In search of the optimal proteosome inhibitor. How, when and for whom?

Monika Engelhardt,[1] Sara Bringhen,[2] Philippe Moreau,[3] Ralph Wäsch[1] and Johannes Waldschmidt[1]

[1]University of Freiburg, Hematology & Oncology, Faculty of Freiburg, Freiburg, Germany
[2]Myeloma Unit, Division of Hematology, University of Turino, Azienda Ospedaliero-Universitaria Citta della Salute e della Scienza di Torino, Torino, Italy and [3]University Hospital of Nantes, Nantes, France

E-mail: MONIKA ENGELHARDT - monika.engelhardt@uniklinik-freiburg.de

doi:10.3324/haematol.2021.278838

The article by Yong and colleagues published in this issue of *Haematologica* presents results from MUK*five*, a randomized phase II study in which carfilzomib or bortezomib was used in combination with cyclophosphamide and dexamethasone (KCd *vs*. VCd, respectively) as second-line treatment in patients with relapsed or refractory multiple myeloma (RRMM).[1] The authors utilized a parallel group trial design with a 2:1 randomization, fixed duration of therapy and involved 300 patients. In the second part, 141 patients were randomized 1:1 to carfilzomib maintenance *versus* observation. Very good partial response or better was observed in 40.2% of patients in the KCd arm and in 31.9% of those treated with VCd. This translated into a median progression-free survival (PFS) of 11.7 *versus* 10.2 months for KCd and VCd, respectively, with a trend favoring KCd over VCd in patients with high-risk cytogenetics, defined by the presence of del(17p), gain(1q), t(4;14), t(14;16), or t(14;20). Moreover, the PFS in the carfilzomib maintenance and observation arms was 11.9 *versus* 5.6 months, respectively.[1]

Side-by-side comparisons of bortezomib and carfilzomib doubles (ENDEAVOR)[2] and triplets (CLARION, ENDURANCE)[3,4] have been reported. However, a direct comparison of VCd *versus* KCd is unprecedented, given that both represent important regimens in worldwide practice.[5-7] Since daratumumab and immunomodulatory drugs are increasingly being used earlier, proteasome inhibitor-based therapies may also be needed as potent subsequent protocols. Cost efficacy is another concern,[8] and VCd and KCd may be particularly advantageous in this regard.[5-7]

Our UK colleagues should therefore be congratulated on having performed a head-to-head comparison of carfilzomib *versus* bortezomib in RRMM patients, given that ENDEAVOR, CLARION and ENDURANCE had seemingly generated conflicting results: ENDEAVOR had shown improved response, PFS and overall survival (OS) with carfilzomib and dexamethasone (Kd) *versus* bortezomib plus dexamethasone (Vd) in patients with RRMM (the dose of carfilzomib in ENDEAVOR was 56 mg/m^2 compared to 36 mg/m^2 in MUK*five*, and Vd was reused in some patients),[2] whereas in newly diagnosed MM (NDMM), the CLARION trial with carfilzomib, melphalan and prednisone (KMP) *versus* bortezomib, melphalan and prednisone (VMP) and the ENDURANCE trial with carfilzomib, lenalidomide and dexamethasone (KRd) *versus* bortezomib, lenalidomide and dexamethasone (VRd), showed similar responses, PFS and OS (carfilzomib: 36 mg/m^2).[3,4] This suggests that the optimal choice of proteasome inhibitor, combination, dose, duration and therapy tolerance requires more than the latter three studies and cautions us that cross-trial comparisons are deceptive, unless treatment groups are randomly compared in one study.

The MUK*five* trial randomized patients to KCd or VCd, since both are effective and economically less challenging than triplets that contain two novel agents. Moreover, although therapy in RRMM is now given until progression, the role of carfilzomib maintenance in RRMM remains fairly unexplored. The results add to our knowledge, because both regimens are well-used, i.e., VCd for NDMM and RRMM as a very effective and well-tolerated regimen.[5,8] So is KCd – apart from KRd, Kd and the recently introduced carfilzomib-daratumumab-dexamethasone (KDd) regimen.[6,7] Unfortunately VCd has not been licensed for NDMM or RRMM; an omission that has often been criticized. Therefore, the MUK*five* study is timely and of interest, with a view to answering the questions for which patients, after what prior therapy and with what other backbone agents should carfilzomib or bortezomib be used?

Table 1 summarizes the information regarding selected carfilzomib- and bortezomib-containing doublets, triplets and quadruplets in RRMM/NDMM, and in transplant-eligible and –ineligible patients. Although MUK*five* failed to show significantly different median PFS and OS between recipients of KCd or VCd, treatment was restricted to 24 weeks, with six 28-day cycles of KCd and eight 21-day cycles of VCd. Carfilzomib doses were 36 mg/m^2, whereas in ENDEAVOR, Kd and Vd were given until progression and the doses of carfilzomib were higher (56 mg/m^2).[2] As a consequence of the 24-week treatment time limit in both the KCd and VCd arms in MUK*five*, treatment intensity was 36 (6x6) for carfilzomib *versus* 32 (4x8) for bortezomib doses (approximately similar), but 18 (3x6) *versus* 24 (3x8) for the cyclophosphamide-dexamethasone doses (lower in the KCd arm than in the VCd arm). This speaks for the UK trialists in designing equally long relapse schedules (6 months) and titrating novel agents to their possibly best efficacy and tolerance (carfilzomib 20/27/36 mg/m^2, inducing fewer side effects than 56 or 70 mg/m^2),[6,7,9] but most likely accounting for their lesser ability to show a superiority of this regimen over VCd.

Another potential hypothesis to explain the time to progression benefit in the CLARION study (KMP: 27.5 *versus* VMP: 23.5 months), but lack of PFS benefit with a higher percentage of deaths in the carfilzomib group was that KMP was less well tolerated, possibly because of more experience with management strategies for bortezomib-based combinations (Table 1). Moreover, the rate of polyneuropathy in the VMP arm was lower than anticipat-

Table 1. Selected carfilzomib- and bortezomib-containing phase I-III clinical trials in relapsed and newly diagnosed multiple myeloma.

Study name	1st author (Ref)	N of pts	Treatment arms	Median age	ORR (range)	Median PFS	Median OS	Notable findings
Relapsed or refractory multiple myeloma								
MUKfive	Yong KL (1)	300 (201:99) + 141 (69:72)	KCd : VCd; K : No maint. in 2.LT	68 (32-85)	84% : 68.1%	11.7 : 10.2 m (HR 0.95; 80%CI: 0.77-1.18)	30.9 : 28.1 m (HR 1.1; 90%CI: 0.68-1.8)	NP ≥3 or ≥2 w pain: 1.5% *vs*. 19.8% ≥3 cardiac events + hypertention: only w KCd (3.6% each) K-maintenance: median longer PFS 11.9 *vs.* 5.6 m
Endeavor	Dimopoulos MA (2)	929 (464:465)	Kd : Vd	65 (30-89)	77% : 63%	18.7 : 9.4 m (HR 0.53 (0.44-0.65)	47.6 : 40 m (HR 0.791 (0.648-0.964)	NP: Vd > Kd, cardiac events: Kd>Vd more grade 3 AE: Kd>Vd, discontinuation + related deaths: =
Endeavor, Arrow, Champion-1	Moreau P (9)	363 (217:146)	Kd56 (BIW) : Kd70 (QW)	Mean: 64:65	72.4 : 69.9%	14.5 : 12.1 m	=	≥G3 AEs 85.3%:67.6%
Newly diagnosed multiple myeloma; non-transplant eligible								
Clarion	Facon T (3)	955: (478:477)	KMP : VMP	72 (42-91)	84.3% : 78.8% (OR: 1.412; 1.01-1.973)	22.3 : 22.1 m (HR 0.906; 0.746-1.101)	= ; n.r. (HR 1.08 0.82-1.43)	CR: 25.9 : 23.1% MRD negativity: 15.7%:15.5% Acute RF: 13.9 : 6.2%, CF: 10.8% : 4.3%, ≥G2 PNP 2.5% : 35.1%
Endurance	Kumar SK (4)	1087 (545:542)	KRd : VRd	65 (57-71)	87% : 84%	34.6 : 34.4 m (HR 1.04 (0.83-1.31)	n.r.	≥G3 PNP <1% : 8%; treatment-related death:2:<1%
wKCd	Bringhen S (6)	63	Weekly KCd 45,56,70	72 (69-74)	85%	2y PFS: 53.2%	2y OS: 81%	≥G3 tox.: neutropenia (22%), cardiopulmonary (9%)
KCd QW:BIW	Mina R (7)	94	9x KCd (70mg/m^2 QW + 36mg/m^2 BIW)	72 (68-75)	88% (SR/HR: 86/92%)	Median PFS SR/HR: nr/27.8m 3y PFS: 52/43%	Median OS: nr 3y OS: 78/73%	Hematological and CF
Newly diagnosed multiple myeloma; transplant-eligible								
DSMM XI	Einsele H (5)	414	VCd + Tx	54 (32-67)	post VCD: 85.4%, post Tx: 95.5%	Median PFS 35.3 m	Median OS: nr	Well tolerable, outpt.treatment
Forte	Gay F (11)	474	KRd+Tx:KRd12: KCd+Tx	<65y	MRD before maint:62:56:43%	Median PFS KRd_ASCT: nr, KRD12 57m, KCd_ASCT: 53 m	3y OS: 90% w KRd_ASCT+KRd12 : 83%	Benefit KR *vs*. R maint., MRD> w KRd *vs*. KCd, known AEs
Myeloma XI+	Jackson GH (10)	1056	KRdc *vs*. Rdc/Tdc	61 (33-75)	>VGPR KRdc :82.3% Rdc/Tdc: 58.9%	Median PFS: nr : 36.2 m (HR 0.63 (0.51-0.76)	n.r.	Most common AE: hematologic + low incidence of cardiac events

Ref: reference; ORR: overall response rate; PFS: progression-free survival; OS: overall survival; KCd: carfilzomib, cyclophsophamide, dexamethasone; VCd: bortezomib, cyclophosphamide, dexamethasone; K: carfilzomib; maint.: maintenance; 2.LT: second-line treatment; HR: hazard ratio; CI: confidence interval; m: months; NP: neuropathy; NP: neuropathy; w: with; QW: once per week; BIW: biweekly treatment; Kd: carfilzomib-dexamethasone, Vd: bortezomib-dexamethasone, AE: adverse event; KMP: carfilzomib-melphalan, prednisone, VMP: bortezomib-melphalan, prednisone; OR: odds ratio; MRD: minimal residual disease; RF: renal failure; CF: cardiac failure; G: grade; PNP: polyneuropathy; KRd: carfilzomib, lenalidomide, dexamethasone, VRd: bortezomib, lenalidomide, dexamethasone, SR/HR: standard-risk/high-risk; Tx: transplantation; ASCT: autologous stem cell transplantation; KR: carfilzomib, lenalomide; R maint: lenalidomide maintenance; VGPR: very good partial response; KRdc: carfilzomib-lenalidomide, dexamethasone, cyclophsophamide; Rdc/Tdc: lenalidomide-dexamethasone-cyclophosphamide/thalidomide-dexamethasone-cyclophosphamide.

ed, supporting proposed bortezomib-dose reductions. In line, dose intensity was lower in the bortezomib group than in the carfilzomib group, which suggests that physicians were more familiar with dose modifications for bortezomib than for carfilzomib. Due to the higher toxicity of KMP *versus* VMP, melphalan was possibly also a less ideal drug to combine with carfilzomib, a notion similarly discussed by supporters of cyclophosphamide instead of melphalan.[3]

The ENDURANCE study with 12 cycles of VRd at 3-week intervals *versus* nine cycles of KRd (36 mg/m^2) at 4-week intervals[4] was – with equally designed treatment duration and carfilzomib doses – in line with that of MUK*five*, albeit in NDMM *versus* RRMM patients and for much longer *versus* shorter triplet-exposure, respectively (Table 1). Exclusion criteria for ENDURANCE were high-risk MM patients,[4] postulated to profit better from antibody-based quadruplets. Although the rate of very good partial response or better in ENDURANCE was significantly higher with KRd than with VRd, this did not translate into better 3-year PFS and OS. The absence of improvement was considered to reflect the impact of treatment-related toxicity of KRd, which led to treatment delays and dose modifications, compromising the overall efficacy. The ENDURANCE trialists discussed whether carfilzomib had a better efficacy in high-risk MM,[4] a notion that the MUK*five* study addressed, including 54.5% high-risk patients and observing a trend

for a better outcome with KCd than with VCd.[1]

All the trials reported in Table 1 have therefore contributed to teaching us how current treatment practice may need to evolve: The results of MUK*five* suggest that six 28-day KCd cycles *versus* eight 21-day VCd cycles in second-line treatment with carfilzomib doses of 20/36 mg/m^2 induce comparable survival rates and that addition of carfilzomib is particularly advantageous in high-risk MM patients, those who have received prior bortezomib treatment, those who are refractory to or intolerant of bortezomib and when MM physicians have experience with carfilzomib.[1,6,7] ENDEAVOR and other trials with even higher carfilzomib doses, given at 70 mg/m^2 weekly rather than biweekly, demonstrate that the efficacy of carfilzomib is dose-dependent, but that the incidence of cardiac events must be kept low.[2,6,7,9,10] The role of continuous *versus* fixed-duration therapy is also important, explaining differences in outcome among different trials. Since continuous treatment may affect quality of life, MUK*five*'s fixed duration rather than continuous treatment was probably designed with this in mind, but might have been planned differently today in the light of other experiences (Table 1).

Current carfilzomib studies in transplant-eligible NDMM patients, such as Forte (NCT02203643) and Myeloma XI+ (ISRCTN49407852), show impressive minimal residual disease negativity rates with KRd-autologous stem cell transplantation (ASCT) *versus* KRd12 *versus* KCd-ASCT (62%, 56% and 43%, respectively).[11] The phase III Myeloma XI+ trial is assessing KRd with cyclophosphamide (KRdc) as compared to Rdc/Tdc (lenalidomide-dexamethasone-cyclophosphamide/thalidomide-dexamethasone-cyclophosphamide) in 1,056 transplant-eligible NDMM patients with impressive rates of very good partial response or better of 82% and 59%, respectively.[10] Whether this will translate into better survival and excellent therapy endurance remains to be seen. The future of MM therapies seems bright and exciting, further advances are still to come and the UK study group continues to contribute to this. While longer follow-up for these studies is awaited, the results from the MUK*five* trial represent an important milestone in improving our understanding and expanding the clinical use of proteasome inhibitors for the treatment of MM.

Disclosures

No conflicts of interest to disclose.

Contributions

ME wrote the editorial, SB, PM, RW and JW provided discussion, input and recommendations both on the MUKfive paper and this editorial, and also generated thoughts on future studies that should evolve, plus those that are displayed in Table 1 as a review of the literature.

References

1. Yong K, Hinsley S, Auner HW, et al. Carfilzomib or bortezomib in combination with cyclophosphamide and dexamethasone followed by carfilzomib maintenance for patients with multiple myeloma after one prior therapy: results from a multicenter, phase II, randomized, controlled trial (MUKfive). Haematologica. 2021;106(10):2694-2706.
2. Dimopoulos MA, Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. Lancet Oncol. 2017;18(10):1327-1337.
3. Facon T, Lee JH, Moreau P, et al. Carfilzomib or bortezomib with melphalan-prednisone for transplant-ineligible patients with newly diagnosed multiple myeloma. Blood. 2019;133(18):1953-1963.
4. Kumar SK, Jacobus SJ, Cohen AD, et al. Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol. 2020;21(10):1317-1330.
5. Einsele H, Engelhardt M, Tapprich C, et al. Phase II study of bortezomib, cyclophosphamide and dexamethasone as induction therapy in multiple myeloma: DSMM XI trial. Br J Haematol. 2017;179(4):586-597.
6. Bringhen S, D'Agostino M, De Paoli L, et al. Phase 1/2 study of weekly carfilzomib, cyclophosphamide, dexamethasone in newly diagnosed transplant-ineligible myeloma. Leukemia. 2018;32(4):979-985.
7. Mina R, Bonello F, Petrucci MT, et al. Carfilzomib, cyclophosphamide and dexamethasone for newly diagnosed, high-risk myeloma patients not eligible for transplant: a pooled analysis of two studies. Haematologica. 2021;106(4):1079-1085.
8. Kumar SK, Ma E, Engebretson AE, et al. Treatment outcomes, health-care resource utilization and costs of bortezomib and dexamethasone, with cyclophosphamide or lenalidomide, in newly diagnosed multiple myeloma. Leukemia. 2016;30(4):995-998.
9. Moreau P, Stewart KA, Dimopoulos M, et al. Once-weekly (70 mg/m^2) vs twice-weekly (56 mg/m^2) dosing of carfilzomib in patients with relapsed or refractory multiple myeloma: a post hoc analysis of the ENDEAVOR, A.R.R.O.W., and CHAMPION-1 trials. Cancer Med. 2020;9(9):2989-2996.
10. Jackson GH, Pawlyn C, Cairns DA, et al. Carfilzomib, lenalidomide, dexamethasone, and cyclophosphamide (KRdc) as induction therapy for transplant-eligible, newly diagnosed multiple myeloma patients (Myeloma XI+): Interim analysis of an open-label randomised controlled trial. PLoS Med. 2021;18(1):e1003454.
11. Gay F, Musto P, Rota Scalabrini D, et al. Survival analysis of newly diagnosed transplant-eligible multiple myeloma patients in the randomized Forte trial. Blood. 2020;136(Suppl 1):35-37.