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Carfilzomib combination treatment as first-line therapy in multiple myeloma: where do we go from the Carthadex (KTd)-trial update?

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The prognosis and treatment of multiple myeloma (MM) patients have substantially changed in the last decade due to a better understanding of the disease and the introduction of novel agents (NA) with new mechanisms of action against malignant plasma cells.[1–3] In parallel with the improved understanding of myeloma biology, the field has witnessed a flood of NA, including immunomodulatory drugs (IMiD: thalidomide, lenalidomide, pomalidomide); proteasome inhibitors (PI: bortezomib, carfilzomib, ixazomib), monoclonal antibodies (mAb: daratumumab, elotuzumab),[4] and histone deacetylase inhibitors, which have substantially improved progression-free survival (PFS) and overall survival (OS). Other NA in clinical trials (selinexor, venetoclax, novel immunotherapeutics, iberdomide, and others) are being intensively tested, and specifically immunotherapeutics beyond mAb, such as bispecific T-cell engager (BITE) molecules and chimeric antigen receptor (CAR)-T cells will expand anti-myeloma therapy options.[1–4] Concomitantly, the application of tools that reliably assess "frailty" of patients is also helping with decision making, given that many patients with MM are elderly and often have significant comorbidities.[5–10] Sustained disease response is crucial in fit and in frail patients, since disease response can significantly improve quality of life and may reduce MM-induced comorbidity. Optimizing tolerability for timely treatment delivery has also proved beneficial.[11] However, this may prove challenging with triplet or quadruplet regimens that are being developed for continued therapy, where adverse events (AE) may lead to treatment interruptions and discontinuation.

After the introduction of the first PI bortezomib (Btz/V), second- and third-generation PI were developed, with the aim of providing therapy that would be potentially more efficacious and less toxic, including an improved polyneuropathy (PNP) side effect profile. Carfilzomib (Cfz/K) is a second-in-class, epoxyketone-based, irreversibly binding PI, which is approved in combination with dexamethasone (Kd) or lenalidomide and dexamethasone (KRd) for the treatment of relapsed/refractory MM (RRMM) patients.[12,13] The ENDEAVOR study compared Kd *versus* Btz plus dexamethasone (Vd) and reported a longer PFS and OS, with lower risk of painful PNP with Kd.[13] The ASPIRE study demonstrated the superiority of KRd over Rd, with unprecedented PFS benefit, as well as OS benefit in RRMM.[14] These studies have established the place of Cfz in treating RRMM.

Dyspnea, hypertension and cardiac toxicities stand out as clinically relevant side effects, and a widening experience of these has led to published guidance for the use of Cfz, as well as a re-appraisal of the baseline cardiovascular morbidity present in this patient group.[15] Such guidance provides a helpful description of expected events, as well as suggestions for subsequent monitoring, detection and management.[16,17] The analysis of cardiovascular adverse events (CVAE) in Cfz-treated patients revealed that, in those with CVAE, 91% had uncontrolled hypertension, with acute coronary syndrome or cardiac arrhythmias each present in 4.5%. Subjects with CVAE also had significantly higher blood pressure, left ventricular mass, and pulse wave velocity at baseline evaluation, compared to those without. Baseline uncontrolled blood

pressure, left ventricular hypertrophy, and pulse wave velocity ≥9 m/s identified patients at higher risk of developing CVAE during follow up. These findings indicated that careful monitoring, strict blood pressure control and identification of early symptoms suggestive of cardiac dysfunction, are crucial to ensure safe administration of Cfz.[16–18]

In newly diagnosed MM (NDMM), Cfz has been investigated in several studies, and the updated results of the Carthadex trial of Cfz-thalidomide-dexamethasone (KTd) are now available. In this issue of the Journal, Wester *et al*. report on these findings.[19] With longer median follow up (58.7 months) of this multicenter phase II trial, impressive overall responses (ORR: 93%), with a high rate of CR (63% after consolidation) and substantial PFS and OS results (median: 58 and 83 months, respectively) were obtained.[19] Cfz was escalated from 20/27 (n=50), to 20/36 (n=20), 20/45 (n=21) and 20/56 mg/m^2

Table 1. Carthadex-(KTd) results compared to selected other carfilzomib combinations in newly diagnosed multiple myeloma.

First author	Study phase	# pts	Median age (range)	CFz-dose	Combination treatment	ORR	PFS	OS	Notable findings	FDA/EMA approval
Wester R, Haematologica 2019[19]	II (#NTR2422) Follow-up report (median: 58.7 ms)	111	58 (29-66), Tx-eligible	20/27 (n=50), 20/36 (n=20), 20/45 (n=21) 20/56 (n=20)	CFz 20-> 56mg/m^2 Thal: 200mg/d Dex 40mg weekly, 4 induction C -> ASCT->4 consolidation C	93%; CR: 18%	58 ms	83 ms	Grade 3/4 AE: Infections: 11% Respiratory: 8% Skin: 9%, Vascular: 9% Cardiac 5%	-
Sonneveld P, Blood 2015[20]	II (#NTR2422) Initial report (median: 23 ms)	91	58 (29-66), Tx-eligible	20/27 (n=50), 20/36 (n=20), 20/45 (n=21)	CFz 20-> 45mg/m^2 Thal: 200mg/d Dex 40mg weekly	86%	36-ms-PFS: 72%	Not given	Grade 3/4 AE: Respiratory: 15%, GI: 12%, Skin: 10%	-
MIkhael JR, Br J Haematol 2015[21]	Cyklone: I/II, median follow-up 17.5ms	64	62.5 (27-82), Tx-eligible	20->45	Cfz: 20->45mg/m^2 1x/w Cyclo: 300mg/m^2 d1,8,15, Thal 100mg d1-28, Dex 40,g d1,8,15,22, MTD: 36, 9 C -> maint.	91%	2y-PFS: 76%	2y-OS: 96%	G3/4 hypertension 6% Cardiac events: 6% Renal events: 5% Thromboembolic events: 5%, Dyspnea: 3%	-
Jackson, Blood (Suppl) 2018[22]	III	526	61 (33-75) Tx-eligible	20/36	Cfz 36mg/m^2 d1, 2, 8, 9, 15, 16 Cyclo: 500mg d1,8,15, Len 25mg d1-21 Dex 40mg d1,8,15,22,	≥VGPR: 82.3%	36-ms-PFS: 64.5%	Not given	All grade cardiac: 4% All grade VTE: 12.5% Discont. 4.8%	-
Gay F, Blood (Suppl.) 2018[23]	III, median follow-up 20 ms	474	57 (52-62) Tx-eligible	20/36	KRd-ASCT-KRd *vs.* KRd12 *vs*. KCd-ASCT-KCd	≥VGPR: 89:87:76%	Not given	Not given	G3/4 cardiac AE:3:2:4%, Thrombosis: 1:2:2% Discont. 6:8:7%	-
Moreau P, Blood 2015[24]	I/II	68	72 (66-86), Tx-inelegible	20, 27, 36, 45; MTD: 36	Cfz: 20-45mg/m^2 M 9mg/m^2, P 60mg/m^2 d1-4, 9 C	90%	Median: 21 ms	3y-OS: 80%	Death in n=12: PD (n=7), infection (n=2) cardiac failure (n=1) respiratory distress (n=1) urothelial ca (n=1)	-
Bringhen S, Blood 2014[26]	II, Median follow-up: 18ms	58	71 (68-75), Tx-inelegible	20->36 2x/w	Cfz: 20->36mg/m^2 Cyclo: 300mg/m^2 d1,8,15, Dex 40,g d1,8,15,22, 9 C ≥ maint.	95%	2y-PFS: 76%	2y-OS: 87%	AE 3-5: cardiopulmonary: 7% Discontinuation: 14% Cfz-dose reductions: 21%	-
Bringhen S, Leukemia 2018[27]	I/II, Median follow-up: 18ms	63	72 (69-74), Tx-inelegible	45,56,70 ≥ 70 1x/w	Cfz: 45->70mg/m^2 1x/w Cyclo: 300mg/m^2 d1,8,15, dex 40,g d1,8,15,22, 9 C ≥ maint.	89%	2y-PFS: 53.2%	2y-OS: 81%	AE 3-5: cardiopulmonary: 9%, Discontinuation: 22% Cfz-dose reductions: 9% 6 pts died: 2 PD + AE (pulm. thromboembolism, resp. failure,pneumonia, sudden death)	-
Facon T, Blood 2019[25]	III, Clarion	955	72 (42-91), Tx-inelegible	KMP (n=478) 20≥36	Cfz: 20->36mg/m^2 M 9mg/m^2, P 60mg/m^2 d1-4, 9 C	84.3%	22.3	HR 1.08 (0.82-1.43)	Renal failure: 13.9 : 6.2% Cardiac failure: 10.8 : 4.3% >G3 AE rates: 74.7 : 76.2% >G2 PNP: 2.5% : 35.1%	-
				VMP (n=477)	V 1.3mg/m^2 d1,4,8,11,22,25,29,32 ≥ d4,11,25,32, C5-9	78.8%	22.1			+

#: number, pts: patients; ND: newly diagnosed; RR: relapsed/refratory; MM: multiple myeloma; Cfz: carfilzomib; T: thalidomide;d: day; Dex: dexamethasone; M: melphalan; P: prednisone; v: bortezomib; L: lenalidomide; ORR: overall response rate; PFS: progression free survival; OS: overall survival; AE: adverse events; pts: patients; ms: months; C: cycle; MTD: max.tolerated dose; maint: maintenance therapy; FDA: Food and Drug Adminstration; CR: complete remission; GI: gastrointestinal; Tx: transplantation; VTE: venous thrombo-embolism; discontin.: discontinuation; PD: disease progression; ca: carcinoma; pulm.: pulmonary; resp: respiratory, HR: hazard risk.

(n=20 patients), given twice weekly combined with daily thalidomide [200 mg day (d) 1-28] and weekly dexamethasone for four KTd induction cycles before autologous stem cell transplantation (ASCT) was performed. These promptly induced responses allowed peripheral blood stem cell (PBSC) mobilization in 92%, and were followed by ASCT in 88% and Cfz-consolidation in 85% of patients. Since this was an updated study report,[20] with a last cohort of further escalated Cfz (20/56), a specific aim of the study had been to compare tolerability and efficacy between the various Cfz doses. This objective is clinically highly relevant; however, the small patient numbers allowed only preliminary observations to be made on this. Nevertheless, increasing Cfz doses beyond 20/36 did not seem to improve efficacy in terms of CR rates. Of note, CVAE did not seem to increase with Cfz dose escalation and were generally low (12% all grade, 5% grade ≥3), while infection rates, particularly pneumonia, did. The authors comment that their previous experience with this regimen likely contributed to the low incidence of SAE.[19]

With the usual caveats of conducting cross-trial comparisons, Table 1 summarizes selected Cfz-combination trials in NDMM, with the Carthadex results shown first.[19]

As compared to the Carthadex-trial with KTd, the Cyklone trial[21] investigated Cfz in quadruplet-combination in 64 transplant-eligible NDMM patients and was similar in its treatment combination: patients were treated with Cfz (d1, 2, 8, 9, 15, and 16), 300 mg/m^2 cyclophosphamide (d1, 8, and 15), 100 mg thalidomide (d1-28), and 40 mg dexamethasone (d1, 8, 15, and 22) in 28-day cycles. Cfz was dose-escalated at four dose levels to determine the maximum tolerated dose (MTD), which was 20/36 mg/m^2. OS was similar as that reported by Wester *et al*. and Sonneveld *et al*.,[19,20] as were the 2-year PFS (76%) and OS (96%) (Table 1). Similar to the Carthadex trial, the Cyklone-quadruplet led to rapid and deep responses with limited PNP, cardiac or pulmonary toxicity.[21] Although due to PNP risks thalidomide is less used in Europe, and particularly in the US, than lenalidomide or pomalidomide, both Carthadex and Cyklone results illustrate the safety and efficacy of combining novel PI with IMiD, steroids and cyclophosphamide to a quadruplet. The UK Myeloma XI+ study evaluated a similar quadruplet, but with lenalidomide instead of thalidomide, KCRd (Cfz 20/36) as induction prior to ASCT, followed by randomization to lenalidomide maintenance or no further treatment.[22] This quadruplet was well tolerated, and response rates and PFS rates were remarkably similar to those in the Carthadex study (Table 1).[22]

In transplant-eligible patients, the combination of Cfz with lenalidomide (KRd) or cyclophosphamide (KCD), with or without ASCT (KRd-ASCT-KRd *vs*. KRd12 *vs*. KCd-ASCT-KCd), is also being assessed in the Forte trial:[23] the three Forte trial arms show high and deep very good partial response (VGPR) rates of 89%, 87% and 76%, respectively, with so far well manageable SAE signals, especially low grade 3/4 cardiac AE, thrombosis or discontinuation rates (Table 1).

In transplant-ineligible patients, Moreau *et al.* showed tolerability and efficacy of Cfz-melphalan-prednisone (KMP) in a phase I/II trial.[24] MTD of Cfz was 36 mg/m^2, the combination of KMP was feasible and ORR, PFS and 3-year OS were remarkable with 90%, 21 months, and 80%, respectively. This led to the randomized Clarion study of KMP *versus* VMP for nine 6-week cycles, the results of which showed that both regimens resulted in similar PFS and response rates, while PNP rates were higher with VMP, and acute renal failure and cardiac failure were higher with KMP (Table 1).[25] The reason for the lack of superior results with KMP may be the high level of experience of physicians managing VMP-treatment, the lower tolerability of KMP than VMP in elderly patients, and the much lower than anticipated PNP rate of VMP, so that the study endurance in both groups were similar.

Since cyclophosphamide is better tolerated than melphalan and a useful backbone for numerous MM protocols, Bringhen *et al.* assessed the safety and efficacy of Cfz in combination with cyclophosphamide and dexamethasone (KCd) in NDMM patients ≥65 years, ineligible for ASCT, both in twice- and once-weekly schedules.[26–28] In the twice-weekly Cfz-study, 58 patients were enrolled and received KCd for up to nine cycles, followed by maintenance with Cfz until progression or intolerance. Patients received oral cyclophosphamide 300 mg/m^2 and dexamethasone 40 mg on d1, 8 and 15; Cfz (20/36) was administered as 30-minute infusions on d1, 2, 8, 9, 15, and 16. In the maintenance phase, patients were treated with 36 mg/m^2 Cfz on d1, 2, 15, and 16 every 28 days. After a median of nine cycles of KCd, 71% of patients achieved ≥ VGPR and the 2-year PFS and OS after a median follow up of 18 months were 76% and 87%, respectively. The rate of ≥ grade 3 AE was low, and the most common toxicities were neutropenia (20%), anemia (11%), and cardiopulmonary events (7%).[26]

The once-weekly KCd-combination escalated Cfz initially from 45 to 56 and 70 mg/m^2. Patients were treated with Cfz on d1, 8 and 15 of a 28-day cycle. A total of 63 patients were enrolled in the phase I and II of the study; 54 of them received recommended phase II dose 70 mg/m^2. At least VGPR was achieved in 36 (66%). The frequency of hematologic and non-hematologic AE was similar or lower than that reported in previous studies with twice weekly Cfz.[26–28]

Several triplet and quadruplet schedules of KRd, KCD, e.g. with both elotuzumab and daratumumab antibodies, are being assessed in phase II/III clinical trials (e.g. the Deutsche Studiengruppe Multiples Myelom, the German-Speaking Multiple Myeloma Group, and others). The results of these studies are eagerly awaited, and preliminary safety and efficacy results have been highly promising.

The Carthadex trial investigating KTd in transplant-eligible NDMM is also of interest in the light of the Cassiopeia (VTd-Dara) transplant-eligible NDMM study that was presented at the recent 2019 ASCO and EHA meetings.[29] Although Cassiopeia is a randomized phase III trial and Carthadex was not, the responses in both are impressive and remarkably similar. In Carthadex, the sCR after induction and consolidation therapy for the triplet was 30%; in Cassiopeia the sCR for the experimental arm (VTd-Dara: quadruplet) was 28.9% after induction and consolidation. While such comparisons should be made

with caution, it may be that an antibody containing quadruplet with VRD will prove to have similar activity to a Cfz triplet without antibody.

In conclusion, given the updated Carthadex results,[19,20] Cfz proves to be a potent PI and important component of anti-myeloma treatment in a variety of regimens (KTd, KRd, KCd, Kd) (Table 1). Cfz has been investigated with other IMiD, such as pomalidomide, with different alkylators (e.g. Cfz-Bendamustin-Dex) and antibodies like daratumumab or elotuzumab in clinical trials. Due to its substantial efficacy and good tolerability it is used in doublets, triplets and quadruplets, both in younger and older, fit and frail patients, and in ASCT-eligible and -ineligible patients. Cfz is considered a potent relapse option in MM patients who have relapsed after and/or are refractory to both Btz and IMiD. Unfortunately, for NDMM patients, Cfz has not yet been approved, and all clinical trials, including the Carthadex trial, have not yet led to a change in Cfz registration status (Table 1). The findings from ongoing phase II and multiple phase III studies will help to determine optimum dosing regimens, to establish the position of Cfz in relapse, first-line and subsequent therapies, and for consolidation and maintenance approaches. The evidence from clinical trials should be supplemented by reports of real-world evidence in the near future, as experience with managing the toxicity profile continues to grow.[30]

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