Association of hypertension and cardiac events in patients with multiple myeloma receiving carfilzomib: practical management recommendations

Multiple myeloma (MM) is a common incurable haematological malignancy with an incidence of approximately 5500 patients per year in the UK.[1] Carfilzomib (CFZ), a second generation, irreversible proteasome inhibitor[2] is licensed for patients with relapsed MM, having demonstrated improved outcomes compared to standard therapies.[3,4] However, CFZ is also associated with hypertension (HTN) and rarely cardiac events. The pathogenesis remains unclear, but may be related to changes in endothelial nitric oxide synthase levels and nitric oxide bioavailability with consequent endothelial dysfunction and vasoconstriction.[5] Murine models have demonstrated that CFZ can reduce left ventricular function through adenosine monophosphate-kinase signalling pathways with resultant cardiotoxicity.[6] The incidence of CFZ-associated HTN in a pooled analysis of clinical trials (n = 2044) showed an all grade HTN incidence of 18·5%, with ≥G3 toxicity rates of 5·9%.[7] However, real-world data are lacking.

The primary objective was to identify HTN rates and cardiac events in MM patients being treated with CFZ at varying doses. A retrospective analysis of electronic records of 89 patients treated with CFZ (December 2015–May 2019) at University College Hospital, London, UK was undertaken. BP readings were performed in triplicate, 10 min apart, prior to each CFZ infusion and median BP recorded. HTN was graded as per Common Toxicity Criteria for Adverse Events (CTCAE) criteria V4: Grade (G) 1: pre-HTN: 120–139/80–89 mm Hg, G2: Stage 1 HTN: 140–159/90–99 mmHg or to >140/90 mmHg if previously in normal range or symptomatic increase in diastolic BP > 20 mmHg , G3: Stage 2 HTN ≥ 160/100 mmHg , G4: malignant HTN or hypertensive crisis. Clinically significant HTN was defined as ≥G2 HTN. Pulmonary hypertension was defined as per American College of Cardiology Criteria [mean pulmonary arterial pressure (mPASP > 25 mm Hg)] by echocardiography.

In total, 89 patients and 2 093 consecutive BP readings were evaluated with a mean of 24 BP assessments per patient (1–74) (see Fig 1 for demographics). Thirty patients (33·7%) had a prior history of HTN and 10 (11·2%) had a prior history of cardiac co-morbidities including ischaemic heart disease and arrhythmias. Initial dosing of CFZ was 20 mg/m^2, increasing to biweekly 27 mg/m^2 [n = 35 (39·3%)], 36 mg/m^2 [n = 19 (21·3%)], 45 mg/m^2 [n = 3 (3·4%)], 56 mg/m^2 [biweekly n = 34 (38·2%), weekly n = 1 (1·1%)], 70 mg/m^2 weekly [n = 1 (1·1%)] (Fig 1). Median time on therapy was five months (0–27) with a median of 6 (1–27) cycles.

HTN (all grade) was recorded in 60 patients (67·4%) , with clinically significant HTN (≥G2) occurring in 31 patients (34·8%) [G2: n = 10 (11·2%)]. Incidence of treatment-emergent HTN was similar for those with and without pre-existing HTN (χ^2 test, P = 0·77) [G1–2 HTN: n = 19 (21·3%) in patients with a prior history of HTN vs. n = 20 (22·5%) for those with no prior history of HTN, and ≥G3 HTN n = 9 (10·1%) vs. ≥G3 HTN n = 12 (13·5%) with no prior history of HTN]. Twelve (13·5%) required intervention with antihypertensive medications for ≥G2 HTN which then returned BP to baseline levels (Fig 1).

Patients treated at ≥45 mg/m^2 of CFZ had more episodes of HTN compared to tb and dexamethasone versus bortezomib and dexamethose at 27–36 mg/m^2 (OR 3·7, 95% CI 1·45–8·81, P < 0·01) despite similar co-morbidities. Age >65 years was not associated with increased risk of HTN (OR 1·81, 95% CI 0·71–4·49, P = 0·21) nor was ethnicity (χ^2 test, P = 0·21).

Twenty-five (28·1%) patients required treatment interruption for any cause, of which 12 (13·4%) were due to ≥G2 HTN [median seven days (1–23)]. Thirteen (14·6%) patients required dose reduction for any cause, of which nine (9·7%) were for HTN, predominantly at CFZ 56 mg/m^2, [n = 7 (7·5%), 27 mg/m^2: n = 1 (1·1%), 36 mg/m^2: n = 2 (2·2%)]. The planned median cumulative dose for the number of cycles received was 792 mg/m^2 overall (36–4 144), similar to actual median cumulative dose delivered: 776 mg/m^2 (36–3248). However, higher CFZ doses were less likely to have the planned dose delivered (≥45 vs. 27–45 mg/m^2 (χ^2 test, P < 0·01)). Median planned *versus* actual dose delivered for number of cycles of CFZ received was: 27 mg/m^2, 472 vs. 364; 36 mg/m^2, 756 vs. 688; 45 mg/m^2, 785 vs. 727; 56 mg/m^2, 2 616 vs. 1 204; 70 mg/m^2, 1 110 vs. 770.

Seventeen (19·1%) patients developed cardiac complications including pulmonary HTN [n = 11, (12·4%)] and cardiac failure [n = 6 (6·7%)]. Four patients had a previous history of cardiac disease [ischaemic heart disease (IHD) n = 3, and arrhythmias n = 1], and one had elevated pulmonary pressures pre-therapy. Unlike HTN, cardiac complications were not associated with CFZ dose (<36 vs. ≥36 mg/m^2 OR 1·6, 95% CI 0·55–4·82, P = 0·40). Cardiac complications, however, were associated with development of HTN (OR 4·2, 95% CI 1·43–13·24, P < 0·01) but not a prior history (OR 1·3,

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Patient Characteristics (n = 89)	
Sex	M 56 (62·9%) F 33 (37·1%)
Median Age	61 (34-87)
Ethnicity	
Caucasian	59 (66·3%)
African/Caribbean	11 (12·4%)
Arabic	4 (4·5%)
Other	8 (9·0%)
Unknown	7 (7·8%)
ISS	
Stage 1	46 (51·7%)
Stage 2	14 (15·7%)
Stage 3	25 (28·1%)
Unknown	4 (4·5%)
Cytogenetics	
Standard Risk	56 (62·9%)
High Risk	16 (18·0%)
Unknown	17 (19·1%)
Prior HTN history	30 (33·7%)
No Prior HTN history	59 (66·3%)
Prior cardiac comorbidities:	
Total	10 (11·2%)
Ischaemic heart disease	4 (4·5%)
Dysrhythmias	6 (6·7%)
CFZ regimens used	
Kd	13 (14·6%)
KCd	46 (51·7%)
KRd	20 (22·5%)
Other CFZ containing regimens	10 (11·2%)
Median prior lines of therapy	1 (0-7)
ndMM	41 (46·1%)
Relapse	48 (53·9%)
Treated as standard of care	8 (9·0%)
Treated privately	27 (30·3%)
Treated within clinical trial setting	54 (60·7%)
Prior treatment with PI	39 (43·8%)
No prior treatment with PI	48 (54·0%)
Unknown	2 (2·2%)
No. of antihypertensive medications medications required to control HTN	
1	7 (7·9%)
2	3 (3·4%)
3	2 (2·2%)
Antihypertensive medications used to treat HTN	
ACE inhibitors/Angiotensin II receptor antagonists	4 (4·5%)
Alpha adrenoceptor antagonists	2 (2·2%)
Calcium channel antagonists	8 (9·0%)
Thiazide like diuretics	2 (2·2%)

Fig 1. Baseline characteristics. ISS stage 1: B2 microglobulin <3.5 mg/l and albumin > 35 g/l; ISS stage 3: B2 microglobulin >5.5 mg/l; ISS stage 2: patients not fulfilling criteria for stage 1 or 3. Adverse cytogenetics defined as per International Myeloma Working Group (IMWG) criteria: t (4;14), t(14;16), t(14;20) or del 17p. HTN, hypertension; CFZ, carfilzomib; PI, proteasome inhibitor; Kd, carfilzomib/dexamethasone; KCd, carfilzomib/cyclophosphamide/dexamethasone; KRd, carfilzomib/lenalidomide/dexamethasone; ndMM, newly diagnosed multiple myeloma. Information on CFZ regimens, doses and median number of cycles of CFZ therapy were collected from electronic records.

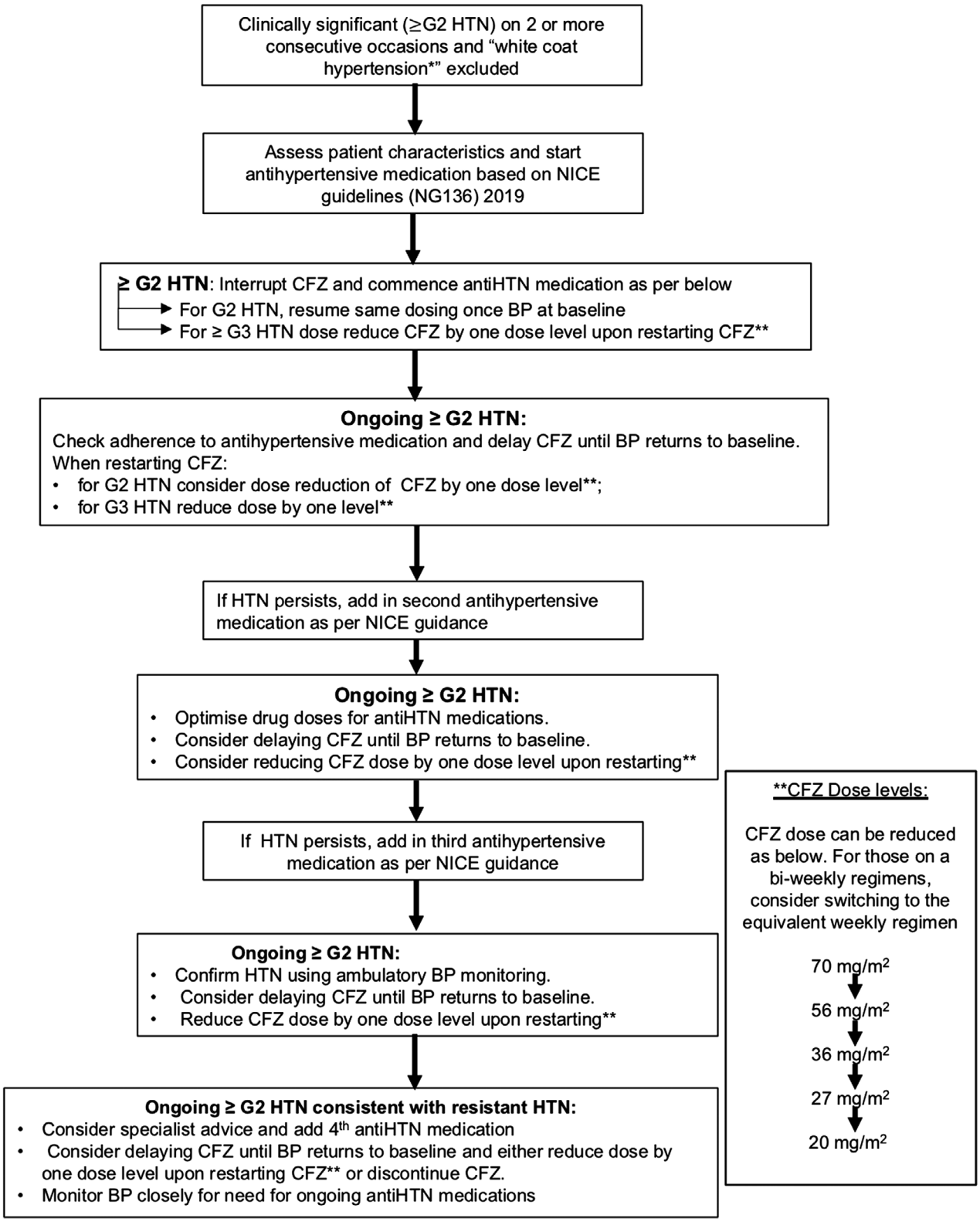

Fig 2. Treatment algorithm for management of HTN in patients treated with CFZ therapy. *White coat HTN definition persistently elevated clinic BP and a normal home or ambulatory BP day time average. i.e. <135/85 mm Hg (NICE 2011). Adapted from NICE guidelines (NG 136) Aug 2019.[8,10]

95% CI 0·43–3·56, $P = 0·68$). One (1·2%) death occurred attributable to cardiac failure and progressive disease.

Despite this, progression-free survival (PFS) and overall survival (OS) were unaffected by HTN, cardiac toxicity, pulmonary HTN or HTN-related treatment delays (Figure S1) (median OS not reached regardless of developing any cardiovascular adverse events, HR 1·41, 95% CI 0·87–2·30, $P = 0·14$); with a median follow-up of 43 months. However, there was a trend towards inferior PFS with cardiac toxicity (13·5 vs. 31 months, HR 1·44, $P = 0·3$).

These data demonstrated a higher incidence of HTN compared to that reported in clinical trials. This may be due to different co-morbidities and cardiovascular risk between real-world and trial populations as well as different management approaches with standard practice *versus* protocol-defined interventions. Additionally, all BP measurements were used in this analysis which may not always be recorded in the databases of trials. Dose reductions were more frequent at higher CFZ doses leading to a reduction in total cumulative dose received. However, treatment with anti-hypertensives was effective in resolving further hypertensive episodes. Of note, PFS was not affected despite dose modifications and interruptions.

This highlights the importance of regular BP monitoring prior to each CFZ infusion and potentially keeping a BP diary at home in cases of white coat HTN (NCGC 18/34 2011). This is of particular relevance at higher CFZ doses. Adequate BP monitoring will allow timely intervention with anti-hypertensives to allow ongoing CFZ dosing and minimise subsequent cardiovascular complications. This is particularly relevant in patients developing pre-HTN on therapy, as they are at increased risk of developing clinically significant HTN and cardiovascular adverse events while on treatment.

In order to optimise HTN management for patients receiving CFZ, we have developed practical recommendations in accordance with National Institute for Health and Care Excellence guidelines for HTN[8,9] and European Myeloma Network consensus guidelines for cardiovascular events in patients treated with CFZ (Fig 2).[10]

In summary, these data demonstrated an association of HTN with CFZ dose and the subsequent development of cardiac events. The rates of HTN reported from our dataset are higher than previously reported trial data. We therefore recommend regular, close BP monitoring and early intervention for low-grade HTN to prevent cardiovascular adverse events.

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Conflicts of interest

DJBM is also an employee of, and holds stocks/shares in, GSK. GSK has had no input in the conception, design, conduct, interpretation, or decision to publish this study. KLY has received funding from Amgen. NKR has received honoraria and travel support from Celgene, Janssen and Takeda. He has also undertaken a consulting/advisory role for Celgene, Amgen, Takeda and Karyopharm.

Author contributions

SJC, RP, ED, KML and SC collected the data. SJC and RP analysed the data. SJC and RP wrote the manuscript. SJC, DJB, CK, LL, JS, AW, NKR, KLY and RP critically revised the manuscript.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Effect of HTN and cardiac toxicity on PFS and OS.

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