, Celgene, Bristol-Myers Squibb, and Takeda. A.S. has received honoraria and research funding from Celgene. M.B. has received honoraria from Sanofi, Celgene, Amgen, Janssen, Novartis, AbbVie, and Bristol-Myers Squibb; research funding from Celgene, Janssen, Amgen, Bristol-Myers Squibb, Mundipharma, Novartis, and Sanofi. S.B. has received honoraria from Bristol-Myers Squibb, Celgene, Amgen, and Janssen, served on the advisory boards for Amgen and Janssen, and consulted for Takeda. The remaining authors have stated that they have no conflicts of interest.

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