Curative Strategy for High-Risk Smoldering Myeloma: Carfilzomib, Lenalidomide, and Dexamethasone (KRd) Followed by Transplant, KRd Consolidation, and Rd Maintenance

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ABSTRACT

PURPOSE Early treatment of high-risk smoldering myeloma has been shown to delay progression to multiple myeloma (MM). We conducted this trial with curative intention using a treatment approach employed for newly diagnosed patients with MM.

METHODS Patients with high-risk smoldering myeloma (>50% progression risk at 2 years) and transplant candidates were included and received induction therapy with carfilzomib, lenalidomide, and dexamethasone (KRd), six cycles, followed by high-dose melphalan (200 mg/m²) autologous stem-cell transplantation (HDM-ASCT), two KRd consolidation cycles, and Rd maintenance for 2 years. The primary end point was undetectable measurable residual disease (uMRD) rate by next-generation flow after ASCT. Sustained uMRD 4 years after ASCT was the secondary end point.

RESULTS Between June 2015 and June 2017, 90 patients were included, and 31% met at least one SixtyLightchain MRI (SLiM)-hypercalcemia, renal impairment, anemia, bone disease (CRAB) criterion. After a median follow-up of 70.1 months, 3 months after ASCT, in the intention-to-treat population, 56 (62%) of 90 patients had uMRD, and 4 years later, it was sustained in 29 patients (31%). Five patients progressed to MM, and the 70-month progression rate was 94% (95% CI, 84 to 89). The presence of any SLiM CRAB criteria predicted progression to MM (four of the five patients; hazard ratio, 0.12; 95% CI, 0.14 to 1.13; $P = .03$). Thirty-six patients showed biochemical progression, and failure to achieve uMRD at the end of treatment predicted it. The 70-month overall survival was 92% (95% CI, 82 to 89). Neutropenia and infections were the most frequent adverse events during treatment, resulting in one treatment-related death. Three second primary malignancies have been reported.

CONCLUSION Although a longer follow-up is needed, this curative approach is encouraging and more effective than active MM, with 31% of the patients maintaining the uMRD 4 years after HDM-ASCT.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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INTRODUCTION

Smoldering multiple myeloma (SMM) is an asymptomatic plasma cell disorder characterized by the presence of either a serum M-component of at least 3 g/dL or a plasma cell bone marrow (PCBM) infiltration ≥10% with the absence of end-organ damage.[1] In 2007, Kyle et al[2] published the outcome of 276 patients with SMM, highlighting the heterogeneity of this entity in progression to multiple myeloma (MM) or other diseases: 10% per year over the first 5 years following

CONTEXT

Key Objective

To evaluate an approach using carfilzomib, lenalidomide, and dexamethasone (KRd) induction followed by high-dose melphalan autologous stem-cell transplantation (HDM-ASCT), KRd consolidation, and lenalidomide maintenance for 2 years with curative intention in patients with high-risk smoldering myeloma.

Knowledge Generated

Of the 90 patients included in the trial, 40 (44%) sustained undetectable measurable residual disease (MRD) 4 years after HDM-ASCT. No safety concerns have been reported.

Relevance *(S. Lentzsch)*

The data are promising, indicating that almost one third of smoldering multiple myeloma (SMM) patients maintain undetectable MRD for 4 years following HDM-ASCT. However, this non-randomized study cannot fully address the impact of early treatment in SMM. A more extensive follow-up period is necessary to accurately ascertain the operational cure rate 10 years beyond therapy completion, and this study will lay the groundwork for future randomized trials.*

*Relevance section written by *JCO* Associate Editor Suzanne Lentzsch, MD, PhD.

diagnosis, 3% per year over the next 5 years, and 1.5% per year thereafter.

On the basis of these data, different models have been proposed to predict the risk of progression. The Mayo Clinic and Spanish Myeloma Group (GEM-Pethema) were the first to identify patients at high risk (50% progression risk at 2 years). The Mayo Clinic identified the high-risk subgroup based on serum M protein ≥3 g/dL and BMPC percentage ≥10, whereas the Spanish model was based on the presence of a clonal immunophenotype in ≥95% of plasma cells and immunoparesis.[2,3]

Although the standard of care for SMM was observation, the Spanish Myeloma Group conducted the QuiRedex trial, the first phase III trial comparing early treatment with lenalidomide plus dexamethasone (Rd) versus observation in 119 patients with high-risk–SMM,[4-6] and after a median follow-up of 12.5 years, the median time to progression (TTP) to MM and overall survival (OS) were 2.1 and 8.5 years, respectively, in the observation arm versus 9.5 years and not reached in the Rd arm. Lonial et al[7] reproduced the results comparing lenalidomide (R) alone with observation. Several other phase II studies have investigated the efficacy of triplets using Rd as backbone, in combination with elotuzumab, ixazomib, or carfilzomib (K).[8-10] Carfilzomib, lenalidomide, and dexamethasone (KRd) followed by R maintenance was evaluated in 54 patients, and the undetectable measurable residual disease (uMRD) complete response (CR) rate was 70.4%. In addition, daratumumab monotherapy was investigated in the Centaurus trial, and although the CR rate was <10%, the median progression-free survival (PFS), including an extension phase, was approximately 80 months. Two phase III randomized trials are ongoing comparing Rd with or without anti CD38 antibodies. The ASCENT trial is also based on D-KRd with encouraging preliminary data.[11] Finally, teclistamab has shown promising efficacy in 12 patients.[12]

The Spanish Myeloma Group, on the basis of the previous studies and the new agents developed in MM, designed a clinical trial with a curative intention. Accordingly, we planned a phase II study with a treatment schedule like that used for newly diagnosed patients with MM eligible for high-dose melphalan autologous stem-cell transplantation (HDM-ASCT). Here, we present the results of the first analysis once all 90 patients completed the planned treatment.

METHODS

Trial Design, Oversight, and Treatment

In this nonrandomized, open-label, multicenter phase II trial, eligible patients received induction therapy with six 4-week induction cycles consisting of intravenous carfilzomib at doses of 20/36 mg/m^2 once daily on days 1-2, 8-9, and 15-16; oral lenalidomide 25 mg once daily on days 1 to 21; and dexamethasone 40 mg once a week (KRd). After induction, ASCT was performed with melphalan 200 mg/m^2 as conditioning regimen (HDM-ASCT), and peripheral blood stem-cell mobilization using granulocyte colony-stimulating factor as the mobilizer was planned after the fourth induction cycle. Consolidation was scheduled 3 months after ASCT and was based on two 4-week KRd cycles, and subsequently, the patients received maintenance for 2 years with R at a dose of 10 mg on days 1-21 plus dexamethasone at a dose of 20 mg once a week.

The study was approved by the ethics committees of all the participating centers. All the participants provided written informed consent before performing any study-related

procedures. This study was registered at ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT02415413).[13]

Patients

For eligibility, patients were required to have been diagnosed with high-risk–SMM within 5 years before inclusion in the study. Patients were required to be between age 18 and 70 years and eligible for HDM-ASCT with an Eastern Cooperative Oncology Group performance status of 0-1. The diagnosis of SMM was based on the IMWG criteria published in 2010, and a high risk of progression to MM was defined according to either the Mayo 2008 model or the GEM-Pethema model. It should be highlighted that since the trial was designed in 2013, before implementation of the SixtyLightchain MRI (SLiM)-hypercalcemia, renal impairment, anemia, bone disease criteria, ultra–high-risk SMM presenting one or more of the following markers was included: more than one focal lesion on MRI, clonal PCBM infiltration ≥60%, or ratio of involved/uninvolved sFLC >100.[14] However, to evaluate the absence of lytic bone disease, low-dose computerized tomography (CT) or positron emission tomography (PET-CT) was mandatory; if normal, whole-body or dorso/lumbar/pelvis MRI was mandatory to exclude the presence of focal lesions.

End Points and Assessments

The primary end point was uMRD rate 3 months after HDM-ASCT. This end point was defined by the absence of phenotypically abnormal PCs in the BM using EuroFlow standard analysis recommendations to detect MRD in MM (minimum sensitivity of one cell in 10^5 nucleated cells).[15]

The secondary end point was sustained uMRD rate at 3 and 5 years after HDM-ASCT. Three years after HDM-ASCT coincided with the SARS-CoV-2 pandemic, the protocol was amended to evaluate the sustained uMRD rate 4 and 5 years after HDM-ASCT. MRD studies were centralized in the three core laboratories of the Spanish GEM-Pethema group.

Patients missing an MRD evaluation were considered to have detectable MRD. For the analysis of the sustained uMRD rate, patients were considered negative if they were negative after HDM-ASCT and maintained the negative status at 4 and 5 years after HDM-ASCT. According to the intention-to-treat (ITT) principle, patients who were positive after transplant, missed the follow-up evaluation, or had a detectable MRD evaluation 4 and 5 years after transplant were considered to have nonsustained MRD.

Other secondary end points were response rates after the different phases of treatment assessed according to the IMWG criteria.[15] TTP to symptomatic disease, PFS, and OS were also evaluated and defined as follows: TTP as the time since inclusion in the trial to the development of symptomatic MM defined by the presence of end-organ damage; PFS as the time since inclusion in the trial to the development of either symptomatic MM or death, whatever occurs first; and OS as the time from inclusion to death of any cause. Time to biochemical progression (TTBP) was defined as the time since inclusion in the trial to biochemical progression defined by biochemical relapse/progressive disease according to the IMWG criteria; of note, under this term, we also included ultrasensitive MRD relapse defined by the reappearance of MRD confirmed at least 2 months apart. Patients experiencing biochemical progression had the opportunity to receive rescue therapy with daratumumab in combination with pomalidomide and dexamethasone (DPd). This approach was included as an amendment to the protocol for a separate analysis.

The safety profile was also evaluated across the different phases of treatment by evaluating the incidence, severity, and type of adverse events (AEs) that were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Statistical Analysis

The rate of uMRD 3 months after HDM-ASCT was the primary end point, carried out in the ITT population, which included all enrolled patients who had begun treatment.

For the calculation of the sample size, there were no previous data with this approach for SMM. As the treatment schedule was similar to that used in newly diagnosed MM, we considered 34% of uMRD after HDM-ASCT as control based on our results of 206 patients treated with a similar schedule.[16] We hypothesized that the percentage of patients with uMRD after HDM-ASCT would increase by up to 50%. The chosen parameters were $\alpha = .05$ and $\beta = .11$. The sample size was calculated using PASS software, given that the required number of patients was 82, and if we assume a dropout rate of 10%, 90 patients should be included in the study. A subanalysis was planned to evaluate the percentage of patients with uMRD 3 and 5 years after HDM-ASCT; however, because of the COVID-19 pandemic, the time point changed to uMRD 4 years after transplantation.

The Kaplan-Meier method was used to characterize event time distributions, and the corresponding treatment hazard ratio was estimated using a stratified Cox regression model to compare outcomes based on baseline characteristics and MRD status. To address the immortal time bias, the analyses conducted to evaluate the impact of achieving uMRD sustained over time were landmarked at the end of maintenance.

RESULTS

Patients and Treatment

Between June 2015 and June 2017, 126 patients were screened, of which 36 were screening failures, with the most frequent reason being the presence of lytic lesions on CT or PET/CT.

Ninety patients started treatment, and the disposition of the patients in this study is shown in Figure 1. Baseline demographic and disease characteristics are shown in Table 1.

The cutoff date for analysis was October 2022; all patients had completed the treatment phase, and the median follow-up time was 70.1 (range, 28.4-89.9) months.

Efficacy

According to the ITT analysis, 3 months after HDM-ASCT, 56 (62%) of 90 patients had uMRD. At the end of the treatment phase, after completing maintenance therapy, 48 patients (53%) had uMRD, and 4 years after HDM-ASCT, the sustained uMRD rate was 31% (Appendix Table A1, online only)

The overall response rate (ORR) and different response categories across the different phases of the study are presented in Table 2. No significant differences were observed between high-risk and SMM with any SLiM criteria in terms of serological responses, but the uMRD rate at the end of maintenance was higher in high-risk (59%) compared with those with any SLiM criteria (39%; Appendix Table A2).

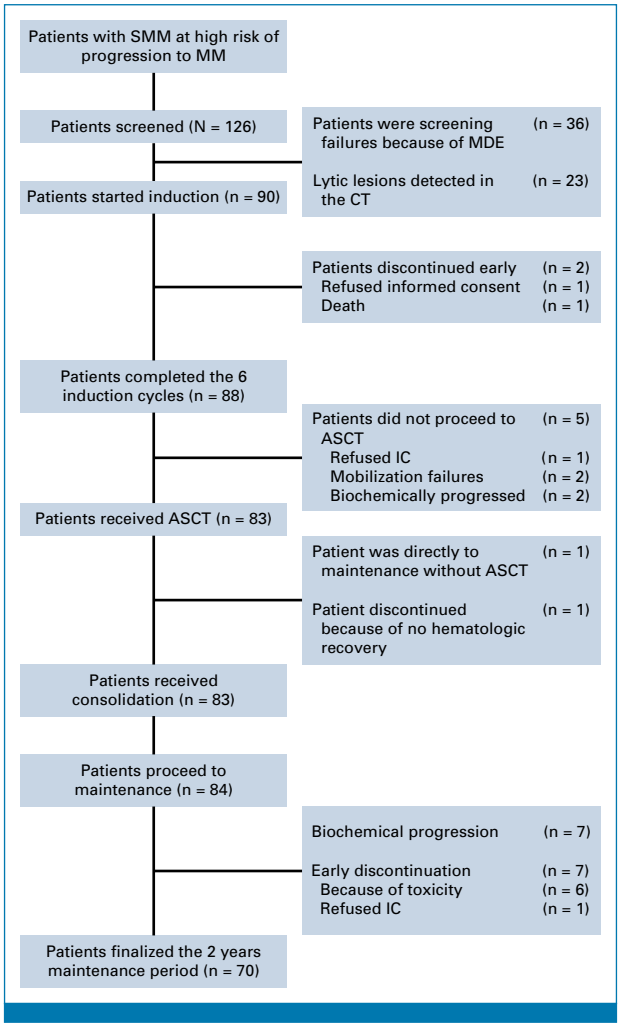

FIG 1. Disposition of patients. ASCT, autologous stem-cell transplantation; CT, computed tomography; IC, informed consent; MDE, myeloma-defining event; SMM, smoldering multiple myeloma.

TABLE 1. Baseline Characteristics of the Patients Included in the Study

Characteristic	All Patients (N = 90)
Median age (range), years	59 (33-70)
Serum/urine, median (range) M-component (g/dL/g/24 h urine)	2.77 (0-8.6)/0.43 (0-7.2)
Plasma cell bone marrow infiltration, median (range), %	22 (10-80)
Time from diagnosis of the precursor disease to being high-risk SMM, median (range)	1.7 (0.03-59.80)
High-risk model, No. (%)	
Mayo clinic only	19 (21)
Spanish only	48 (53)
Both	26 (27)
SLiM-CRAB criteria, No. (%)	28 (31)
sFLC >100	18 (20)
>1 focal lesion in MRI	9 (10)
≥60% PCBMI	7 (8)
PET + w/o lytic lesions, No. (%)	5 (6)
Cytogenetic abnormalities, No. (%)	
Standard risk	54 (63)
High-risk (t(4;14), t(14;16), del17)	26 (29)
High-risk (t(4;14), t(14;16), del17, 1q abnormalities)	51 (57)
Unknown	5 (6)

Abbreviations: CRAB, hypercalcemia, renal impairment, anemia, bone disease; dL, deciliter; g, grams; MRI, magnetic resonance imaging; PCBMI, plasma cell bone marrow infiltration; PET, positron emission tomography; sFLC, serum-free Light Chain; SLiM, SixtyLightchain MRI; SMM, smoldering multiple myeloma; t, translocation; w/o, without.

Time-To-Event End Points

Overall, 36 patients had biochemical progression (40%), nine during the treatment period (Table 2) and 27 during the follow-up period once they had finalized the treatment. These biochemical relapses included eight patients (9%) with biochemical progression, 20 patients (22%) with biochemical relapse from complete remission, and eight patients (9%) with ultrasensitive MRD relapse. The 70-month TTBP was 59% (95% CI, 66 to 76; Fig 2A). Eleven (25%) of 43 patients who completed the maintenance and achieved uMRD experienced biochemical progression versus 15 (55%) of 27 patients in whom the MRD was detectable (hazard ratio [HR], 0.29 [95% CI, 0.13 to 0.66]; P = .003; Fig 2B).

The analysis of other baseline characteristics showed that the presence of at least one high-risk cytogenetic abnormality (HRCA) according to the IMWG resulted in a

TABLE 2. Response Rates Observed Across the Different Phases of the Study in the Intention-To-Treat Patient Population

Response Category	Induction (N = 90)	HDM-ASCT (N = 90)	Consolidation (N = 90)	Maintenance (N = 90)
ORR, No. (%)	85 (94)	82 (91)	85 (94)	80 (95)
≥Complete remission, No. (%)	37 (41)	54 (60)	64 (70)	58 (64)
VGPR, No. (%)	35 (39)	17 (19)	14 (16)	9 (10)
PR, No. (%)	13 (14)	11 (12)	7 (8)	3 (3)
SD, No. (%)	1 (1)	1 (1)	—	—
Progressive disease, No. (%)	2 (3)[a]	—	—	7 (7)[b]
Biochemical progression, No. (%)	2 (2)	—	—	7 (7)
Not evaluable,[c] No. (%)	2 (3)	7(8)	5 (5)	13 (14)
Undetectable measurable residual disease by NGF and 10^{-5}, No. (%)		56 (62)		48 (53)

Abbreviations: HDM-ASCT, high-dose melphalan autologous stem-cell transplantation; NGF, next-generation flow; ORR, overall response rate; PR, partial response; SD, stable disease; VGPR, very good partial response.
[a]Two patients biochemically progressed during induction and one of them progressed to myeloma.
[b]Seven patients biochemically progressed during maintenance and one of them progressed to myeloma.
[c]The patients not evaluable included early discontinuations before each phase of treatment for several reasons included in the flow chart.

higher risk of biochemical progression (70 months TTBP: 38% *v* 67%, HR, 0.42 [95% CI, 0.22 to 0.81]; $P = .01$), and the same effect was maintained when abnormalities of 1q were included (70 months TTBP: 45% *v* 75%, HR, 0.40 [95% CI, 0.18 to 0.85]; $P = .018$; Appendix Figs A1A and A1B). The presence of any SLiM criteria showed a trend to a higher risk of biochemical progression (12 [38.7%] of 31 patients) compared with those without (18 [30.5%] of 59 patients), but the difference was not statistically significant.

In the case of biochemical progression, patients were offered to be included in a subsequent trial with daratumumab plus pomalidomide and dexamethasone (D-Pd). Twenty-one patients have so far been included.

Overall, five patients progressed to MM, two during the treatment phase and three during follow-up. In four patients, the progression was first biochemical. The 70-month TTP was 94% (95% CI, 84 to 89; Fig 3A). As mentioned above, 28 patients presented with any one SLiM biomarker. Although their response rate was not different from that observed in the standard high-risk–SMM population (Appendix Table A2), the presence of any SLiM biomarker predicted progression to MM (HR, 0.10 [95% CI, 0.01 to 0.96]; $P = .046$; Fig 3B).

Seven patients died: three due to progressive disease, one due to early death from respiratory infection and treatment-related disease, two because of second primary malignancies, and one because of cardiac arrest at home. The 70-month OS rate was 92% (95% CI, 82 to 89; Fig 3C).

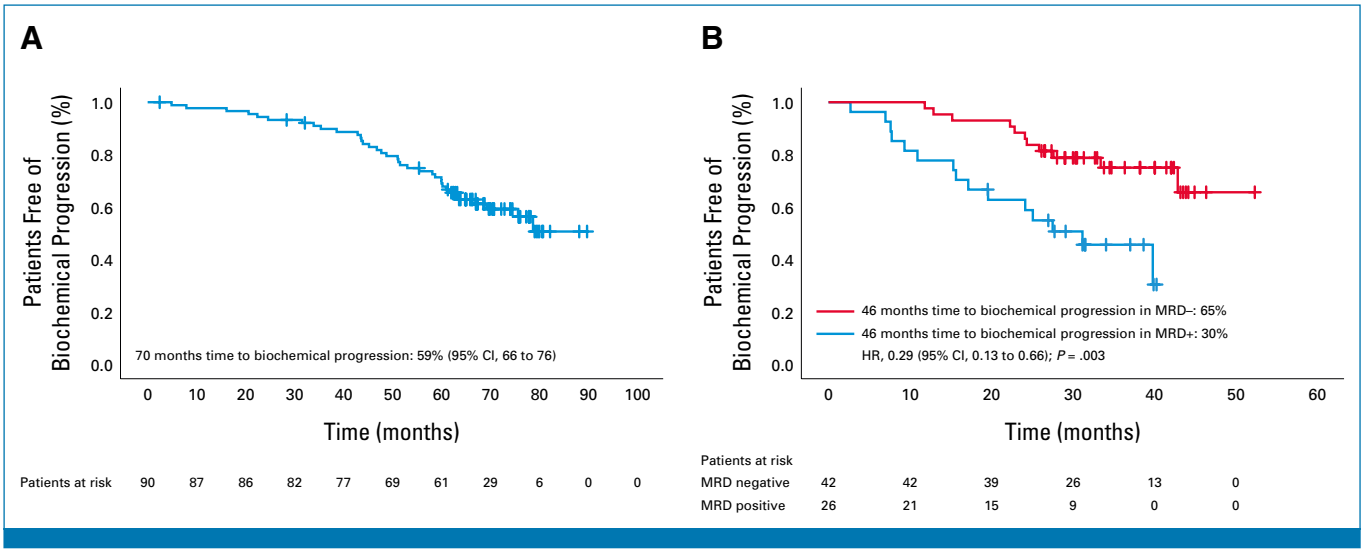

FIG 2. Kaplan-Meier estimates of (A) time to biochemical progression and (B) landmark time to biochemical progression by MRD status at the end of maintenance. MRD, measurable residual disease.

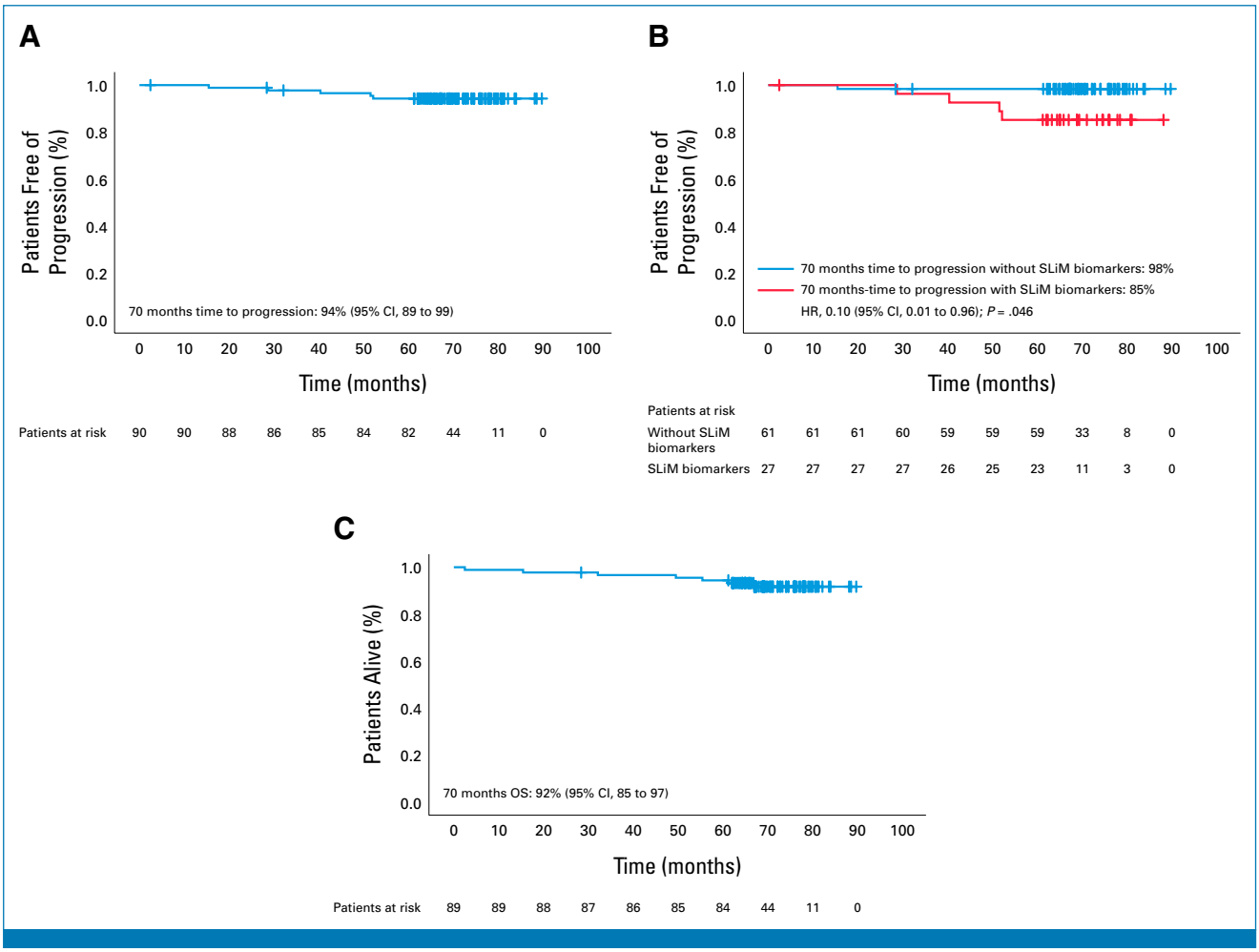

FIG 3. Kaplan-Meier estimates of (A) TTP to myeloma; (B) TTP to myeloma by the presence of any SLiM-CRAB criteria; and (C) OS in the ITT population, which included all patients who started treatment. CRAB, hypercalcemia, renal impairment, anemia, bone disease; ITT, intention-to-treat; MRI, magnetic resonance imaging; OS, overall survival; SliM, SixtyLightchain MRI; TTP, time to progression.

Safety

During the induction phase, three (3%) and five (5%) patients developed grade 3 to 4 neutropenia and thrombocytopenia, respectively. Grade 3 to 4 infections occurred in nine patients (10%), skin rash in eight patients (9%), and G3 cardiac failure was the only cardiologic event reported, presenting in one patient.

Peripheral blood stem-cell collection was planned after the fourth induction cycle, but two patients had previously discontinued treatment; therefore, the process was performed in 88 patients. Only six patients (7%) required plerixafor as a mobilizer. After a median of one apheresis, the mean number of CD34+ cells collected was 4×10^6/kg $\pm$ 2.7×10^6/kg. There were two mobilization failures that proceeded directly to consolidation. HDM followed by ASCT was performed in 83 patients, and all but one were engrafted. Neither transplant-related mortality nor other relevant toxicities were reported.

Eighty-one patients proceeded to consolidation, and eight patients (9%) developed grade 3 to 4 neutropenia and thrombocytopenia. Four patients (5%) developed grade 3 to 4 infections. During maintenance therapy, grade 3 to 4 neutropenia was reported in 20% of patients, and 9% developed any grade 3 to 4 infections (Table 3).

Overall, nine patients discontinued treatment early because of toxicity: one patient during induction due to respiratory infection complicated with massive ischemic stroke resulted in the only treatment-related death; one patient after ASCT because of nonengraftment; seven patients during maintenance mainly because of neutropenia and gastrointestinal toxicity; and one patient who suffered cardiac arrest at home, which was considered nonrelated.

Three patients (3%) developed second primary malignancies: prostate cancer in a patient with a history of prostate hyperplasia who remained alive; lung cancer in another patient with multiple additional risk factors who died with

TABLE 3. Safety Profile Through the Different Phases of the Protocol

Adverse Event (N = 90)	Induction Overall/G3-4, No. (%)	Consolidation Overall/G3-4, No. (%)	Maintenance Overall/G3-4, No. (%)
Hematologic			
Neutropenia	9 (10)/3 (3)	14 (16)/8 (9)	28 (31)/21 (23)
Thrombocytopenia	11 (12)/4 (4)	14 (16)/7 (8)	13 (14)/3 (3)
Anemia	11 (12)/—	8 (9)/—	8 (9)/—
Nonhematologic			
General symptomatology	20 (22)/2 (2)	4 (5)/—	23 (25)/1 (1)
G-I toxicity	19 (21)/2 (2)	5 (6)/—	23 (25)/6 (7)
Skin rash	20 (22)/8 (9)	1 (1)/—	1 (1)/—
Infections	22 (24)/9 (10)[a]	11 (12)/5 (6)	32 (36)/8 (9)
Cardiac events	1 (1)/1 (1)	—/—	1 (1)/—
SPM			3 (4)[b]

Abbreviations: G, Grade; G-I, Gastro International; SPM, second primary malignancies.
[a]Infection was G5 in one patient who died because of massive ischemic stroke after a respiratory infection.
[b]The three second primary malignancies were lung cancer, prostate cancer, and myelodysplastic syndrome.

uMRD; and myelodysplastic syndrome in the third patient, who had no known risk factors but died. This latter case occurred under the rescue therapy the patient was receiving because of progression to active MM, whereas the two solid second primary malignancies emerged during the maintenance period.

DISCUSSION

This clinical trial was designed pursuing the goal of cure for high-risk–SMM through an intensive treatment approach.

The primary end point was the uMRD rate 3 months after HDM-ASCT, which was achieved in 62% of the patients using the ITT analysis, and the trial met its primary end point. We evaluated the sustained uMRD rate planned at 3 and 5 years after ASCT but modified at 4 years because of COVID-19; 28 patients (31%) achieved this goal in the ITT population. We hypothesized that this rate could be 50% after 3 years of ASCT, but the assumption was empirical. Continuous follow-up in this group is required to see if sustained uMRD can be considered as surrogate for cure.

In line with this, Hill et al[10] have recently shown the results of 54 patients with high-risk–SMM treated with KRd eight cycles, followed by R maintenance for 24 months, a similar design but without ASCT. The primary end point was uMRD CR rate at the end of induction, and it was 70%; the sustained uMRD over 2 years was 39%. In our study, uMRD in clinical remission patients after induction was 67% and 88% after consolidation. The sustained uMRD at 4 years was 31%. Both studies indicate that this approach is very effective in patients with high-risk–SMM.

The ASCENT trial is also pursuing a curative objective in high-risk–SMM, but the approach was based on D-KRd, fixed duration as well, and without ASCT.[11] The follow-up was shorter, 26 months, but the 64% stringent complete response (sCR)/CR rate was similar to that of ours.

An alternative of particular interest for frail high-risk–SMM or with comorbidities would be the use of a gentle treatment with Rd, evaluated in the QuiRedex trial, which led to a median TTP of 9.5 years.[5]

To explore the value of early intervention, we also wanted to compare the efficacy of the current trial in SMM with other similar trials but conducted in NDMM. In the phase III randomized Perseus study, D-VRd and VRd as part of the induction and consolidation after HDM-ASCT resulted in an uMRD rate after consolidation of 57.5% and 32.5%, respectively, and these rates are not superior to our data.[17] In the ISKIA study, in which carfilzomib is the proteasome inhibitor, the uMRD rates after induction and consolidation with isatuximab-KRd or KRd following ASCT were 77% and 67%, respectively, and these data are not very different from ours, especially in the arm without monoclonal antibody.[18] As far as uMRD evaluation over time in other trials, the phase II randomized Griffin study reported 44% of uMRD sustained at 1 year after D-VRD, HDM-ASCT, D-VRD, and DR maintenance,[19] and in the FORTE study, KRd followed by ASCT and KRd consolidation followed by maintenance with KR or R, the sustained uMRD rate at 1 year was 47%.[20] These results appear to be inferior to the 65% uMRD rate at 1 year in our study in the ITT population (data not shown). Overall, these data suggest that the sustained uMRD rate is higher in high-risk–SMM than in MM upon treatment with similar approaches, and therefore, the probabilities for operational cure would increase with early intervention. In our study, the only feature predicting progression to MM was the presence of any SLiM biomarker, now incorporated into the definition of MM, which would reinforce this hypothesis.

We decided to evaluate TTBP because of the nature of this disease, without myeloma-defining events, and because we observed that most biochemical relapses occurred after maintenance ended. Interestingly, failure to achieve uMRD at the end of maintenance predicted biochemical progression. Thus, a potential strategy could be to intensify or prolong maintenance to eradicate residual tumor cells.

A potential limitation is the MRD sensitivity level established here, specifically 10^{-5}. To overcome this limitation, we also evaluated MRD at a sensitivity level of 10^{-6} as an exploratory objective, and 4 years after HDM-ASCT, 24 patients had sustained negative MRD and had not yet progressed. Another limitation is the frequency of MRD assessment according to the IMWG, that is, annual. Biochemical progression was detected in only eight patients using MRD, and new sensitive techniques, such as next blood flow and mass spectrometry, will allow to monitor MRD more frequently in peripheral blood.

The safety profile was acceptable. After the induction and consolidation phases, the incidence of G3-4 neutropenia was comparable (3% and 9%, respectively) with that reported in the ASCENT trial with D-KRd (10%) and slightly inferior compared with that reported in the Hill's trial (22%,) but patients received eight cycles.[10] In the ASCENT trial, four patients presented with pneumonia; in the Hill's study, three presented with pneumonia; and in our study, two presented with pneumonia. During maintenance, G3-4 neutropenia (20%) and infections (9%) were the most frequent investigator-based lenalidomide-related AEs, like the rates reported by Hill et al (17% of G3-4 neutropenia with infections not reported). Three patients developed SPMs, a figure that is not different from the four cases reported in the Hill's study, although we cannot exclude that the genotoxic effect of melphalan could have influenced more aggressive tumors and the role of HDM can be questionable.

Despite this and another data, the role of early treatment continues to be a matter of debate, and there is a phase III randomized study comparing daratumumab single agent with observation based on the positive data reported with daratumumab monotherapy in the CENTAURUS study.[21] There are two phase III trials ongoing with registrational purposes comparing Rd ± anti-CD38 monoclonal antibodies. Moreover, immunotherapy approaches targeting B-cell maturation antigen (BCMA) through chimeric antigen receptor T lymphocytes (CAR-T) or CD3 bispecific monoclonal antibodies are also planned for high-risk–SMM, and very encouraging data have been reported in a preliminary study with teclistamab in this population (100% of uMRD after two cycles of treatment).[12]

In summary, our curative approach for high-risk–SMM with a schedule comparable with that used in newly diagnosed patients with MM seems to be encouraging, with nearly one third of the patients maintaining MRD as undetectable 4 years after HDM-ASCT. However, a longer follow-up period is required to show the true operational cure rate at 10 years beyond the end of therapy.

AFFILIATIONS

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Curative Strategy for High-Risk Smoldering Myeloma: Carfilzomib, Lenalidomide, and Dexamethasone (KRd) Followed by Transplant, KRd Consolidation, and Rd Maintenance

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APPENDIX

TABLE A1. Undetectable Measurable Residual Disease Across the Different Phases of Therapy, Including the Sustained uMRD 4 Years After ASCT in the Intention-To-Treat Population

Response Category	Induction (N = 90), No. (%)	HDM-ASCT (N = 90), No. (%)	Consolidation (N = 90), No. (%)	Maintenance (N = 90), No. (%)	4 years after ASCT (N = 90), No. (%)
Undetectable measurable residual disease by NGF and 10^{-5}	36 (42)	56 (62)	61 (68%)	48 (53)	28 (31)

Abbreviations: HDM-ASCT, high-dose melphalan autologous stem-cell transplantation; NGF, next-generation flow.

TABLE A2. Response Rates in Patients Included in the Study by the Presence of Any SLiM CRAB Criteria

	Induction		HDM-ASCT		Consolidation		Maintenance	
Response Category	High Risk (n = 62), No. (%)	Ultra High Risk (n = 28), No. (%)	High Risk (n = 62), No. (%)	Ultra High Risk (n = 28), No. (%)	High Risk (n = 62), No. (%)	Ultra High Risk (n = 28), No. (%)	High Risk (n = 62), No. (%)	Ultra High Risk (n = 28), No. (%)
ORR	59 (95)	26 (93)	57 (92)	25 (89)	59 (95)	26 (93)	61 (98)	19 (68)
≥Complete remission	26 (42)	11 (39)	38 (61)	16 (57)	44 (71)	20 (71)	42 (68)	16 (57)
VGPR	25 (40)	10 (36)	12 (19)	5 (18)	11 (12)	3 (11)	8 (13)	1 (4)
PR	8 (13)	5 (18)	7 (11)	4 (14)	4 (6)	3 (11)	1 (2)	2 (7)
SD	1 (2)	—	1 (2)	—	—	—	—	—
Progressive disease	1 (2)	1 (4)[a]	—	—	—	—	3 (5)	4 (14)[b]
Biochemical progression	1 (2)	1 (4)					3 (5)	4 (14)
Not evaluable[c]	1 (2)	1 (4)	4 (6)	3 (11)	4 (6)	1 (4)	8 (13)	5 (18)
Undetectable measurable residual disease by NGF and 10^{-5}[d]	23/62 (37)	13/28 (46)	41/62 (66)	15/28 (54)	43/62 (69)	18/28 (64)	37/62 (59)	11/28 (39)

Abbreviations: CRAB, hypercalcemia, renal impairment, anemia, bone disease; HDM-ASCT, high-dose melphalan autologous stem-cell transplantation; MRI, magnetic resonance imaging; ORR, overall response rate; PR, partial response; SD, stable disease; SLiM, SixtyLightchain MRI; VGPR, very good partial response.

[a]This patient progressed biochemically and subsequently to myeloma.

[b]Four patients biochemically progressed and one of them progressed to myeloma.

[c]The reasons for not being evaluable are represented in the flow chart.

[d]This rate is evaluated in the intention-to-treat population.

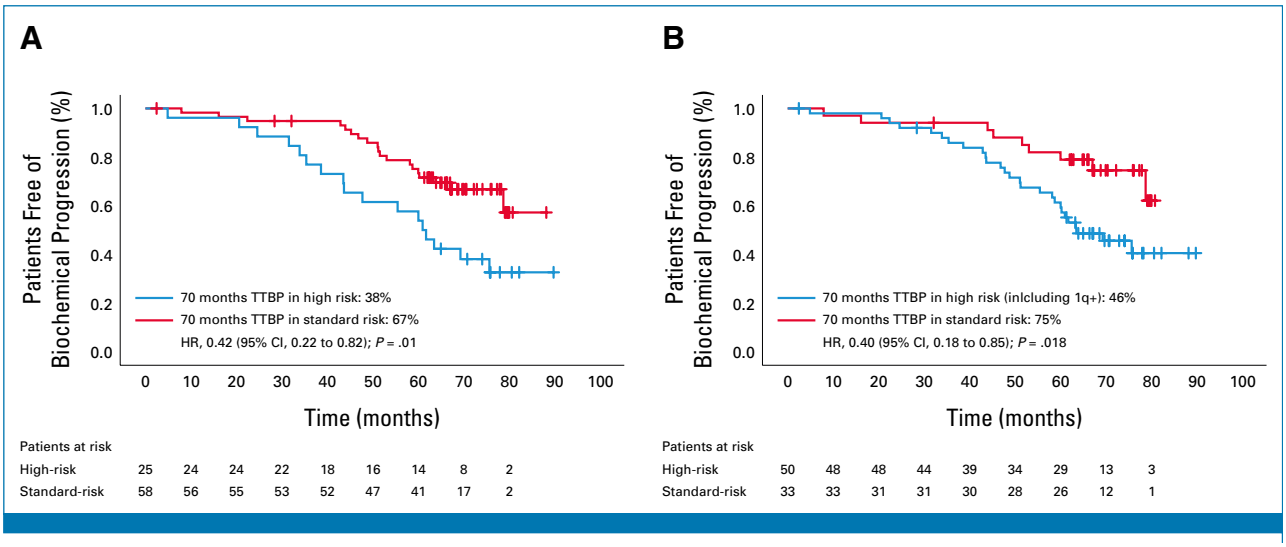

FIG A1. (A) Time to biochemical progression by the presence of HRCAs according to the International Myeloma Working Group [t(4;14), t(14;16) and/or del(17/17p). (B) Time to biochemical progression by the presence of HRCAs according to the International Myeloma Working Group [t(4;14), t(14;16) and/or del(17/17p)] plus abnormalities on 1q chromosome. HRCA, high-risk cytogenetic abnormalities; TTBP, time to biochemical progression.