

Original Investigation

Treatment With Carfilzomib-Lenalidomide-Dexamethasone With Lenalidomide Extension in Patients With Smoldering or Newly Diagnosed Multiple Myeloma

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IMPORTANCE Carfilzomib-lenalidomide-dexamethasone therapy yields deep responses in patients with newly diagnosed multiple myeloma (NDMM). It is important to gain an understanding of this combination's tolerability and impact on minimal residual disease (MRD) negativity because this end point has been associated with improved survival.

OBJECTIVE To assess the safety and efficacy of carfilzomib-lenalidomide-dexamethasone therapy in NDMM and high-risk smoldering multiple myeloma (SMM).

DESIGN, SETTING, AND PARTICIPANTS Clinical and correlative pilot study at the National Institutes of Health Clinical Center. Patients with NDMM or high-risk SMM were enrolled between July 11, 2011, and October 9, 2013. Median follow-up was 17.3 (NDMM) and 15.9 months (SMM).

INTERVENTIONS Eight 28-day cycles were composed of carfilzomib 20/36 mg/m² on days 1, 2, 8, 9, 15, and 16; lenalidomide 25 mg on days 1 through 21; and dexamethasone 20/10 mg (cycles 1-4/5-8) on days 1, 2, 8, 9, 15, 16, 22, and 23. Patients who achieved at least stable disease subsequently received 24 cycles of lenalidomide extended dosing.

MAIN OUTCOMES AND MEASURES Primary end points were neuropathy of grade 3 or greater (NDMM) and at least very good partial response rates (SMM). Minimal residual disease was also assessed.

RESULTS Of 45 patients with NDMM, none had neuropathy of grade 3 or greater. Of 12 patients with high-risk SMM, the most common of any-grade adverse events were lymphopenia (12 [100%]) and gastrointestinal disorders (11 [92%]). All patients with SMM achieved at least a very good partial response during the study period. Among the 28 patients with NDMM and the 12 with SMM achieving at least a near-complete response, MRD negativity was found in 28 of 28 (100% [95% CI, 88%-100%]), 11 of 12 (92% [95% CI, 62%-100%]) (multiparametric flow cytometry), 14 of 21 (67% [95% CI, 43%-85%]), and 9 of 12 (75% [95% CI, 43%-94%]) (next-generation sequencing), respectively. In patients with NDMM, 12-month progression-free survival for MRD-negative vs MRD-positive status by flow cytometry and next-generation sequencing was 100% vs 79% (95% CI, 47%-94%; $P < .001$) and 100% vs 95% (95% CI, 75%-99%; $P = .02$), respectively.

CONCLUSIONS AND RELEVANCE Carfilzomib-lenalidomide-dexamethasone therapy is tolerable and demonstrates high rates of MRD negativity in NDMM, translating into longer progression-free survival in patients achieving MRD negativity. Carfilzomib-lenalidomide-dexamethasone therapy also demonstrates efficacy in high-risk SMM.

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Multiple myeloma (MM) is a plasma cell dyscrasia characterized by high levels of clonal heterogeneity in both the asymptomatic (eg, smoldering multiple myeloma [SMM]) and symptomatic phases of the disease.¹⁻⁵ Clinically, triplet combination therapies are effective in reducing disease burden despite intratumoral clonal heterogeneity.^{6,7} Recent studies indicate that 3-drug combination regimens using proteasome inhibitors and immunomodulatory drugs yield deep responses in patients with newly diagnosed multiple myeloma (NDMM).^{8,9} The combination of the selective proteasome inhibitor carfilzomib with lenalidomide and dexamethasone (CRd) was recently given to 392 patients with relapsed MM participating in a phase 3 study, resulting in an unprecedented deep response rate (31.8% complete response [CR] or better) and a median progression-free survival (PFS) of 26.3 months.¹⁰ Furthermore, based on a phase 1/2 study that included 52 patients with NDMM, 61% achieved a stringent complete response (sCR) after at least 8 cycles.⁸ Treatment with CRd was found to have a favorable peripheral neuropathy (PN) profile (all grade: 23%; grade ≥ 2 : 6%), which may allow for greater treatment adherence and an increased likelihood to reach negativity for minimal residual disease (MRD) compared with use of other proteasome inhibitors.⁸

Given that many patients with NDMM who are treated with CRd achieved the deepest level of responses recognized by current standardized criteria, there is a need to assess MRD in patients treated with CRd. Minimal residual disease negativity is associated with improved PFS and overall survival both in patients who receive stem cell transplants and in those who do not.¹¹⁻¹³ Several approaches have been used to determine MRD status in MM, including multiparametric flow cytometry (MFC),^{11,12,14} next-generation sequencing (NGS),¹³⁻¹⁵ and fluorodeoxyglucose positron-emission tomography/computed tomography (FDG-PET/CT)^{14,16}; however, these techniques have not been assessed head to head in a prospective clinical study.

We were motivated to expand our knowledge of effective, nonintensive anti-MM therapy. Specifically, we administered CRd therapy followed by lenalidomide extension (CRd-R) to patients with NDMM and studied MRD in the absence of PN of grade at least 3. Furthermore, the same treatment combination was studied in patients with high-risk SMM, a population in which, if left untreated, median time to symptomatic disease progression is less than 2 years.

Methods

The studies in patients with NDMM (NCT01402284) and SMM (NCT01572480) were approved by the National Cancer Institute Institutional Review Board and complied with the Declaration of Helsinki, the International Conference on Harmonisation, and the Guidelines for Good Clinical Practice. All patients provided written informed consent.

Patients

Patients with NDMM or high-risk SMM were eligible for enrollment (see eMethods in the Supplement).

At a Glance

- We administered carfilzomib with lenalidomide and dexamethasone followed by lenalidomide extension to patients with newly diagnosed or smoldering myeloma and studied minimal residual disease in the absence of neuropathy of grade 3 or greater.
- Among 45 patients with newly diagnosed multiple myeloma, none had neuropathy of grade 3 or greater (primary end point).
- Among patients with newly diagnosed multiple myeloma who achieved a near-complete response or better ($n = 28$), minimal residual disease negativity was 100% by multiparametric flow cytometry and 67% by next-generation sequencing.
- All 12 patients with high-risk smoldering multiple myeloma achieved a very good partial response or better during the study period (primary end point).
- Carfilzomib-lenalidomide-dexamethasone therapy is tolerable and demonstrates deep responses in patients with newly diagnosed or high-risk smoldering multiple myeloma.

Study Design and Procedures

Patients received 8 28-day cycles of CRd (eFigure 1 in the Supplement). Carfilzomib was administered intravenously over 30 minutes on days 1, 2, 8, 9, 15, and 16 (starting dose, 20 mg/m² on days 1 and 2 of cycle 1; target dose, 36 mg/m² thereafter). Lenalidomide was administered orally on days 2 through 21 of cycle 1 and on days 1 through 21 of cycles 2 through 8 (25 mg). Dexamethasone was administered intravenously or orally on days 1, 2, 8, 9, 15, 16, 22, and 23 (20 mg for cycles 1-4 and 10 mg for cycles 5-8; dexamethasone was not administered on day 1 of cycle 1). Transplant-eligible patients underwent stem cell collection after 4 cycles of CRd treatment and continued with treatment. After 8 cycles of CRd, all patients with at least stable disease were to receive 2 years of extended dosing with lenalidomide. Patients received thrombotic prophylaxis, antiviral prophylaxis for herpes zoster reactivation, and bisphosphonates.

Response and toxicity assessments occurred on day 1 of each cycle (cycles 1-8) and day 1 of every third cycle during lenalidomide extension (cycles 9-32). Response criteria were categorized according to International Myeloma Workshop Consensus Panel 1¹⁷ with the addition of near CR (nCR).¹⁸ Toxic effects were graded according to the Common Terminology Criteria for Adverse Events, version 4.0.

Serial MRD monitoring and FDG-PET/CTs were performed at the following time points: baseline, achievement of a CR and/or at the completion of cycles 8, 20, and 32, and at termination of protocol therapy. For MRD assessment using MFC, a discrete population of at least 20 abnormal plasma cells defined MRD-positive disease status. In MRD samples using the NGS LymphoSIGHT (Sequentia, Inc) platform, immunoglobulin-heavy and κ chain variable, diversity, and joining gene segments from genomic DNA obtained from CD138⁺ bone marrow cell lysate or cell-free supernatant bone marrow aspirate were amplified using universal primer sets as described elsewhere.^{13,19} An MM clonotype was defined as an immunoglobulin rearrangement identified by NGS at a frequency of at least 5%. Additional MRD methodology, FDG-PET/CT responses (adapted from Zamagni et al criteria¹⁶), preplanned

Table 1. Baseline Characteristics

Characteristic	With NDMM (n = 45)	With SMM (n = 12)
Age		
Median (range), y	60 (40-88)	58 (48-65)
≥65 y, No. (%)	19 (42)	1 (8)
Male sex, No. (%)	27 (60)	5 (42)
Isotype, No. (%)		
IgG	30 (67)	11 (92)
IgA	10 (22)	0
Light chain	5 (11)	1 (8)
International staging system stage, No. (%)		
I	22 (49)	NA
II	22 (49)	NA
III	1 (2)	NA
Unfavorable cytogenetics, proportion (%)		
Unfavorable G-banded karyotype analysis	2/37 (5) ^b	NA
FISH del 17p	5/33 (15)	1/12 (8)
FISH IGH rearrangement other than t(11;14), ie, CCND1	3/33 (9)	3/12 (25)
Radiographic results, No. (%)		
Skeletal surveys, lytic lesions, or pathological fracture	32 (71)	NA ^c
Abnormal PET/CT result	38 (84)	NA ^c
≥3 Focal lesions on PET/CT	28 (62)	NA ^c
Extramedullary plasmacytomas	7 (16)	NA ^c

Abbreviations: FISH, fluorescence in situ hybridization; NA, not applicable; NDMM, newly diagnosed multiple myeloma; PET/CT, positron-emission tomography/computed tomography; SMM, smoldering multiple myeloma.

^a Cytogenetic data were available for 42 patients.

^b Unfavorable G-banded karyotype analysis includes 1 patient with del 13q and 1 patient with del 13q and del 17p.

^c Per diagnostic criteria, these had to be negative.

carfilzomib pharmacokinetics, and other study design details are described in the eMethods in the Supplement.

Statistical Methods

The statistical methods are described in the eMethods in the Supplement.

Results

Patients and Treatment

Between July 11, 2011, and October 9, 2013, 45 patients with NDMM were enrolled and treated with the outlined treatment regimen. Given promising early results with patients with NDMM, a pilot study (N = 12) investigating the same treatment regimen in high-risk SMM was conducted between May 29, 2012, and April 16, 2013.

For NDMM, data cutoff for the analysis was April 4, 2014. Baseline characteristics are summarized in Table 1. Twenty-seven (60%) of the patients with NDMM were male. Median (range) potential follow-up was 17.3 (5.6-31.6) months with a median (range) of 16 (4-30) cycles delivered. The first 20 patients completed at least 2 cycles of therapy without development of PN of grade at least 3; enrollment continued to the full

45 patients. All 45 patients completed 2 cycles and were considered evaluable for the primary end point. At the analysis date, 38 patients continued to receive study therapy; 7 patients discontinued treatment: 4 due to progressive disease (PD) during lenalidomide extension, 1 due to PD during CRd induction, 1 due to personal reasons (obtained sCR and opted not to proceed to lenalidomide extension), and 1 due to cognitive decline. Forty-two patients completed 8 cycles, and 17 patients completed 20 cycles.

All 12 patients with high-risk SMM were evaluable for safety and efficacy. Baseline characteristics are summarized in Table 1. Five (42%) of the patients with high-risk SMM were male. All 12 were classified as high-risk SMM according to PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatías Malignas)²⁰ criteria; 1 also met high-risk criteria from the Mayo Clinic.²¹ No patients had lytic lesions by skeletal surveys and FDG-PET/CT. The cutoff date for the efficacy analysis was April 17, 2014. Median (range) follow-up was 15.9 months (11.8-22.3) months. Patients completed a median (range) of 16 (6-23) cycles of treatment. Eleven patients completed 8 cycles of CRd and subsequently received lenalidomide extended dosing. At the analysis date, 11 patients continued to receive treatment with no symptomatic or biochemical PD; 1 patient discontinued treatment due to congestive heart failure (CHF).

Safety and Tolerability

No patients with NDMM experienced grade 3 or 4 PN (primary end point); the incidences of grade 1 and 2 PN were 33% and 9%, respectively. The most common any-grade hematologic and nonhematologic adverse events (AEs) among patients with NDMM were lymphopenia and electrolyte or metabolism abnormalities, respectively (Table 2). Two of 6 patients with infections of grade 3 or greater had opportunistic infections (*Pneumocystis jiroveci* and *Cryptococcus neoformans*, n = 1 each). The specific grade 3 or 4 cardiac events included CHF (n = 2) and hypertension (n = 3). Two patients had clinical symptoms consistent with CHF and elevated pro-brain natriuretic peptide but no change in ejection fractions. Patients with cardiac events were managed medically with fluid management and antihypertensive therapy, and they continued to receive the study medication. Venous thromboembolism developed in 11 (24%) patients. Three secondary malignant neoplasms occurred during study participation (basal cell [n = 2] and squamous cell carcinoma of the skin [n = 1]). Only 1 patient discontinued study therapy (due to cognitive decline), and 20 (44%) patients required dosing modifications (carfilzomib [n = 1], lenalidomide [n = 5], dexamethasone [n = 6], carfilzomib-dexamethasone [n = 1], lenalidomide-dexamethasone [n = 7]). There were no grade 5 AEs reported in patients with NDMM.

High-risk patients with SMM had similar AEs; the most common of any-grade AEs were lymphopenia (100%) and gastrointestinal disorders (n = 11 [92%]). Second primary malignant neoplasms were reported in 2 patients (17%) with non-melanoma skin cancers. One patient discontinued treatment after cycle 6 of combination therapy, owing to a serious AE of grade 3 CHF; this was assessed as likely being related to carfilzomib therapy. Based on the protocol, 6 patients required dos-

Table 2. Adverse Events

Adverse Event Type	Grade									
	Patients With Newly Diagnosed Multiple Myeloma (n = 45)					Patients With Smoldering Multiple Myeloma (n = 12)				
	1	2	3	4	Any	1	2	3	4	Any
Hematologic										
Lymphopenia	42 (93)	29 (64)	30 (67)	4 (9)	45 (100)	12 (100)	11 (92)	5 (42)	1 (8)	12 (100)
Thrombocytopenia	41 (91)	14 (31)	9 (20)	2 (4)	42 (93)	11 (92)	4 (33)	2 (17)	2 (17)	11 (92)
Leukopenia	37 (82)	21 (47)	7 (16)	2 (4)	37 (82)	11 (92)	3 (25)	1 (8)	1 (8)	11 (92)
Anemia	27 (60)	18 (40)	12 (27)	0	33 (73)	7 (58)	4 (33)	2 (17)	0	8 (67)
Neutropenia	25 (56)	23 (51)	11 (24)	4 (9)	30 (67)	2 (17)	5 (42)	2 (17)	0	5 (42)
Nonhematologic										
Electrolytes/metabolism/nutritional	44 (98)	31 (69)	16 (36)	0	44 (98)	10 (83)	7 (58)	2 (17)	0	11 (92)
Hepatobiliary	43 (96)	16 (36)	5 (11)	0	43 (96)	11 (92)	3 (25)	1 (8)	0	11 (92)
Constitutional	42 (93)	14 (31)	5 (11)	0	42 (93)	8 (67)	4 (33)	0	0	9 (75)
Gastrointestinal	40 (89)	15 (33)	2 (4)	0	41 (91)	11 (92)	4 (33)	0	0	11 (92)
Musculoskeletal	37 (82)	10 (22)	1 (2)	0	38 (84)	8 (67)	2 (17)	1 (8)	0	8 (67)
Skin	27 (60)	13 (29)	5 (11)	0	30 (67)	8 (67)	3 (25)	4 (33)	0	9 (75)
Pulmonary	26 (58)	6 (13)	4 (9)	3 (7)	26 (58)	7 (58)	2 (17)	1 (8)	0	8 (67)
Head/neck and labyrinth/ear	26 (58)	3 (7)	1 (2)	0	28 (62)	7 (58)	2 (17)	0	0	8 (67)
Vascular	17 (38)	14 (31)	5 (11)	1 (2)	25 (56)	5 (42)	4 (33)	1 (8)	0	7 (58)
Peripheral neuropathy	15 (33)	4 (9)	0	0	17 (38)	7 (58)	1 (8)	0	0	7 (58)
Genitourinary/renal	13 (29)	5 (11)	0	0	14 (31)	1 (8)	1 (8)	1 (8)	0	2 (17)
Infusion related	17 (38)	27 (60)	0	0	35 (78)	6 (50)	8 (67)	0	0	11 (92)
Infection	4 (9)	23 (51)	6 (13)	0	27 (60)	1 (8)	6 (50)	1 (8)	0	7 (58)
Mood	13 (29)	4 (9)	1 (2)	0	15 (33)	9 (75)	1 (8)	0	0	9 (75)
Cardiac	13 (29)	6 (13)	5 (11)	0	17 (38)	3 (25)	2 (17)	1 (8)	0	3 (25)
Eye	11 (24)	3 (7)	1 (2)	0	15 (33)	0	0	0	0	0
Endocrine	5 (11)	3 (7)	1 (2)	0	7 (16)	1 (8)	1 (8)	2 (17)	0	2 (17)
Bleeding	4 (9)	0	0	0	4 (9)	2 (17)	0	0	0	2 (17)

ing modifications: 3 with lenalidomide, 2 with dexamethasone, and 1 with lenalidomide-dexamethasone. There were no grade 5 AEs reported in patients with SMM.

Efficacy

Among patients with NDMM, 25 (56% [95% CI, 40%-70%]) achieved a CR or sCR, 28 (62% [95% CI, 46%-76%]) achieved at least an nCR, 40 (89% [95% CI, 76%-96%]) achieved at least a very good partial response (VGPR), and 44 (98% [95% CI, 88%-100%]) achieved at least a partial response (PR) (Table 3). Responses improved as patients received more therapy: the CR or sCR rate increased from 7% after 2 cycles to 43% after 8 cycles. Among the 25 patients with NDMM with a CR or sCR, the median (range) time to CR or sCR was 5 (2-17) cycles; 6 patients reached CR or sCR during the lenalidomide extension phase. The median duration of response was not reached; 84% of patients who achieved at least a PR (n = 37) maintained a PR for at least 24 months and 88% of patients who achieved a CR or sCR (n = 22) maintained a CR for at least 24 months (eFigure 2 in the Supplement). Plasma albumin level, which appears to be related to the rate of plasma breakdown of carfilzomib, was noted to be elevated among 4 of 5 patients with clinically progressing disease ($P = .004$) (see eResults and eFigure 3 in the Supplement).

Results were similar in patients with high-risk SMM. After 2 cycles, all 12 patients had achieved at least a PR; 6 (50%) achieved at least a VGPR. Eleven patients completed 8 cycles; of those, 11 (100% [95% CI, 72%-100%]) had at least a VGPR, including 6 (55% [95% CI, 23%-83%]) with an sCR, 2 (18% [95% CI, 2%-52%]) with a CR, and 3 (27% [95% CI, 6%-61%]) with an nCR. Over the study period, all patients achieved at least a CR. The median (range) time to CR or sCR was 6 (2-20) cycles.

Among the 57 patients with NDMM or SMM, MRD testing was feasible in 55 of 56 (98%) patient samples by MFC. For NGS, 3 of 46 (7%) patients with bone marrow CD138⁺ cell samples were unable to have baseline calibration, thus precluding MRD assessment (see eResults in the Supplement). Among patients with NDMM or SMM who achieved a best overall response of at least nCR over the study period, 28 of 28 (100% [95% CI, 88%-100%]) and 11 of 12 (92% [95% CI, 62%-100%]) were MRD negative by MFC after CRd treatment, respectively. For patients with NDMM achieving no more than a VGPR as a best overall response (n = 15), MFC showed that 10 (67% [95% CI, 38%-88%]) were MRD positive and 5 (33%) were MRD negative. Minimal residual negative disease status by MFC was associated with patients with NDMM or SMM achieving at least an nCR (Fisher exact test, $P < .001$). Next-generation sequencing testing in patients with NDMM or SMM with a best overall

Table 3. Best Response and Best Overall Response by Treatment Duration

Response	After 2 Cycles		After 8 Cycles		After 20 Cycles		Overall ^a	
	Patients With NDMM (n = 44) ^b	Patients With SMM (n = 12)	Patients With NDMM (n = 42) ^c	Patients With SMM (n = 11) ^d	Patients With NDMM (n = 16) ^e	Patients With SMM (n = 3) ^f	Patients With NDMM (n = 45)	Patients With SMM (n = 12)
Best Response, No. (%)								
CR or sCR	3 (7)	1 (8)	18 (43)	8 (73)	10 (63)	3 (100)	25 (56)	12 (100)
nCR	4 (9)	0	8 (19)	3 (27)	2 (13)	0	3 (7)	0
VGPR	12 (27)	5 (42)	12 (29)	0	3 (19)	0	12 (27)	0
PR	23 (52)	6 (50)	3 (7)	0	1 (6)	0	4 (9)	0
SD	2 (5)	0	1 (2)	0	0	0	1 (2)	0
Best Overall Response, No. (%)								
At least nCR	7 (16)	1 (8)	26 (62)	11 (100)	12 (75)	3 (100)	28 (62)	12 (100)
At least VGPR	19 (43)	6 (50)	38 (90)	11 (100)	15 (94)	3 (100)	40 (89)	12 (100)
ORR, at least PR	42 (95)	12 (100)	41 (98)	11 (100)	16 (100)	3 (100)	44 (98)	12 (100)

Abbreviations: CR, complete response; nCR, near complete response; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; PR, partial response; sCR, stringent complete response; SD, stable disease; SMM, smoldering multiple myeloma; VGPR, very good partial response.

^a Overall designated as best responses after a median potential follow-up of 17.3 months (patients with NDMM) or 15.9 months (patients with SMM).

^b One of 45 patients was not evaluable after 2 cycles (data not collected).

^c Three patients were not evaluable after 8 cycles (2 had not completed 8 cycles, and 1 patient's disease had progressed prior to completion of 8 cycles).

^d One patient discontinued study participation before completing 8 cycles.

^e Twenty-nine patients were not evaluable after 20 cycles (26 patients had not completed 20 cycles, 1 patient's disease had progressed prior to completion of 20 cycles, 1 patient's disease had progressed just after completion of 20 cycles, and 1 patient had discontinued study participation for personal reasons).

^f Nine patients were not evaluable after 20 cycles (8 patients had not completed 20 cycles, and 1 patient had discontinued study participation before completing 8 cycles).

response of at least nCR demonstrated that 14 of 21 (67% [95% CI, 43%-85%]) and 9 of 12 (75% [95% CI, 43%-94%]), respectively, were MRD negative after CRd therapy. Among patients assessed by both MRD methods (n = 44), 33 (75% [95% CI, 60%-87%]) samples were concordant (10 positive, 23 negative) and 11 (25% [95% CI, 13%-40%]) were discordant (all were positive by NGS and negative by MFC; McNemar test, $P < .001$) (Figure 1).

The FDG-PET/CT responses after CRd treatment among patients with NDMM with best overall response of at least nCR showed 11 of 27 (41% [95% CI, 22%-61%]) negative, 7 (26% [95% CI, 11%-46%]) decreased, 9 (33% [95% CI, 16%-54%]) partial, and no positive responses compared with patients with no more than a VGPR, who demonstrated 4 of 16 (25% [95% CI, 7%-52%]) negative, 4 (25% [95% CI, 7%-52%]) decreased, 5 (31% [95% CI, 11%-59%]) partial, and 3 (19% [95% CI, 4%-46%]) positive responses (Cochran-Armitage test, $P = .11$) (eTable in the Supplement). After repeating the analysis (FDG-PET/CT not positive vs positive response), the association between clinical response and FDG-PET/CT response was stronger (Fisher exact test, $P = .045$). The FDG-PET/CT and MFC responses were evaluated together after CRd and sequentially after 1 year of lenalidomide therapy (Figure 2).

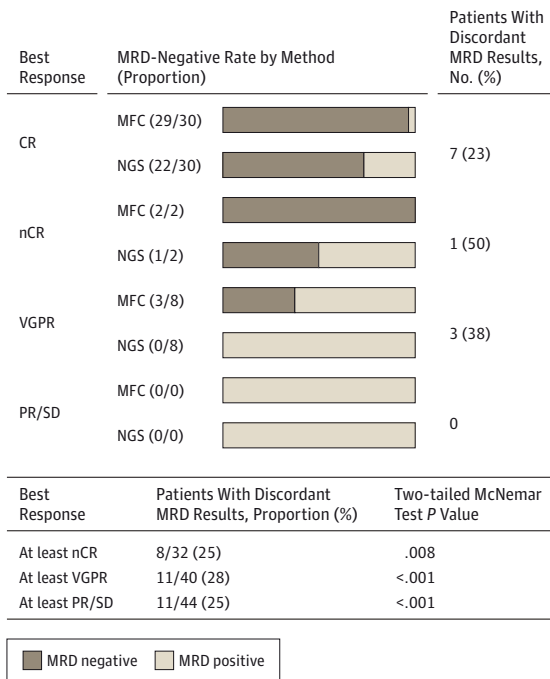
Overall, the 12- and 18-month Kaplan-Meier estimates for PFS in NDMM were 95% (95% CI, 84%-99%) and 92% (95% CI, 78%-97%), respectively (Figure 3A). Median PFS was not reached. Among the 5 patients with NDMM whose disease progressed, 3 have received second-line treatment with high-dose therapy with stem cell rescue and 2 have continued to receive no therapy with monitoring. All 45 patients remain alive. Progression-free survival probabilities at 12 and 18 months for MRD-negative vs MRD-positive

patients by MFC after treatment were 100% vs 79% (95% CI, 47%-94%) and 100% vs 63% (95% CI, 30%-87%), respectively (exact 2-tailed log-rank, $P < .001$) (Figure 3B). Estimated 12- and 18-month PFS for MRD-negative vs MRD-positive patients by NGS was 100% vs 95% (95% CI, 75%-99%) and 100% vs 84% (95% CI, 55%-96%), respectively (exact 2-tailed log-rank, $P = .02$) (Figure 3C). At 12 and 18 months, PFS by FDG-PET/CT response negative/decreased vs positive/partial was 100% vs 89% (95% CI, 68%-97%) and 92% (95% CI, 67%-99%) vs 89% (95% CI, 68%-97%), respectively (exact 2-tailed log-rank, $P = .54$) (Figure 3D). No patients with SMM experienced disease progression while participating in the study; all have maintained their best response at the time of data cutoff. Subset analyses of patients with NDMM, including by age, cytogenetic risk group, and presence of extramedullary disease at baseline, are shown in the eResults in the Supplement.

Discussion

In patients with NDMM and SMM, the CRd-R regimen was well tolerated, without emergence of severe, debilitating PN of grade 3 or greater, possibly leading to high rates of MRD-negative disease. Overall, both NDMM and SMM patients experienced infrequent severe AEs and toxic effects of grade 3 or greater. Despite high rates of grade 3 or 4 lymphopenia, atypical infections were limited. Future work is needed to determine which lymphocyte subsets were affected, which may be important when considering rational combinations incorporating immunomodulatory therapies. One patient with SMM experienced an episode of symptomatic CHF with decreased ejection frac-

Figure 1. Measuring Minimal Residual Disease (MRD) Status by Multiparametric Flow Cytometry (MFC) and Next-Generation Sequencing (NGS)



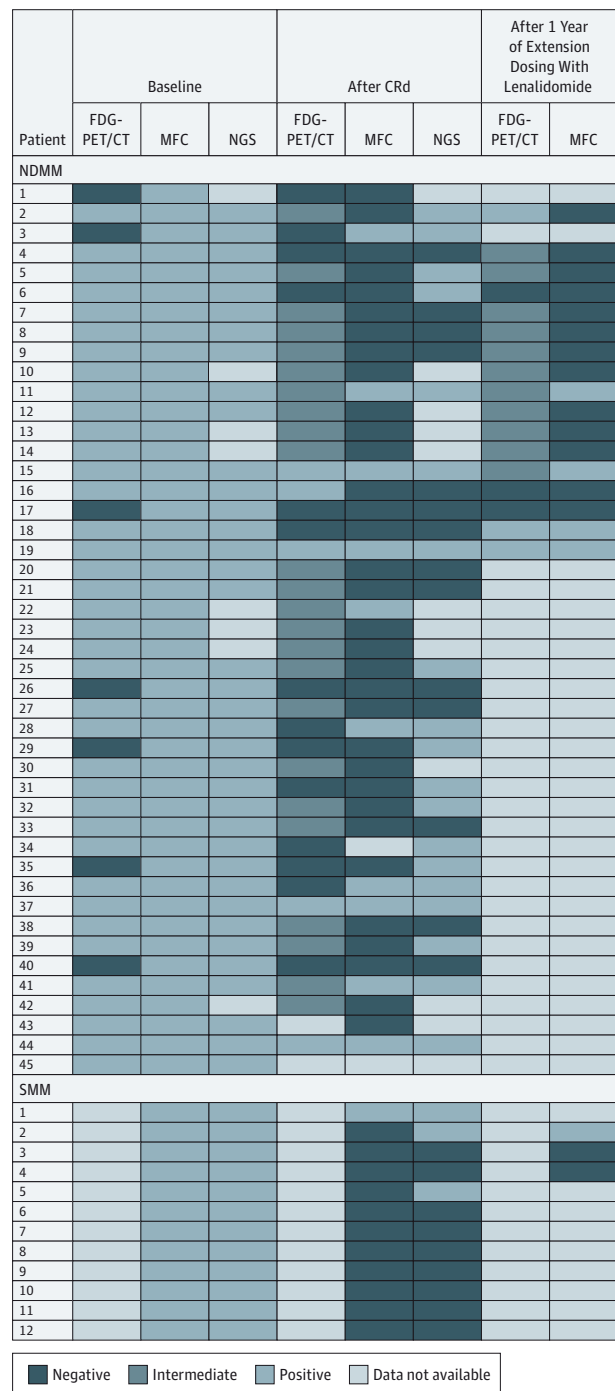
Comparison of MRD status among newly diagnosed multiple myeloma (NDMM) and smoldering multiple myeloma (SMM) patients who underwent testing by both MFC and NGS methodologies. CR indicates complete response; nCR, near complete response; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

tion and discontinued treatment after completing 6 cycles and reaching an sCR. The mechanisms underlying this cardiotoxicity are poorly understood. The patient was prescribed cardiac therapy and symptoms reverted back to baseline without any residual symptoms. The patient was monitored with repeated assessment of the ejection fraction and continues to receive cardiac therapy.

In patients with NDMM, best overall response rates of at least VGPR and at least nCR were 89% and 62%, respectively. A potential mechanism for poor responses and PFS may be attributed to metabolism of carfilzomib in the plasma. Further work is needed to validate these findings. Importantly, among patients with NDMM achieving at least nCR, MRD-negative disease status was found to be 100% (MFC) and 67% (NGS). Similar to studies that evaluated MRD status after autologous stem cell transplant,^{11,12} MRD negativity was associated with improved PFS. Whereas these trials demonstrated that MRD negativity was also associated with prolonged overall survival and the utility of MRD as a surrogate end point is currently being explored, our trial is limited by shortened follow-up and small numbers.

A recent phase 3 study with lenalidomide and dexamethasone demonstrated that the treatment of patients with high-risk SMM, a population in which patients generally do not receive treatment per existing guidelines, translated into survival

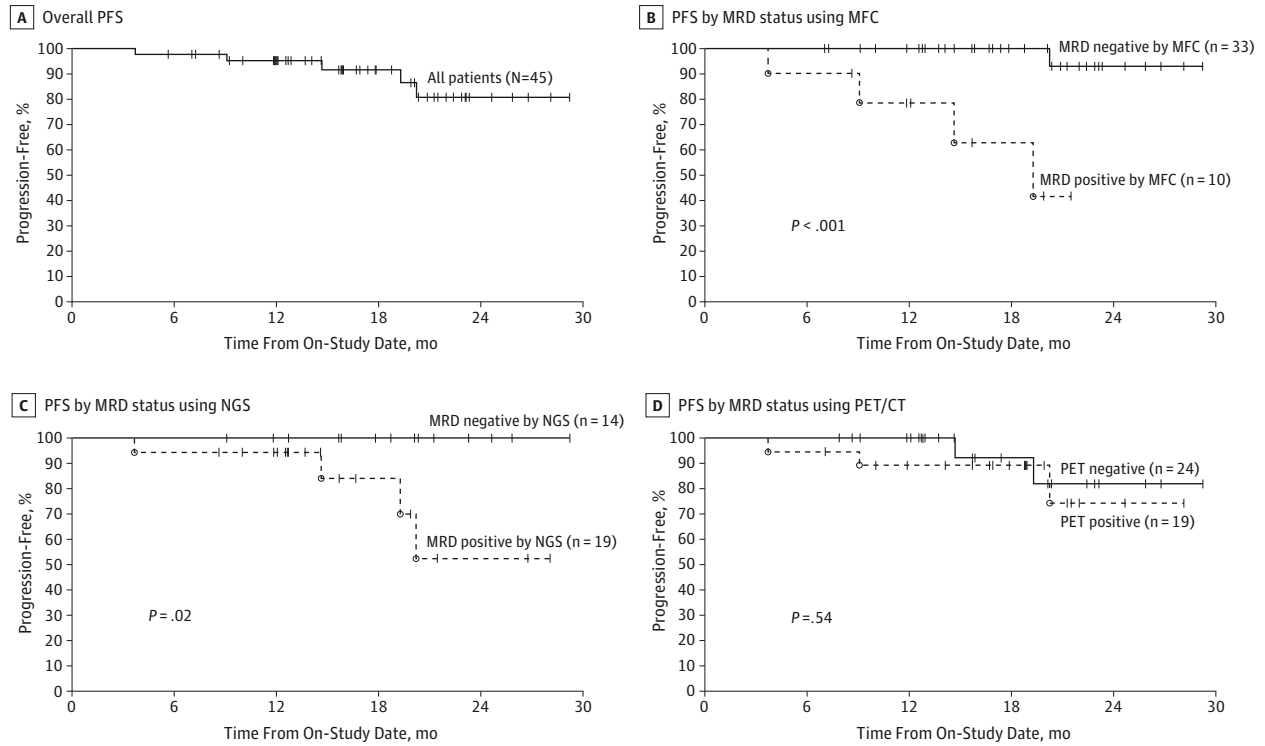
Figure 2. Individual Sequential Minimal Residual Disease Status by Multiparametric Flow Cytometry (MFC), Next-Generation Sequencing (NGS), and Fluorodeoxyglucose Positron-Emission Tomography/Computed Tomography (FDG-PET/CT)



Individual sequential MRD status among newly diagnosed multiple myeloma (NDMM) and smoldering multiple myeloma (SMM) patients who underwent testing by MFC, NGS, and FDG-PET/CT methodologies.

benefits compared with patients who did not receive this regimen. In these patients, a 14% rate of at least CR was observed after combination therapy.²²

Figure 3. Progression-Free Survival (PFS) by Status for Newly Diagnosed Multiple Myeloma (NDMM) Using Multiparametric Flow Cytometry (MFC), Next-Generation Sequencing (NGS), and Positron-Emission Tomography/Computed Tomography (PET/CT)



A, Overall. B, By MRD status using MFC. C, By MRD status using NGS. D, By PET/CT status. The PET-negative group includes patients with PET-negative results and patients with decreased PET standardized uptake values. The

PET-positive group includes patients with PET-positive results and patients with partial positive PET results (see eMethods in the Supplement).

Given the clinical successes of the aforementioned high-risk SMM trial and the preliminary response rates seen in the NDMM lenalidomide and dexamethasone extension trial, we designed a pilot study in patients with high-risk SMM. Deeper responses were observed in patients with high-risk SMM than in patients with NDMM (at least nCR rate of 100% vs 62%, respectively). Longer follow-up and additional studies are needed to determine whether deeper responses in high-risk SMM translate into a clinical benefit beyond waiting to treat after symptom development. Although cross-trial comparisons should be viewed cautiously, we conclude that our observed unprecedented high rates of deep response (CR and MRD-negativity) in patients with NDMM or SMM, with the addition of carfilzomib to a lenalidomide and dexamethasone backbone, confirm and expand on prior CRd results, including those from NDMM⁸ and patients with relapsed or refractory disease.¹⁰

Given the high degree of CR rates achievable by 3-drug combination regimens, there is an increased need for clinical trials to detect MRD beyond traditional methods and characterize optimal MRD technique. In the past, we have noted substantial heterogeneity in how MFC is used, which has affected MRD detection rates.^{23,24} Our current MFC assay (sensitivity of 1×10^{-5}) reports 98% negativity among patients with NDMM or SMM who have achieved at least an nCR. The NGS assay was able to detect 30% additional MRD-positive cases among patients who achieved at least an nCR.

Although this result highlights the intermethodologic differences between both platforms and the potential increased sensitivity with NGS, use of both platforms was feasible. The feasibility of MRD measurement was 98% using MFC; for NGS, 93% of patients were able to have baseline calibration. Thus far in follow-up, additional detection of MRD-positive cases using NGS has not significantly affected PFS or survival outcomes. Interestingly, NGS was able to detect MRD in an sCR patient (NDMM) for whom MFC had failed. This patient's disease clinically progressed after 1 year of MRD-positive detection by NGS. The relationship between PET/CT responses and clinical outcomes is less apparent, with no significant association found between the degree of PET/CT response and clinical response, MRD status, or PFS. Further work is needed to characterize residual FDG-avid areas in the context of tumor biology and long-term outcomes.

Conclusions

The present study confirms and expands our knowledge of effective, nonintensive anti-MM therapy, building on previous studies of CRd in relapsed MM¹⁰ and NDMM.⁸ Taken together, our results provide further evidence for the role for proteasome inhibitor-immunomodulatory drug combination therapy in NDMM and demonstrate that MRD evaluation may

be an important tool for measuring the depth of response.¹⁴ Longitudinal tracking of MRD status may shed light on mechanisms of resistance and late relapses, as we further elucidate the role of maintenance therapy. In addition, the pilot study

in high-risk SMM provides proof of principle to support future large-scale trials of tolerable regimens capable of achieving high rates of sustainable MRD-negative responses in this population.

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Invited Commentary

Multiple Myeloma—Better Drugs Ask for More Stringent Evaluations

Pieter Sonneveld, MD, PhD

In this issue of *JAMA Oncology*, Korde and colleagues¹ report an elegant pilot study of carfilzomib combined with lenalidomide and dexamethasone (CRd) for 45 patients with newly diagnosed multiple myeloma (NDMM). Their study renders 3 im-



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portant conclusions that are a prelude to the future of myeloma treatment. First, with this combination of effective and well-tolerated drugs, more and deep responses can be achieved across different prognostic subgroups defined by fluorescent in situ hybridization (FISH). Second, the level of tumor reduction goes beyond morphological complete response (CR) as is shown by serial measurements of minimal residual disease (MRD). In addition, in a group of 12 patients with high-risk but asymptomatic smoldering multiple myeloma, substantial disease eradication was observed, resulting in MRD negativity in all patients. Finally, this study is an example of informative clinical research.

The treatment that was investigated in this pilot study combines a next-generation proteasome inhibitor (carfilzomib) with an immune-modulatory agent (lenalidomide) and a corticosteroid. The concept is based on good clinical results obtained with bortezomib plus thalidomide and dexamethasone in Europe and with bortezomib plus lenalidomide and dexamethasone in the United States.^{2,3} Recently the Aspire trial was published, which compared CRd with lenalidomide plus dexamethasone in patients with relapsed multiple myeloma. In this randomized trial, progression-free survival with CRd was 26 months compared with 17 months in the control group with no difference between high-risk vs standard-risk FISH subgroups.⁴ This and other trials set the stage for use of carfilzomib combinations in the front-line treatment of multiple myeloma. A phase 2 trial of CRd in NDMM demonstrated the feasibility of this approach and reported a stringent CR rate of 62%.⁵ In a dose-escalating trial in transplant-eligible patients with NDMM, use of carfilzomib combined with thalidomide and dexamethasone for induction before and consolidation after high-dose therapy also

was well tolerated and showed 60% CR across different prognostic subgroups of patients.⁶ Both trials, as well as Aspire, demonstrate the high efficacy of triple-drug regimens combining a proteasome inhibitor with an immune-modulatory agent and dexamethasone at the cost of limited toxicity. More trial results are forthcoming, and additional modifications such as subcutaneous administration and a weekly schedule of carfilzomib administration will further enhance the tolerability and acceptance of such combinations. With lenalidomide-dexamethasone being or becoming a standard treatment for NDMM in the United States and Europe, CRd could become the next step for induction treatment in transplant-eligible and elderly patients with NDMM.

This study also demonstrates that patients with cytogenetically high-risk smoldering multiple myeloma may benefit from early treatment with an effective regimen before end organ damage develops. Because these patients have a high probability (>90%) of disease progression within 2 years, there is a need to treat them with well-tolerated and effective regimens. The International Myeloma Working Group recently has included this category of patients into the diagnosis of multiple myeloma.⁷ The study by Korde et al,¹ like others, indicates how these patients can be effectively treated without a risk of excessive toxicity.

Another important aspect of the study by Korde et al¹ is the complete and consistent analysis of the patients, which sets the stage for future clinical trials. All patients were well documented for several biological aspects of the disease at diagnosis, such as FISH abnormalities and clinical staging. This allows the prognostic classification of patients based on objective criteria. Moreover, serial response assessments were performed using MRD criteria and sensitive imaging techniques such as positron-emission tomography/computed tomography (PET/CT) scans. The careful and consistent documentation provides us with the full impact of a highly effective regimen such as CRd. By monitoring the MRD status during and after treatment, it became evident that 12-month progression-free survival was 100% in patients who became MRD nega-