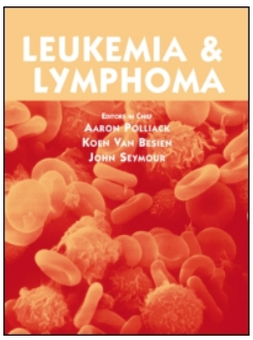

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Carfilzomib-based combination regimens are highly effective frontline therapies for multiple myeloma and Waldenström's macroglobulinemia

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ABSTRACT

Multiple myeloma (MM) and Waldenström's macroglobulinemia (WM) are plasma cell disorders often treated with proteasome inhibitors. Recently, several studies evaluated carfilzomib as an initial treatment for these diseases and reported outstanding clinical outcomes. We conducted a retrospective study to report the efficacy and safety of frontline carfilzomib-based combinations in a standard of care setting. From 2014 until 2016 we identified newly diagnosed MM ($n = 54$) and WM ($n = 6$) patients treated with carfilzomib as initial therapy who met study inclusion criteria. The response rate for myeloma patients was 98% with 77% of patients undergoing upfront autologous stem cell transplant. The clinical benefit for WM was 100% with all patients having a resolution of B symptoms and anemia after treatment. Carfilzomib-based regimens are well tolerated and offer a neuropathy sparing approach with excellent responses both in newly diagnosed MM and WM making them a good choice for the frontline treatment of these diseases.

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Myeloma; waldenström; carfilzomib; efficacy; toxicity; frontline

Introduction

Multiple myeloma (MM) is the second most common hematological malignancy. It is a plasma cell disorder and represents about 1.8% of all new cancer diagnoses. Worldwide, about 154,000 patients are diagnosed each year with MM and 101,000 dies of this disease [1]. Although MM remains incurable, the recent approval and availability of novel agents (proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies) have dramatically changed the management landscape of MM. The main goals of treatment are to prolong survival by achieving the best possible response while minimizing treatment-related toxicities to maintain quality of life. Three-drug regimens that include bortezomib, lenalidomide (or thalidomide) with dexamethasone have emerged as a favorable frontline strategy but maintaining dose levels over the long term can be limited by toxicities especially peripheral neuropathy [2–5].

Waldenström's macroglobulinemia (WM) is a rare, incurable disease characterized by the infiltration of the bone marrow by clonal lymphoplasmacytic cells and a monoclonal IgM gammopathy in the blood [6]. About 1400 cases are diagnosed in the United States alone each year [7]. There is no standard of care for frontline treatment. The proteasome inhibitor bortezomib is active in WM and has shown response rates up to 95% in combination with rituximab, with a median progression-free survival (PFS) exceeding four years [8]. Unfortunately, in this study, 70% of patients developed grade >2 peripheral neuropathy resulting in premature discontinuation of bortezomib in 61% of patients.

Carfilzomib is a second-generation highly selective and irreversible proteasome inhibitor that has shown impressive response rates in relapsed and refractory MM with an acceptable toxicity profile including limited neuropathy after prolonged treatment [9–12]. Preclinical studies have shown lack of neurodegeneration in vitro and less neurotoxicity in animal studies [13]. To our knowledge, two phase II clinical trials have been published using KRd (carfilzomib, lenalidomide, and dexamethasone) for newly diagnosed MM. In the

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first study 53 patients were treated. After a median of 12 cycles, ORR (overall response rate) was 98% [81% ≥VGPR (very good partial response)] and PFS at 24 months was 92%. The most common severe (grade 3/4) toxicities were hypophosphatemia (25%), hyperglycemia (23%), anemia (21%), thrombocytopenia (17%), and neutropenia (17%). Mild to moderate peripheral neuropathy was seen in 23% of patients [14]. In the second study involving 45 patients, ORR after follow up of 17.3 months was 98% with 56% CR (complete response) (all CR patients achieved MRD (minimal residual disease) negative by flow or next-generation sequencing) and 89% ≥VGPR. Eighteen months PFS and OS (overall survival) were 92% and 100% respectively. Most common grade 3/4 adverse events were electrolyte imbalance (36%), neutropenia (33%), anemia (27%) and thrombocytopenia (24%). None of the patients had neuropathy grade 3 or greater [15]. These two studies set the stage for a phase III international, multicenter study that is comparing carfilzomib to bortezomib with lenalidomide and dexamethasone for NDMM (NCT01863550). This study is currently accruing and results could change the standard of care for NDMM treatment.

Carfilzomib has also been studied in combination with cyclophosphamide in frontline myeloma. A phase II study included 58 older patients who received up to nine cycles of carfilzomib, cyclophosphamide, and dexamethasone followed by carfilzomib maintenance until disease progression or intolerance [16]. ORR was 95% (71% ≥VGPR) and PFS was 76% at 18 months.

In patients with symptomatic WM, Treon et al. reported a phase II study where 31 patients were treated with carfilzomib, rituximab, and dexamethasone [17]. Long-term results for this study showed an ORR of 81% and major response rate of 71% [18]. These responses were independent of $MYD88^{L265P}$ or $CXCR4^{WHIM}$ mutation status. The median PFS for all patients was 52 months and all patients were alive. Most common Grade ≥3 toxicities were hyperglycemia (23%), hyperlipasemia (16%) and neutropenia (10%). Only one patient had grade 2 peripheral neuropathy.

These studies provide the rationale for using carfilzomib based combinations in the frontline setting both in MM and WM. In this study, we aim to report the efficacy and safety of frontline carfilzomib based combinations in MM and WM in a standard of care setting.

Methods

Patients and study design

In this retrospective, single-center study conducted at the University of Texas MD Anderson Cancer Center (Houston, TX, USA), we queried our ambulatory and inpatient (IPATC) database to identify subjects who were diagnosed with symptomatic MM or WM and received carfilzomib as initial therapy from 4/1/2014 to 11/30/2016 (Figure 1). Investigational carfilzomib was excluded. The study was approved by our Institutional Review Board. We identified 54 patients with MM

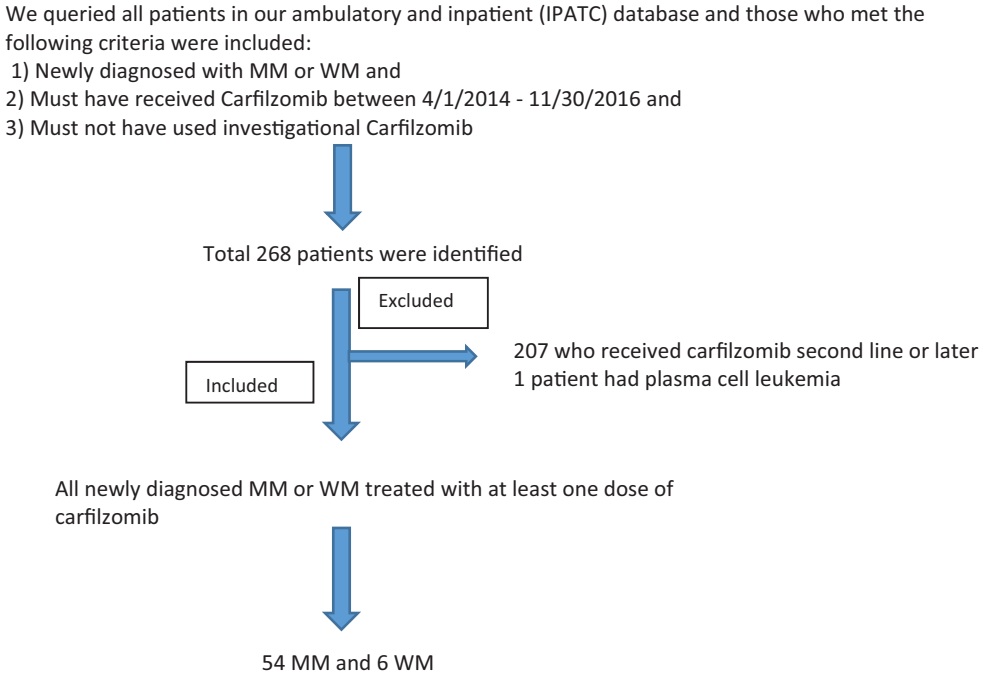

Figure 1. Study design and inclusion criteria.

(including one with concurrent lambda AL amyloidosis) and six patients with WM. Responses were retrospectively assessed based on guidelines published by the International Myeloma Working Group [19] and the VI international workshop on WM [20].

Treatment

Transplant eligible patients with multiple myeloma received carfilzomib based induction for 2–4 cycles followed by autologous stem cell transplantation (ASCT) and then maintenance (as per treating physician's discretion). Transplant ineligible patients (or those who chose to delay transplant) received carfilzomib based induction until best response followed by maintenance (as per treating physician's discretion). Patients with WM received treatment as published by Treon et al [17].

Statistical analysis

Descriptive statistics including median and range for continuous variables, and frequency counts and percentages for categorical variables are provided. The Kaplan Meier method was used to estimate time to event endpoint such as progression-free survival (PFS). Statistical software SAS 9.3 (SAS, Cary, NC) and SPlus 8.2 (TIBCO Software Inc., Palo Alto, CA) were used for all the analyses.

Results

Patient characteristics

Baseline patient characteristic for both cohorts is listed in Table 1 and Table 2. In MM cohort ($n = 54$), the median age at diagnosis was 66 years (range 60–70). Revised International Staging System (RISS) stage I, II or III was present in 20 (37%), 28 (52%) and 6 (11%) patients, respectively. Patients presented with either CRAB criteria ($n = 51$, 94%) or biomarkers of malignancy [i.e. bone marrow plasma cells $\geq$60% or involved/uninvolved serum free light chain ratio $\geq$100] ($n = 3$, 6%) and 22% had extramedullary disease. FISH at diagnosis was available for all patients. Gene expression profiling70 (GEP70, Signal Genetics, Little Rock, AR) was available for 25 patients (Table 3). All MM patients were treated with either KRd (carfilzomib, lenalidomide, and dexamethasone) ($n = 52$, 96%) or KCd (carfilzomib, cyclophosphamide and dexamethasone) ($n = 2$, 4%). Maximum doses of carfilzomib used were 36 mg/m^2 ($n = 44$), 27 mg/m^2 ($n = 6$) and not available ($n = 4$). Patients were treated in 28 day cycles of carfilzomib 20/27/36 mg/m^2 on days 1,2,8,9,15,16; lenalidomide 25 mg orally on days 1–21 and dexamethasone 20 mg on days 1,2,8,9,15,16. Thromboprophylaxis was given with either low molecular weight heparin (40 mg daily SQ) or aspirin (325 mg daily or 81 mg daily). For KCd regimen, patients were treated in 28 day cycles of carfilzomib 20/27/36 mg/m^2 on days 1,2,8,9,15,16; cyclophosphamide 300 mg/m^2 on days 1,8,15 and dexamethasone 20 mg on days 1,2,8,9,15,16. Valtrex/acyclovir adjusted for creatinine clearance was given for shingles prophylaxis with both regimens.

In WM cohort ($n = 6$), median age was 57 years (range 52–74). MYD88 mutation was positive in 5 (83%) while none harbored a CXCR4 mutation. Patients presented with B symptoms ($n = 6$, 100%) and anemia ($n = 5$, 83%). Patients were treated according to the regimen described by Treon et al. [17]. Treatment protocol was; carfilzomib, 20 mg/m^2 (cycle 1)

Table 1. Multiple myeloma patient characteristics.

Characteristics	
Age, median (range)	66 years, (60–70)
R-ISS[a], *n* (%)	
stage I	20 (37)
stage II	28 (52)
stage III	6 (11)
FISH, *n* (%)	
t(11:14)	9 (17)
t(4:14)	4 (7)
t(14;16)	1 (2)
deletion 17p	8 (15)
amplification CKS1B (chromosome 1)	17 (32)
Presentation[b], *n* (%)	
CRAB criteria	51 (94)
Biomarkers of malignancy	3 (6)
Extramedullary disease at diagnosis, *n* (%)	12 (22)
GEP-70 available[c], *n* (%)	25 (46)
Autologous stem cell transplant (ASCT) after initial therapy	36 (77)

[a]Revised - International Staging System; [b]CRAB criteria: hypercalcemia, renal dysfunction, anemia or lytic lesions related to myeloma. Biomarkers of malignancy: involved:uninvolved sFLC ratio $\geq$100, bone marrow plasma cells $\geq$60%, $>$than one 5 mm lesion on MRI;. [c]gene expression profiling through MyPRS Signal Genetics, see Table 3 and Table 4 for more details.

Table 2. Waldenström's macroglobulinemia patient characteristics.

Characteristics	
Age, median (range)	57 (52–74)
Mutation status, *n* (%)	
MYD88 mutated	5 (83)
CXCR4 mutated	0
Presentation at diagnosis, *n* (%)	
B symptoms	6 (100)
Anemia	5 (83)
ISSWM[a] *n* (%)	
Low	1 (17)
Intermediate	4 (67)
High	1 (17)

[a]International Prognostic Scoring System for Waldenström's macroglobulinemia [25,26].

Table 3. GEP70 in NDMM patients ($n = 25$).

GEP70 RISK	Score, median (range)	Subtype, *n*(%)	Best response
Low Risk, $n = 19$ (76%)	32.59 (27.34–39.65)	LB, $n = 4$ (21%) HY, $n = 6$ (32%) MS, $n = 1$ (5%) CD-1, $n = 1$ (5%) CD-2, $n = 7$ (37%)	PR, $n = 6$ (32%) VGPR, $n = 9$ (47%) CR, $n = 3$ (16%) MR, $n = 1$(5%)
Low Risk Borderline, $n = 0$		–	–
High Risk Borderline, $n = 3$ (12%)	45.64 (45.73–48.79)	HY, $n = 1$ (33%) PR, $n = 1$ (33%) CD-1, $n = 1$ (33%)	PR, $n = 2$ (67%) CR, $n = 1$ (33%)
High Risk, $n = 3$ (12%)	57.95 (58.86–60.66)	HY, $n = 1$ (33%) PR, $n = 2$ (67%)	PR, $n = 1$ (33%) VGPR, $n = 1$ (33%) CR, $n = 1$ (33%)

Table 4. GEP/FISH and clinical responses.

Number of patients	FISH	GEP-70	Best response	Progression at median follow up of 7.4 months
4	t (4;14)	Low-risk	1 CR, 1 VGPR, 2 PR	No patients progressed
5	del17p	Low-risk	4 VGPR, 1 PR	No patients progressed
0	t (14;16)	–	–	–
2	del17p	High risk	1 CR, 1 PR	1 patient progressed after 3 cycles of treatment

Using paired *t*-test with two-tailed *p*-value.

and 36 mg/m^2 (cycles 2–6), with dexamethasone, 20 mg, days 1, 2, 8, and 9, and rituximab, 375 mg/m^2, days 2 and 9 every 21 days. Maintenance therapy followed 8 weeks later with carfilzomib, 36 mg/m^2, and dexamethasone, 20 mg, days 1 and 2, and rituximab, 375 mg/m^2, day 2 every 8 weeks for 8 cycles.

Clinical outcomes

In the MM cohort, 52 patients were evaluable for response. After a median of 3 cycles of initial treatment, the ORR was 98% [CR $n = 9$, 17%; VGPR $n = 27$, 52% and PR $n = 15$, 29%]. After ASCT, responses deepened to CR ($n = 18$, 58%), VGPR ($n = 9$, 29%) and PR (partial response) ($n = 4$, 13%). Eleven patients did not undergo ASCT due to comorbidities ($n = 6$), insurance approval ($n = 1$), delayed transplant due to patient preference ($n = 3$) and progressive disease ($n = 1$). The median number of cycles received in this group was 4 and best responses were CR ($n = 3$, 30%), VGPR ($n = 2$, 20%), PR ($n = 5$, 50%) while one patient was not evaluable. At a median follow up of 7.4 months, OS was 100% while median PFS was not reached (Figure 2). Patients with both high-risk GEP and FISH had an early relapse with worse prognosis while patients with high-risk FISH and low-risk GEP did not (Table 4). Five patients discontinued therapy due to toxicity (one of each with pericarditis, shortness of breath, pulmonary toxicity, neuropathy, retroperitoneal bleeding) and three patients due to progressive disease. Data regarding development of hypertension in patients on the

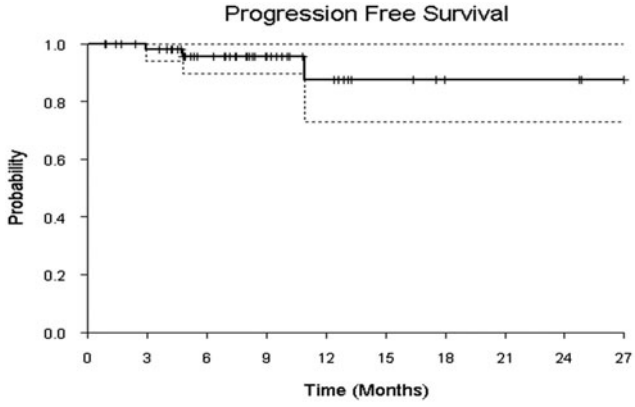

Figure 2. Progression free survival of the multiple myeloma cohort.

study was not available, but there were no reported cases of heart failure in this cohort.

In WM cohort, after a median of 6 cycles of therapy, the major response rate was 67% [CR: $n = 1$ (17%), PR: $n = 3$ (50%)] while 2 (33%) had minor responses. All patients had resolution of B symptoms and anemia after treatment. One patient (MYD88 positive, CXCR4 negative) who achieved a partial response with initial treatment relapsed after 14 months and was subsequently treated with ibrutinib single agent with continued response at the time of writing of this manuscript of 30 months. Only one patient had severe toxicity (debilitating neuropathy attributed to rituximab) prompting therapy discontinuation after 3 cycles [21]. None of the patients developed cardiomyopathy during or after treatment. A decline in immunoglobulin A (IgA) and G (IgG) levels was noted at the end of

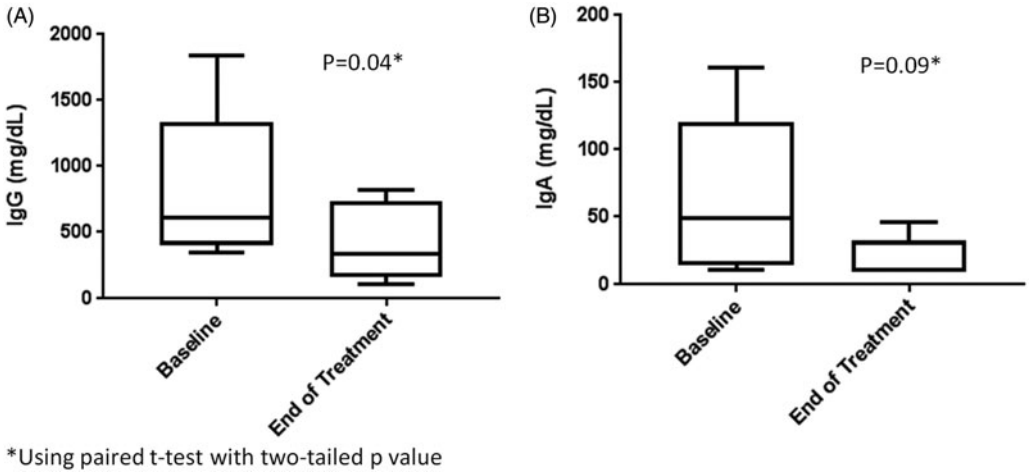

Figure 3. Uninvolved immunoglobulin decline after treatment in WM patients.

treatment (EoT), before maintenance, when compared to baseline for all patients (Figure 3(A,B)) [median and standard deviation IgG baseline 611 ± 575 mg/dL to EoT 344 ± 286 mg/dL and median IgA baseline 48 ± 58 mg/dL to EoT 10 ± 15 mg/dL]. Two patients (33%) started intravenous immunoglobulin (IVIG) treatment for recurrent respiratory infections (bronchitis, pneumonia) 15 and 33 months after initial treatment was completed. Both patients experienced clinical improvement. At a median follow up of 33.5 months, OS was 100% and PFS was 66%. Mutational status did not seem to impact response to therapy.

Discussion

In this study, triple therapy with carfilzomib as a frontline treatment for multiple myeloma showed an overall response rate of 98% after median 3 cycles with 69% VGPR or more. The vast majority of patients were also able to either proceed to ASCT or to collect and store stem cells for use in future ASCT. Responses deepened after ASCT with complete remissions reaching up to 50% of the patients. Eleven patients, who did not undergo upfront ASCT, received a median of 4 cycles of treatment and half of them had either a VGPR or greater response. The results of our study provide further evidence of the efficacy of carfilzomib combinations for newly diagnosed myeloma patients.

Bortezomib-based regimens have been preferred as frontline strategies for patients with multiple myeloma based on efficacy [2,5]. However, toxicities especially peripheral neuropathy can limit administration of planned dose levels over long-term and this could potentially lead to suboptimal clinical outcome. Carfilzomib is a second-generation proteasome inhibitor with great efficacy and a favorable toxicity profile. For example, grade III/IV peripheral neuropathy has been reported in less than 1% of cases [3,10]. Carfilzomib does have the potential of cardiac toxicity and incidence of treatment-related dyspnea has been reported in up to 15% of patients [14]. All patients in this retrospective study had routine monitoring of their cardiac function using echocardiogram before initiation of therapy with repeat cardiac assessment if the patients had any symptoms of cardiac toxicity. Forty-four patients in our study received carfilzomib at a dose of 36 mg/m^2 and only five patients had to discontinue therapy due to toxicities. No cases of heart failure were observed in this cohort of patients.

GEP-70 from CD138+ plasma cells was available for almost half of the patients at diagnosis. Six patients had a high-risk GEP signature and responses were seen in all of them (two had CR, one had VGPR and two had PR). Nine patients also had high-risk FISH (four had t(4:14), and five had del17p) but were low risk on GEP. These nine patients continue to have a response to treatment without progression at the time of this publication. Two patients had high-risk GEP-70 as well as high-risk FISH (del17p). One of them progressed after only 3 cycles of treatment. This data aligns with previous studies that show that a high-risk GEP myeloma signature at diagnosis predicts relapse-free survival [22–24].

Carfilzomib in combination with rituximab and dexamethasone was also very effective in this WM cohort with a major response of 67% and all patients achieving clinical benefit. These responses were durable with only one patient having relapsed at the time of this publication. This regimen was overall very well tolerated with only one incidence of severe peripheral neuropathy following initial treatment which was deemed to be unlikely related to carfilzomib/

dexamethasone [21]. All patients had decreased levels of IgA and IgG after treatment and two patients required initiation of IVIG therapy due to recurrent respiratory infections which resulted in clinical improvement.

Some of the limitations of our data include the short follow up, relatively low number of patients and the retrospective nature of this study. Despite this, we analyzed all consecutive patients seen at our institution who received carfilzomib from 2014 to 2016 as front-line treatment and based on clinical characteristics the patients are representative of a newly diagnosed MM and WM cohort.

In conclusion, our data suggest that carfilzomib based regimens are well tolerated and offer a neuropathy sparing approach with excellent responses in newly diagnosed MM and WM making them a good choice for frontline treatment of these diseases. GEP may identify patients who have a high risk of early relapsed after treatment with carfilzomib and reduced relapsed free survival. A randomized phase III study is comparing the efficacy of carfilzomib or bortezomib with lenalidomide and dexamethasone as frontline therapy in MM and could lead to changes in the treatment of choice for this disease *(NCT01863550)*.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article online at https://doi.org/10.1080/10428194.2018.1508668.

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