ORIGINAL ARTICLE

Phase 1/2 study of weekly carfilzomib, cyclophosphamide, dexamethasone in newly diagnosed transplant-ineligible myeloma

S Bringhen[1], M D'Agostino[1], L De Paoli[2], V Montefusco[3], AM Liberati[4], P Galieni[5], S Grammatico[6], VE Muccio[1], F Esma[1], C De Angelis[4], P Musto[7], S Ballanti[8], M Offidani[9], MT Petrucci[6], G Gaidano[2], P Corradini[10], A Palumbo[1,12], P Sonneveld[11] and M Boccadoro[1]

This multicentre, open-label phase 1/2 trial determined safety and efficacy of weekly carfilzomib plus cyclophosphamide–dexamethasone (wKCyd) in newly diagnosed multiple myeloma (NDMM) patients aged ⩾ 65 years or transplant ineligible. Patients received wKCyd for up to nine 28-day cycles, followed by maintenance with carfilzomib until progression/intolerance. The phase 1 portion used a 3+3 dose-escalation scheme to determine the maximum tolerated dose of weekly carfilzomib: 12 patients received wKCyd with carfilzomib doses of 45, 56 and 70 mg/m^2. The recommended phase 2 dose was established at 70 mg/m^2 and 54 patients (phase 1 and 2) received weekly carfilzomib 70 mg/m^2: 85% of them achieved ⩾ partial response (PR), 66% ⩾ very good PR, 30% ⩾ near-complete response (CR) and 15% CR. Responses improved in 40 patients who started maintenance: 98% achieved ⩾ PR, including 29% CR and 10% stringent CR. After a median follow-up of 18 months, the 2-year progression-free survival and overall survival rates were 53.2% and 81%, respectively. The most frequent grade 3–5 toxicities were neutropenia (22%) and cardiopulmonary adverse events (9%). This is the first study of weekly carfilzomib plus an alkylating agent in elderly patients with NDMM. wKCyd was effective, with an acceptable risk/benefit ratio, and thus can be a valid option in this setting.

INTRODUCTION

In the last decade, the increased use of novel agents as initial therapy of multiple myeloma (MM) significantly improved overall survival (OS) in patients ineligible for autologous transplantation.[1] In Europe, bortezomib–melphalan–prednisone (VMP) and melphalan–prednisone–thalidomide combinations are considered standards of care in elderly patients ineligible for autologous stem cell transplantation.[2,3] Dose-limiting haematological toxicity from melphalan and peripheral neuropathy from bortezomib or thalidomide limit their optimal use.[4,5] Better tolerated alkylating agents, such as cyclophosphamide, which lack the cumulative haematological toxicity of melphalan, have been used successfully in combination with dexamethasone and either thalidomide[6] or bortezomib[7] in elderly newly diagnosed MM (NDMM) patients. Recently, based on the results of MM020 trial, a new standard of care with no alkylating agent has been introduced for the treatment of elderly patients with NDMM. Indeed, that study prospectively compared outcomes of melphalan-prednisone-thalidomide versus lenalidomide and low-dose dexamethasone, and found that treatment with lenalidomide and dexamethasone until disease progression improved progression-free survival (PFS) and OS compared with melphalan-prednisone-thalidomide.[8]

Carfilzomib, a novel and selective proteasome inhibitor, received accelerated approval in the United States in 2012 for the treatment of patients with relapsed and refractory MM. It is approved in the United States and Europe when used in combination with dexamethasone or lenalidomide plus dexamethasone for patients with relapsed MM (one to three prior lines of therapy).[9] Under the initial approvals, carfilzomib is administered as a 10 min infusion on a twice-weekly dosing schedule, with a starting dose of 20 mg/m^2 on cycle 1 days 1 and 2, and stepped up to a target dose of 27 mg/m^2 thereafter. Prolonged infusion over 30 min has been assessed in clinical studies showing that higher carfilzomib doses (56 mg/m^2) in combination with dexamethasone were safe and effective.[10,11] These findings were confirmed with the results of the randomized phase 3 ENDEAVOR trial (RandomizEd, opeN Label, Phase 3 Study of carfilzomib plus DExamethAsone Vs bortezomib plus DexamethasOne in Patients With Relapsed Multiple Myeloma; NCT01568866) comparing carfilzomib plus dexamethasone versus bortezomib plus dexamethasone in relapsed/refractory MM, which supported the approval of twice-weekly carfilzomib (at 56 mg/m^2) with dexamethasone for patients with relapsed MM.[12]

[1]Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy; [2]Division of Hematology, Department of Translational Medicine, Università del Piemonte Orientale and Azienda Ospedaliero-Universitaria Maggiore della Carità, Novara, Italy; [3]Hematology Departement, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy; [4]Department of Oncohematology, Hospital S. Maria, Terni, Italy; [5]UOC di Ematologia e Terapia Cellulare, Ospedale C. e G. Mazzoni, Ascoli Piceno, Italy; [6]Hematology, Department of Cellular Biotechnologies and Hematology, Sapienza University of Rome, Rome, Italy; [7]Scientific Direction, IRCCS-CROB, Referral Cancer Center of Basilicata, Rionero in Vulture (Pz), Italy; [8]Sezione di Ematologia e Immunologia Clinica, Ospedale Santa Maria della Misericordia di Perugia, Perugia, Italy; [9]Clinica di Ematologia, AOU Ospedali Riuniti di Ancona, Ancona, Italy; [10]Department of Oncology-Hematology, University of Milano, Italy and [11]Department of Hematology, Erasmus Medical Center, Rotterdam, The Netherlands. Correspondence: Dr S Bringhen, Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria (AOU) Città della Salute e della Scienza di Torino, S. Giovanni Battista, Via Giuseppe Verdi, 8, Torino 10124, Italy.
E-mail: sarabringhen@yahoo.com
[12]This author is currently an employee of Takeda.

Twice-weekly intravenous administration of anti-myeloma therapy can be burdensome for patients, especially for those who are elderly, suffer from myeloma-related symptoms, or who live far from the clinic. Based on results from studies showing that once-weekly bortezomib has similar efficacy and a better safety profile compared with the conventional twice-weekly administration,[13] and to follow up on the CHAMPION-1 study evaluating weekly carfilzomib plus dexamethasone in the relapse setting,[14] we aimed to evaluate efficacy and tolerability of once-weekly carfilzomib plus cyclophosphamide and dexamethasone (wKCyd) in NDMM elderly patients. We previously showed that treatment with twice-weekly carfilzomib in combination with cyclophosphamide-dexamethasone (KCyd) was highly effective and well tolerated in elderly NDMM patients. Responses were rapid and deep, and showed improvement over time. Forty-nine percent of patients achieved ≥ near-complete response (nCR) and 20% of patients achieved a stringent CR (sCR). After a median follow-up of 18 months, the 2-year PFS rate was 76%. Severe haematological adverse events (AEs) occurred in < 20% of patients and non-haematological AEs occurred in < 10% of patients, with a low (18%) rate of discontinuation.[15] Given the improved haematological safety profile of cyclophosphamide and the previous encouraging results with KCyd,[15] we conducted a phase 1/2 study to determine the maximum tolerated dose (MTD) and evaluated the safety and efficacy of once-weekly wKCyd in elderly NDMM patients. We report the safety and efficacy results of the trial herein.

PATIENTS AND METHODS

Patients
Patients with symptomatic NDMM, who were aged ≥ 65 years or ineligible for autologous transplantation were included in the study. Further eligibility criteria included measurable disease, Eastern Cooperative Oncology Group performance status ≤ 2, creatinine clearance ≥ 15 ml/min, platelet count ≥ 50 × 10^9/l (≥30 × 10^9/l if myeloma involvement in the bone marrow was > 50%) and absolute neutrophil count of ≥ 1 × 10^9/l without the use of growth factors. Patients were excluded from the study if they had non-secretory MM (unless serum-free light chains were present and the ratio was abnormal, namely < 0.26 or > 1.65), grade > 2 peripheral neuropathy and active infection.[16] In addition, per protocol, patients had to undergo echocardiogram (ECHO) and electrocardiogram, and were excluded from the trial if they had left ventricular ejection fraction < 40% evaluated with two-dimensional transthoracic ECHO (or Multigated Acquisition Scan if ECHO was not available), myocardial infarction or unstable angina ≤ 4 months before enrolment, uncontrolled angina, history of severe coronary artery disease, or electrocardiographic evidence of acute ischaemia or grade 3 conduction system abnormalities unless the subject had a pacemaker, uncontrolled hypertension, uncontrolled congestive heart failure or uncontrolled diabetes within 14 days before enrolment.

All patients gave written informed consent to participate in the study, which had been approved by the institutional ethics committees. The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The study is registered at Clinicaltrials.gov NCTNCT01857115.

Study design and treatment
This multicentre, non-randomized, open-label, dose-escalation phase 1/2 study determined the safety and efficacy of wKCyd in NDMM patients. The primary objective of the phase 1 portion was to determine the MTD of once-weekly carfilzomib with cyclophosphamide and dexamethasone. The primary objective of the phase 2 portion was to determine the overall response rate. Secondary endpoints included response rates, PFS, time to progression, duration of response, OS, time to next therapy, subgroup analyses of prognostic factors, the evaluation of the effect of maintenance on PFS and OS, and the relationship between responses and PFS in responding and non-responding patients.

All patients received oral cyclophosphamide 300 mg/m^2 on days 1, 8 and 15, and oral dexamethasone 40 mg on days 1, 8, 15 and 22. Carfilzomib was administered as a 30 min, intravenous infusion on days 1,

8 and 15 of a 28-day cycle. In the phase 1 dose-escalation portion, patients received carfilzomib at 20 mg/m^2 on cycle 1, day 1; subsequent doses were escalated in a standard 3+3 dose-escalation scheme at 45, 56 and 70 mg/m^2 to determine the MTD. In the phase 2 portion, patients received carfilzomib at the MTD with the same schedule as in the phase 1 portion (Supplementary Figure S1). Treatment was given every 28 days for nine cycles. Patients then received maintenance therapy with carfilzomib at the MTD on days 1, 15 every 28 days until progression or intolerance. Intravenous hydration (250 ml) before and after dose administration was given during cycle 1 and at the investigator's discretion thereafter.

Any toxicity requiring a dose reduction within cycle 1, inability to receive day-1 dose of cycle 2 due to drug-related toxicity persisting from cycle 1, including cardiovascular events, represents a dose-limiting toxicity (DLT). In addition, regardless of dose modification or treatment delay, among haematologic toxicities, grade 4 neutropenia or thrombocytopenia lasting for ≥ 7 days, febrile neutropenia, grade 3–4 thrombocytopenia associated with bleeding are considered DLTs. Among non-haematologic toxicities, grade ≥ 3 nausea, vomiting or diarrhoea despite maximal antiemetic/antidiarrhoeal therapy, grade 4 fatigue lasting for ≥ 7 days are DLTs, as well as the first occurrence of grade ≥ 2 neuropathy with pain in the first treatment cycle.

Assessment
For all patients receiving at ≥ 1 dose of any study drug, toxicity was assessed according to the National Cancer Institute Common Terminology Criteria, version 4.0.[17] Response was assessed according to the International Myeloma Working Group criteria[18] with the addition of nCR, defined as the absence of monoclonal component in the serum and/or urine with immunofixation positive. The response assessments were undertaken at the beginning of each treatment cycle (Supplementary Figure S1) during induction and every three cycles during maintenance. Fluorescence in situ hybridization was used to detect t(4:14), t(11:14), t(14;16), del13 and del (17p). Bone marrow samples were collected at study entry and investigations were performed at one central laboratory. For the present analysis, the cutoff value of 60% for the proportion of plasma cells with del (17p) was used, according to the recommendation from the International Myeloma Workshop Consensus panel 2.[19]

Statistical analysis
For the sample size of the phase 1 portion of the study, each wKCyd dose level cohort could have a minimum of three patients and a maximum of six patients. Therefore, a maximum of 18 patients could be recruited in the phase 1. The sample size of the phase 2 portion of the study was estimated according two-stage Simon optimal design, with early stopping rules in case of efficacy lower than a predefined uninteresting response rate. We assumed an overall response rate p0 of 0.40, under which further study of the wKCyd combination would not be justified, and an overall response rate p1 of 0.60, which could justify additional investigation of this combination. Probability of type I (α) error was set to be 0.05 and type II (β) error 0.20. In the first stage of phase 2, 16 patients had to be accrued. If seven or less responses had been observed, the trial would have been stopped for futility. Otherwise, 30 additional patients would have been accrued in the second stage: if 23 or fewer responses had been observed by the end of this stage, no further investigation would have been warranted. With this design, the expected number of enrolled patients was 46 and the probability of early termination was 71.6%. Assuming ~ 10% of patients lost to follow-up, an adequate sample size was 53 patients.

Response rates and safety were analysed in patients who received ≥ 1 dose of study treatment. Time-to-event endpoints were determined using the intent-to-treat population. The Kaplan–Meier product limit method was used to estimate survivorship functions for time-to-event endpoints. Cox proportional hazards regression was used to assess the effects of demographic and prognostic variables on relative treatment differences. Continuous and categorical data were summarized using descriptive statistics. SAS System version 8.2 system (SAS Institute Inc., Cary, NC, USA) was used.

Table 1. Patient characteristics at baseline

Characteristic	Phase 1 patients N = 12	RP2D patients N = 54	All patients N = 63
Male, n (%)	5 (42)	22 (41)	26 (41)
Age			
Median (IQR), years	73 (68–75)	72 (69–74)	72 (69–74)
≥ 75 years, n (%)	4 (33)	11 (20)	14 (22)
ISS stage, n (%)			
I	4 (33)	20 (37)	24 (38)
II	4 (33)	16 (30)	19 (30)
III	4 (33)	18 (33)	20 (32)
Creatinine clearance, ml/min, n (%)			
< 30	1 (8)	3 (6)	4 (6)
30–60	4 (33)	11 (20)	14 (22)
>60	7 (59)	40 (74)	45 (71)
Left ventricular ejection fraction (LVEF)			
Median % (range)	60 (55–72)	60 (55–75)	60 (55–75)
Chromosomal abnormalities, n (%)			
t (4;14)	0	3 (6)	3 (5)
t (14;16)	1 (8)	2 (4)	3 (5)
Del 17	3 (25)	11 (20)	14 (22)
Unfavourable profile[a]	3 (25)	16 (30)	19 (30)
Data missing	3 (25)	17 (31)	19 (30)

Abbreviations: IQR, interquartile range; ISS, International Staging System; RP2D, recommended phase 2 dose. [a]Unfavourable profile was defined as the presence of t(4;14) or t(14;16), or deletion of chromosome 17.

Table 2. Response to treatment by patient characteristics and by treatment duration in RP2D patients

Patient subgroup	n	Response category, n (%)				
		≥ PR	≥ VGPR	≥ nCR	≥ CR	sCR
Overall—Induction[a]	54	46 (85)	36 (66)	16 (30)	7 (13)	1 (2)
Overall—Induction +Maintenance[a]	54	48 (89)	37 (69)	22 (41)	12 (22)	4 (7)
ISS stage						
I	20	18 (90)	17 (85)	11 (55)	6 (30)	3 (15)
II	16	16 (100)	11 (69)	7 (44)	2 (13)	1 (6)
III	18	14 (78)	9 (50)	4 (22)	4 (22)	0
Chromosomal abnormalities						
Normal/favourable	21	17 (81)	12 (57)	6 (29)	3 (14)	0
Unfavourable[b]	16	16 (100)	11 (69)	7 (44)	4 (25)	2 (13)
Treatment duration[c]						
Second cycle	50	45 (90)	36 (72)	18 (36)	7 (14)	1 (2)
Fourth cycle	48	43 (90)	36 (75)	18 (38)	7 (15)	1 (2)
Sixth cycle	44	40 (91)	36 (82)	18 (41)	7 (16)	1 (2)
Ninth cycle	40	37 (93)	34 (85)	18 (44)	7 (18)	1 (3)
Maintenance	40	39 (98)	35 (88)	22 (54)	12 (29)	4 (10)

Abbreviations: CR, complete response; ISS, International Staging System; nCR, near-complete response; PR, partial response; RP2D, recommended phase 2 dose; sCR, stringent complete response; VGPR, very good partial response. [a]Intention-to-treat analysis: all patients enrolled at the RP2D were evaluated. [b]Presence of t(4;14) or t(14;16) or deletion chromosome 17. [c]Per-protocol analysis: only patients who received at least 2, 4, 6 and 9 cycles, and maintenance were evaluated.

all data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Patients

Patients were enrolled from 10 April 2013 to 24 August 2015, in 8 centres in Italy. Twelve patients were enrolled in the phase 1 dose-escalation portion of the study and 51 patients were enrolled in the phase 2 portion. A total of 54 patients were treated at the recommended phase 2 dose (RP2D) and could be assessed for efficacy and safety (Supplementary Figure S2). Baseline demographics and disease characteristics for patients enrolled in all study phases are listed in Table 1. Median age of all patients was 72 years (interquartile range 69–74); the median left ventricular ejection fraction was 60% (range 55–75); 14 patients (22%) were ≥ 75 years; 19 patients (30%) had an unfavourable chromosomal profile (the presence of t(4;14), del17p or t(14;16)) and 20 (32%) had International Staging System stage III. All patients could be evaluated for safety and response; the median duration of induction treatment was nine cycles (range 1–9 cycles). At the time of analysis, 47 patients had proceeded to maintenance therapy, 40 at the RP2D and 7 at lower doses in the phase 1 portion of the study.

MTD definition

During phase 1, in the dose-escalation portion of the study, no DLTs were observed in the 45 mg/m^2 dose cohort, 1/6 DLT was reported in the 56 mg/m^2 dose cohort (grade 3 creatinine increase) and no DLTs were observed in the 70 mg/m^2 dose cohort. The RP2D of once-weekly carfilzomib with cyclophosphamide and dexamethasone was determined to be 70 mg/m^2 (Supplementary Table S1).

Efficacy of RP2D

Overall, among patients receiving carfilzomib at the MTD, 46/54 (85%) patients had at least a partial response (≥ PR), 36/54 (66%) patients had at least a very good PR (≥ VGPR) and 16/54 (30%) patients had at least a ≥ nCR (Supplementary Table S1). Depth of response increased with prolonged treatment. At the end of four cycles, 43/48 (90%) patients achieved ≥ PR, including 18/48 (38%) patients with ≥ nCR. Among patients who completed nine cycles of treatment, 37/40 (93%) had ≥ PR and 18/40 (44%) had ≥ nCR. Among patients who received maintenance, 39/40 (98%) had ≥ PR and 22/40 (54%) had ≥ nCR, including 12/40 (29%) CR and 4/40 (10%) sCR (Table 2). The median time to achieve PR was 2.4 months, but median time to sCR was 12 months and ~50% of patients with CR achieved CR during maintenance (Figure 1). The quality of response impacted on long-term outcome. At 2 years, the proportion of patients alive and in remission was 100% in patients who achieved sCR, 60% in those who achieved VGPR or CR and 44% in those who achieved PR. Response rates were generally similar across patient groups according to International Staging System stage and chromosomal profile (Table 2).

After a median follow-up of 19.7 months (interquartile range 14.3–28.3), the 2-year PFS and OS rates were 53.2% and 81%, respectively (Figure 2). The risk of progression was slightly higher in patients with International Staging System III (hazard ratio 2.46; 95% confidence interval 0·99–6.1, P = 0.05) but not with high-risk chromosomal abnormalities. The 2-year PFS was 68% in high-risk patients and 53% in standard-risk ones (hazard ratio 0.45; 95% confidence interval 0.12–1.7, P = 0.24).

Safety of RP2D

During induction, the most common toxicities of any grade were anaemia (39%), thrombocytopenia (33%), neutropenia (31%),

Figure 1. Time to response onset.
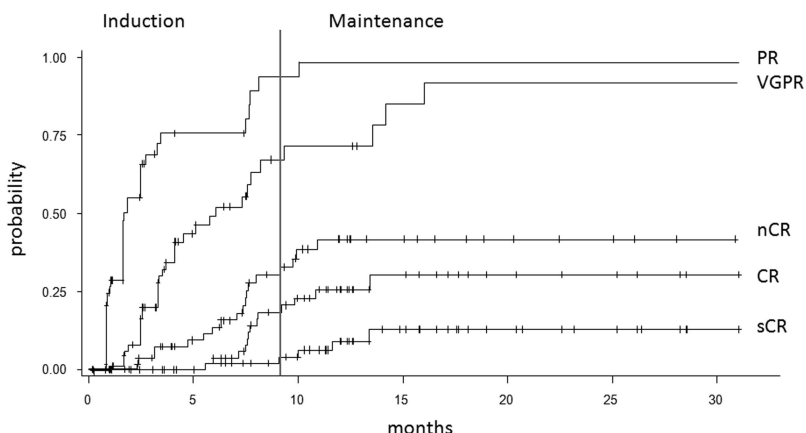
PR, partial response; VGPR, very good partial response; nCR, near complete response; CR, complete response; sCR, stringent complete response.
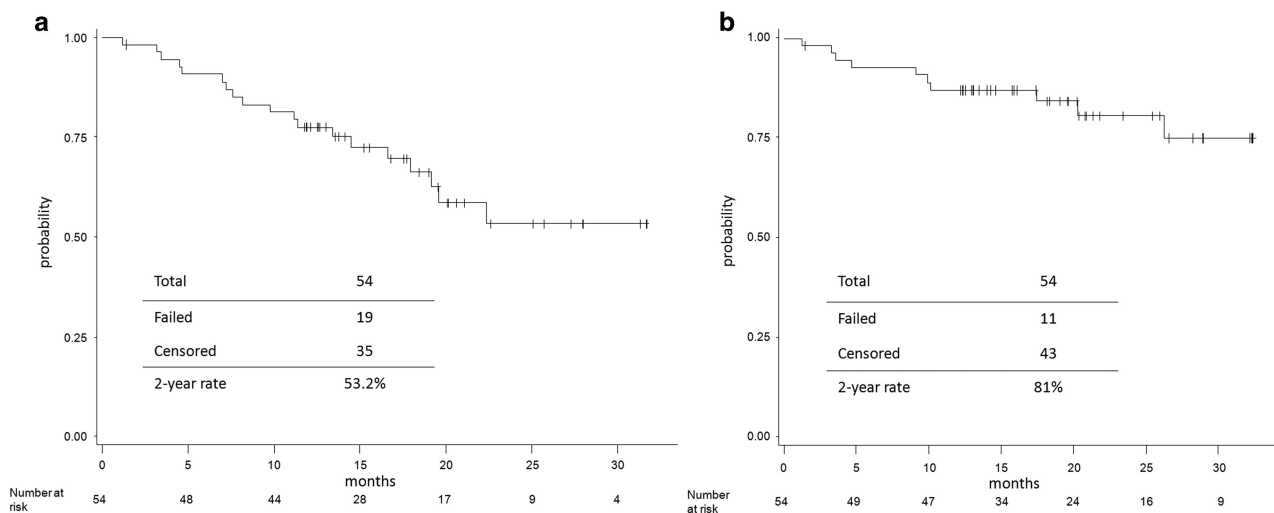

Figure 2. Treatment outcome: (**a**) progression-free survival and (**b**) overall survival in patients treated with the RP2D schedule.

cardiovascular events (24%), nausea/vomiting (19%), fever (13%), infections (13%) and fatigue (9%). Grade 3–5 haematological toxicities included neutropenia (22%), thrombocytopenia (7%) and anaemia (2%). The most common grade 3–5 non-haematological AEs were cardiovascular events (9%), metabolic events (6%), infections (7%) and renal events (4%) (Table 3).

Treatment-emergent serious AEs occurred during induction in 14 patients (26%) and included four renal failures, eight cardiac events (three heart failures, three pulmonary oedemas, one sudden death and one hypertension), four infections (two pneumonias, one sepsis and one upper respiratory tract), one reversible posterior leukoencephalopathy, one hyponatremia, one respiratory failure, one adult respiratory distress syndrome and one pulmonary thromboembolism. A limited number of patients required dose modification during induction: 12 patients (22%) discontinued treatment owing to AEs and 5 patients (9%) required carfilzomib dose reductions (Supplementary Table S2).

A total of six patients died during induction; causes of death were disease progression (two patients) and AEs (pulmonary thromboembolism, acute respiratory failure, pneumonia and sudden death in one patient each) (Supplementary Table S2).

During maintenance, the most common toxicities of any grade were anaemia (8%), thrombocytopenia (20%), neutropenia (5%), fever (15%), hypertension (15%) and nausea/vomiting (10%). No grade 3–5 haematological toxicities were reported. Grade 3–5 non-haematological AEs were rare and occurred in < 5% of patients, with the exception of hypertension, which was reported in 10% and cardiovascular AEs in 5% (one heart failure and one myocardial infarction). Treatment-emergent serious AEs occurred during maintenance in three patients and included urinary tract infection, heart failure and myocardial infarction.

DISCUSSION

This trial is the first to investigate carfilzomib on a once-weekly dosing schedule with cyclophosphamide and dexamethasone as part of frontline therapy in patients over 65 years of age with symptomatic MM. The MTD of weekly carfilzomib incorporated into the wKCyd regimen was found to be 70 mg/m^2. Severe haematological AEs occurred in 26% of patients and non-haematological AEs occurred in 35% of patients, with 22% of discontinuation.

These results compare favourably with other studies assessing twice weekly carfilzomib-based regimens as frontline therapy in elderly patients ineligible for autologous transplantation. The rate of haematological and non-haematological AEs were similar to, or

Table 3. Treatment-related adverse events during induction in RP2D patients

Events, n (%)	N = 54	
	Any grade	Grades 3–5
Haematological		
⩾1 Event	39 (72)	14 (26)
Neutropenia	17 (31)	12 (22)
Thrombocytopenia	18 (33)	4 (7)
Anaemia	21 (39)	1 (2)
Non-haematological		
⩾1 event	50 (92)	19 (35)
Cardiac events	13 (24)	5 (9)
Hypertension	6	—
Acute pulmonary oedema	3	3
Heart failure	3	2
Arrhythmia	1	—
Vascular events	2 (4)	1 (2)
Pulmonary thromboembolism	1	1
Other	1	—
Constitutional events	16 (30)	2 (4)
Oedema	2	—
Fever	7	1
Fatigue	5	1
Other	2	—
Dermatological events	0	0
Gastrointestinal events	21 (39)	2 (4)
Constipation	4	1
Diarrhoea	4	—
Nausea/vomiting	10	—
Other	3	1
Infections events	7 (13)	4 (7)
Upper respiratory tract	4	1
Pneumonia	2	2
Sepsis	1	1
Neurological events	10 (18)	3 (6)
Insomnia	2	—
Reversible posterior leukoencephalopathy	1	1
Mood alteration	4	1
Headache	2	1
Other	1	—
Metabolic events	10 (18)	3 (6)
AST/ALT increase	4	2
Hyperglycaemia	1	—
Hyponatriemia	1	1
Hyperkaliemia	1	—
Renal events	6 (11)	2 (4)
Acute renal failure	3	1
Chronic renal failure	1	—
Creatinine increase	1	1
Other	1	—
Respiratory events	4 (7)	1 (2)
Dyspnoea	1	—
Adult respiratory distress syndrome	1	1
Other	2	—
Other events	2 (4)	0

lower than, those reported in our previous study with twice weekly carfilzomib at the dose of 36 mg/m^{2} in combination with cyclophosphamide and dexamethasone.[15] Myelosuppression induced by cyclophosphamide was lower than the one observed with melphalan in combination with twice-weekly carfilzomib and prednisone, which led to grade 3–4 neutropenia in 38% of patients and grade 3–4 thrombocytopenia in 28%.[20] This lower myelosuppression translated in a lower incidence of infections (13% in our trial versus 53% in the carfilzomib and prednisone trial).[20] The recent results of CLARION study comparing carfilzomib

and prednisone with VMP showed no difference in PFS between the two regimens.[21] This is probably due to a higher incidence of severe AEs and of toxic deaths in patients receiving carfilzomib and prednisone. Cyclophosphamide may therefore represent a valid, less toxic alternative to melphalan for elderly patients with NDMM.

This effect has been observed even in the context of bortezomib-based treatments with higher rates of grade 3 neutropenia (40% vs 30%, respectively) and thrombocytopenia (37% vs 12%, respectively) in the VMP therapeutic scheme compared with bortezomib–cyclophosphamide–dexamethasone.[7,22]

Regarding the choice of the optimal upfront proteasome inhibitor in elderly NDMM patients, a direct comparison between wKCyd regimen and similar bortezomib-based regimens is difficult because of the heterogeneity of involved studies. However, wKCyd compared favourably with VMP (⩾VGPR rate 69% vs 41%) and bortezomib–cyclophosphamide–dexamethasone (⩾VGPR rate 69% vs 41%) in terms of efficacy.[7,22] As for safety, grade 3 peripheral neuropathy rate was 15% with the above-mentioned bortezomib-based regimens, whereas it was not an issue in the current trial. However, AEs resulting in discontinuation of therapy were slightly more frequent with the wKCyd regimen than with VMP and bortezomib–cyclophosphamide–dexamethasone (22% vs 15% vs 12%, respectively).

During induction, cardiovascular events occurred in 24% of patients, including 9% of grade 3–5 AEs, although all patients had a baseline left ventricular ejection fraction ⩾55%. Among severe cardiac AEs, the most frequent were heart failure and pulmonary oedema. The rate of hypertension was 11% during induction, limited to grade 1–2, but it increased to 15% during maintenance, including 10% of grade 3–4. In the present study, cardiovascular toxicity was higher compared with our previous KCyD trial with twice-weekly carfilzomib at 36 mg/m^{2}, but similar to that reported in more recent trials in NDMM setting, such as the CLARION study,[21] as well as in relapsed/refractory multiple myeloma patients, such as the ASPIRE and the ENDEAVOR trials.[12,23] The effect of proteasome inhibition on cardiovascular system has only recently begun to be understood. Yet, there is some evidence, suggesting that the ubiquitine-proteasome system must be considered a modulator of endothelial (dys)-function by interaction with several essential regulatory pathways and regulation of endothelial-dependent contracting and vasodilation factors. Endothelial dysfunction is accompanied by deterioration in this balance, with progressive reduction in vasodilation factors and with an increase in vasoconstriction mediators. Available data suggest that short-term, non-toxic proteasome inhibitors may be beneficial, whereas higher proteasome-inhibitor doses and long-term administration are associated with more disadvantageous effects in the vasculature.[24] These data suggested a time- and dose-dependent effect of carfilzomib. For patients, especially elderly ones, candidate to treatment with carfilzomib, a careful assessment before starting treatment and monitoring during treatment is suggested. Before starting treatment, clinicians should evaluate medical history—to determine previous cardiac events and cardiovascular risk factors—and perform a physical examination to assess blood pressure (BP), valvular heart disease and signs of heart failure. A 12-lead electrocardiogram is essential to detect possible markers of structural heart disease including the left ventricular damage/dysfunction, arrhythmias, evidence of previous myocardial infarction or evidence of the left ventricular hypertrophy. The ENDEAVOR substudy found limited utility for serial screening with ECHO to mitigate cardiac risk.[25] Nevertheless, four recent guidelines suggest that a baseline ECHO is useful to measure the left ventricular ejection fraction before starting treatment.[26–29] Finally, a 24 h BP monitoring (ambulatory BP monitoring) or home BP monitoring for at least 7–14 days is needed to look for unknown or borderline or uncontrolled

hypertension. The target BP is ⩽ 140/90 mm Hg: patients with BP > 140/90 need adjustments in their BP medication before receiving carfilzomib. During carfilzomib administration, clinicians should screen for and actively manage modifiable cardiovascular risk factors (smoking, hypertension, diabetes, dyslipidemia and obesity) in all patients. There are concerns that fluid overload may have a role in developing cardiovascular AEs. If poorly tolerated, aggressive hydration may be reduced or discontinued, and signs and symptoms of tumour lysis syndrome should be monitored. Home BP monitoring is recommended: if BP > 140/90 mm Hg, carfilzomib should be temporary discontinued and hypertension medication needs adjustments until blood pressure target (< 140/90) is reached. Future collaborative trials including haematologists, cardiologists and regulatory agencies may clarify how to best manage cardiovascular side effects.

We showed that treatment with wKCyd was highly effective in elderly NDMM patients. Responses were rapid and deep, and improved over time. During induction, 66% of patients achieved ⩾ VGPR, including 30% nCR and 15% CR. During maintenance, 88% of patients achieved ⩾ VGPR, including 54% nCR and 29% CR. Fifty percent of CR/sCR patients achieved CR/sCR during maintenance with a mean time to CR/sCR > 12 months. After a median follow-up of 19.7 months, the 2-year PFS and OS rates were 53.2% and 81%, respectively. The achievement of CR has been associated with prolonged PFS and OS, also in elderly patients.[30] In addition, maintenance therapy improves outcome, and its role has been extensively investigated.[31–33]The ideal treatment should combine high response rates and continuous therapy to prolong long-term outcome. Despite the limitations of cross-trial comparisons, the promising antitumour activity observed with weekly carfilzomib in this study was similar to—or even better than—that reported in our prior study with twice weekly carfilzomib and also to the one observed in the French phase 1/2 trial and in the CLARION trial, both with twice weekly carfilzomib plus melphalan–prednisone.[20,21] The improved results with wKCyd were probably due to the better risk/benefit profile and the continuous treatment with carfilzomib. Nevertheless, better results were seen with carfilzomib–lenalidomide–dexamethasone combination, which induced an at least nCR rate of 62–63%, including a sCR rate of 42% and a 2-year PFS rate of 92%.[34,35] The higher CR rate observed in these patients was probably attributable to the combination of a proteasome inhibitor and an immunomodulatory agent, and to the enrolment of younger patients. Indeed, in that studies, median age was 59–60 years, with 57–58% of patients < 65 years and thus potentially transplant eligible. Of note, the combination KCyd has the advantage of a lower cost, providing good efficacy. Furthermore, as survival continues to improve in MM patients, it is essential to consider subsequent treatment options when choosing therapy at diagnosis. As KCyd regimen does not use bortezomib or lenalidomide, patients initially treated with KCyd may still receive these other agents at relapse.

No statistically significant PFS difference was observed in patients with high risk cytogenetic status compared with those with standard risk (2-year PFS 68% versus 53%, hazard ratio 0.45, P = 0.24). Although the number of patients in this subgroup analysis was limited and definitive conclusions cannot be drawn, these data are consistent with those reported in the subgroup analysis of the ASPIRE trial. This pre-planned analysis showed that carfilzomib–lenalidomide–dexamethasone in relapsed/refractory patients improved the poor prognosis associated with high-risk cytogenetics.[36] Similar results were reported in two phase 2 studies with carfilzomib–lenalidomide–dexamethasone in NDMM.[34,35] These data, if confirmed on a larger number of patients, may have important implications regarding risk-adapted therapy.

In conclusion, our study showed that in elderly patients ineligible for transplant, the more convenient dosing schedule wKCyd was highly effective with excellent CR rates and had an acceptable toxicity.

CONFLICT OF INTEREST

ACKNOWLEDGEMENTS

AUTHOR CONTRIBUTIONS

All authors participated in the interpretation of data, and reviewed and approved all drafts of the manuscript, including the decision to submit for publication. SB, LDP, PS and MB contributed to the study design. SB conducted the data analyses. SB and MB wrote the first draft of the manuscript. All authors provided patients and/or study materials.

REFERENCES

1 Palumbo A, Anderson K. Multiple myeloma. N Engl J Med 2011; 364: 1046–1060.
2 Palumbo A, Bringhen S, Caravita T, Merla E, Capparella V, Callea V et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet 2006; 367: 825–831.
3 San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008; 359: 906–917.
4 Richardson PG, Briemberg H, Jagannath S, Wen PY, Barlogie B, Berenson J et al. Frequency, characteristics, and reversibility of peripheral neuropathy during treatment of advanced multiple myeloma with bortezomib. J Clin Oncol 2006; 24: 3113–3120.
5 Palumbo A, Waage A, Hulin C, Beksac M, Zweegman S, Gay F et al. Safety of thalidomide in newly diagnosed elderly myeloma patients: a meta-analysis of data from individual patients in six randomized trials. Haematologica 2013; 98: 87–94.
6 Morgan GJ, Davies FE, Gregory WM, Russell NH, Bell SE, Szubert AJ et al. Cyclophosphamide, thalidomide, and dexamethasone (CTD) as initial therapy for patients with multiple myeloma unsuitable for autologous transplantation. Blood 2011; 118: 1231–1238.
7 Kumar S, Flinn I, Richardson PG, Hari P, Callander N, Noga SJ et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood 2012; 119: 4375–4382.
8 Benboubker L, Dimopoulos MA, Dispenzieri A, Catalano J, Belch AR, Cavo M et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med 2014; 371: 906–917.
9 Onyx Pharmaceuticals Inc. Kyprolis (carfilzomib) for Injection, for intravenous use. Fulll Prescribing Information (Internet). FDA. 2012 (cited 9 May 2017). Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202714lbl.pdf.
10 Jakubowiak AJ. Evolution of carfilzomib dose and schedule in patients with multiple myeloma: a historical overview. Cancer Treat Rev 2014; 40: 781–790.
11 Papadopoulos KP, Siegel DS, Vesole DH, Lee P, Rosen ST, Zojwalla N et al. Phase I study of 30-minute infusion of carfilzomib as single agent or in combination with low-dose dexamethasone in patients with relapsed and/or refractory multiple myeloma. J Clin Oncol 2015; 33: 732–739.
12 Dimopoulos MA, Moreau P, Palumbo A, Joshua D, Pour L, Hájek R et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients

with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *Lancet Oncol* 2016; **17**: 27–38.

13 Bringhen S, Larocca A, Rossi D, Cavalli M, Genuardi M, Ria R *et al*. Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. *Blood* 2010; **116**: 4745–4753.

14 Berenson JR, Cartmell A, Bessudo A, Lyons RM, Harb W, Tzachanis D *et al*. CHAMPION-1: a phase 1/2 study of once-weekly carfilzomib and dexamethasone for relapsed or refractory multiple myeloma. *Blood* 2016; **127**: 3360–3368.

15 Bringhen S, Petrucci MT, Larocca A, Conticello C, Rossi D, Magarotto V *et al*. Carfilzomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed multiple myeloma: a multicenter, phase 2 study. *Blood* 2014; **124**: 63–69.

16 Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos M-V *et al*. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol* 2014; **15**: e538–e548.

17 US Dept of Health and Human Services - National Institutes of Health - National Cancer InstituteCommon Terminology Criteria for Adverse Events (CTCAE) v.4 (Internet). 2017 (cited 9 May 2017). Available from https://evs.nci.nih.gov/ftp1/CTCAE/About.html.

18 Rajkumar SV, Harousseau J-L, Durie B, Anderson KC, Dimopoulos M, Kyle R *et al*. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood* 2011; **117**: 4691–4695.

19 Munshi NC, Anderson KC, Bergsagel PL, Shaughnessy J, Palumbo A, Durie B *et al*. Consensus recommendations for risk stratification in multiple myeloma: report of the International Myeloma Workshop Consensus Panel 2. *Blood* 2011; **117**: 4696–4700.

20 Moreau P, Kolb B, Attal M, Caillot D, Benboubker L, Tiab M *et al*. Phase 1/2 study of carfilzomib plus melphalan and prednisone in patients aged over 65 years with newly diagnosed multiple myeloma. *Blood* 2015; **125**: 3100–3104.

21 Facon T, Lee JH, Moreau P, Niesvizky R, Dimopoulos MA, Hajek R *et al*. Phase 3 study (CLARION) of carfilzomib, melphalan, prednisone (KMP) v bortezomib, melphalan, prednisone (VMP) in newly diagnosed multiple myeloma (NDMM). In: *International Myeloma Workshop* 2017 Abstract OP-044 e37–e38.

22 San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M *et al*. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med* 2008; **359**: 906–917.

23 Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Špička I, Oriol A *et al*. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2015; **372**: 142–152.

24 Stangl K, Stangl V. The ubiquitin-proteasome pathway and endothelial (dys) function. *Cardiovasc Res* 2010; **85**: 281–290.

25 Russell SD, Lyon A, Lenihan DJ, Moreau P, Joshua D, Chng W-J *et al*. Serial echocardiographic assessment of patients (Pts) with relapsed multiple myeloma (RMM) receiving carfilzomib and dexamethasone (Kd) Vs bortezomib and dexamethasone (Vd): a substudy of the Phase 3 Endeavor Trial (NCT01568866). *Blood* 2015; **126**, Abstr. 4250.

26 Armenian SH, Lacchetti C, Barac A, Carver J, Constine LS, Denduluri N *et al*. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2017; **35**: 893–911.

27 Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M *et al*. ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J* 2016; **37**: 2768–2801.

28 Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M *et al*. ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013; **34**: 2159–2219.

29 Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG *et al*. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. *J Clin Hypertens (Greenwich)* 2014; **16**: 14–26.

30 Gay F, Larocca A, Wijermans P, Cavallo F, Rossi D, Schaafsma R *et al*. Complete response correlates with long-term progression-free and overall survival in elderly myeloma treated with novel agents: analysis of 1175 patients. *Blood* 2011; **117**: 3025–3031.

31 Ludwig H, Durie BGM, McCarthy P, Palumbo A, San Miguel J, Barlogie B *et al*. IMWG consensus on maintenance therapy in multiple myeloma. *Blood* 2012; **119**: 3003–3015.

32 Sonneveld P, Schmidt-Wolf IGH, van der Holt B, El Jarari L, Bertsch U, Salwender H *et al*. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/GMMG-HD4 trial. *J Clin Oncol* 2012; **30**: 2946–2955.

33 Palumbo A, Hajek R, Delforge M, Kropff M, Petrucci MT, Catalano J *et al*. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. *N Engl J Med* 2012; **366**: 1759–1769.

34 Jakubowiak AJ, Dytfeld D, Griffith KA, Lebovic D, Vesole DH, Jagannath S *et al*. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. *Blood* 2012; **120**: 1801–1809.

35 Korde N, Roschewski M, Zingone A, Kwok M, Manasanch EE, Bhutani M *et al*. Treatment with carfilzomib-lenalidomide-dexamethasone with lenalidomide extension in patients with smoldering or newly diagnosed multiple myeloma. *JAMA Oncol* 2015; **1**: 746.

36 Avet-Loiseau H, Fonseca R, Siegel D, Dimopoulos MA, pi ka I, Masszi T *et al*. Carfilzomib significantly improves the progression-free survival of high-risk patients in multiple myeloma. *Blood* 2016; **128**: 1174–1180.

Supplementary Information accompanies this paper on the Leukemia website (http://www.nature.com/leu)