

Are 4-Drug Regimens Here to Stay? Role in Induction and Salvage Therapies

Joshua Richter, MD and Sundar Jagannath, MBBS

Abstract: With 10 novel therapies approved across the decade, the multiple myeloma (MM) treatment paradigm continues to evolve in breadth and complexity. The current gestalt of the day has been the emergence of data to support 3-drug combinations over their 2-drug counterparts. Current guidelines and consensus statements support this approach. With the recent incorporation of monoclonal antibodies into the fray of myeloma therapy, we have begun to ask what the roles of 4-drug combinations are in both the upfront and the relapsed and refractory settings. The recent approval of daratumumab in combination with bortezomib, melphalan, and prednisone (Dara-VMP/ALCYONE) supports the role of quadruplet therapy in some patients with newly diagnosed disease who do not plan to proceed toward autologous transplant. There are a number of ongoing studies evaluating this type of strategy in both transplant-eligible and non-transplant-eligible newly diagnosed MM patients and in relapsed and refractory MM patients. Many of these seek to enhance standard-of-care treatments with the addition of monoclonal antibodies. We evaluate the historical and current data supporting the role of quadruplet- versus triplet-based therapies in MM.

Key Words: 4-drug regimens, multiple myeloma, multiple myeloma treatment

(*Cancer J* 2019;25: 32–37)

Over the last decade, the evolution of myeloma therapy has led to the *triplet* being the preferred choice in many clinical settings. This has been most prevalent in the induction setting for transplant-eligible patients as well as the relapsed and refractory settings. Although this triumvirate comes in many forms; the combination of a steroid, an immunomodulatory drug, and a proteasome inhibitor (PI) is one of the mainstay industry standards. In November 2015, the US Food and Drug Administration approved 2 monoclonal antibodies (mAbs) for the treatment of multiple myeloma (MM): daratumumab (Dara) and Elotuzumab (Elo).^{1,2} As has become standard of care in other diseases such as lymphomas, the next logical step was to combine mAbs with the current standards. In turn, the myeloma landscape is now seeing *triplets* being promoted to *quadruplets* with the addition of Elo and Dara to the standard regimens. From an efficacy, toxicity, and cost standpoint, are 4-drug regimens here to stay?

INDUCTION

Choice of induction therapy for MM (at the time of this publication) still remains intertwined with the notion of transplant-eligible patients versus transplant-ineligible patients, with the former currently more associated with *triplet* regimens and the latter frequently consisting of *doublets*.

The chart below details the key phase III randomized trials for newly diagnosed MM. Although there is a general trend toward improved overall response rate (ORR) as we evolve toward more triplets and even quadruplets, what is perhaps more notable is the depth of responses. We see a general increase in very good partial response (VGPR) and complete response (CR). The ability to achieve deeper remissions is what is likely yielding improvements in progression-free survival (PFS) and ultimately overall survival (OS). With the incorporation of novel therapies (with an emphasis on the mAbs), we can now combine 3- and 4-drug combinations and achieve deep and durable responses without adding significant toxicities^{3–11} (Table 1).

TRIPLET INDUCTION REGIMENS

The general gestalt for induction therapy for transplant-eligible patients in the modern day has been a triplet regimen. The more common therapeutic choices in the United States are bortezomib/cyclophosphamide/dexamethasone (CyBorD), bortezomib/lenalidomide/dexamethasone (VRd), and carfilzomib/lenalidomide/dexamethasone (KRd). These regimens have been associated with high ORR as well as manageable toxicities.

Bortezomib/cyclophosphamide/dexamethasone has been widely used as an induction regimen given the ability for urgent administration as well as ease of dosing in patients with renal impairment. The regimen is associated with high rates of response (ORR; 90%) as well as deep remissions with VGPR rates of 67% and near CR/CR rates of 41%.¹² Ultimately, however, the combination of a PI (plus a steroid) appears to be superior when combined with an immunomodulatory drug as opposed to an alkylator. The IFM 2013-04 trial compared CyBorD with bortezomib/thalidomide/dexamethasone (VTD). The ORR was significantly higher in the VTD arm (92.3% vs. 83.4% in the CyBorD arm; $P = 0.01$); 66.3% of the patients in the VTD arm achieved at least a VGPR versus 56.2% in the CyBorD arm ($P = 0.05$). Hematologic toxicity was higher with CyBorD, with significantly increased rates of grades 3 and 4 anemia, thrombocytopenia, and neutropenia. However, the rate of peripheral neuropathy was significantly higher in the VTD arm.¹³

The Southwest Oncology Group 0777 trial evaluated the VRd regimen as compared with RD alone in the induction setting.¹⁰ The ORR was 82% (176/216) in the VRd group and 72% (153/214) in the lenalidomide, dexamethasone (Rd) group. The CR rate in the VRd group was 16% (34/216) and 8% (18/214) in the Rd cohort. Adverse events of grade 3 or higher were reported in 198 (82%) of 241 patients in the VRd group and 169 (75%) of 226 patients in the Rd group. Ultimately, 55 (23%) in the VRd group and 22 (10%) in the Rd group discontinued treatment because of adverse events (AEs).

With the advent of the next generation of PIs came the substitution of carfilzomib for bortezomib in the induction setting. Carfilzomib/lenalidomide/dexamethasone in a phase I/II study shows extreme promise and has been adopted by some as the induction regimen of choice. The ORR was 100%, and the PFS rates were 97% at 12 months and 92% at 24 months. The

From the Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY.

Reprints: Sundar Jagannath, MBBS, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, 1 Gustave L Levy Place, Box 1185, New York, NY 10029. E-mail: sundar.jagannath@mssm.edu.

Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.
ISSN: 1528-9117

TABLE 1. Modern-Day Randomized Phase III Studies in Newly Diagnosed Myeloma

Authors	Regimen	N	ORR, %	CR + VGPR	median PFS, mo	p for PFS	3-y OS Rate, %	median OS, mo	p for OS
Harrousseau et al. ³	VAD	242	63	15	30		77	NR	
	VD	240	79	38	36	0.06	81	NR	0.46
Moreau et al. ⁴	VD	99	81	36	30		NA	NA	
	VTD	100	88	49	26	0.22	NA	NA	
Cavo et al. ⁵	TD	238	79	28	40		84	NR	
	VTD	236	93	62	NR	0.006	86	NR	0.3
Rajkumar et al. ⁶	RD	223	81	50	19.1		75	NR	
	Rd	222	70	40	25.3	0.026	74	NR	0.47
Palumbo et al. ⁷	MP	164	48	11	14.5		65	47.6	
	MPT	167	69	29	21.8	0.004	65	45	0.79
Mateos et al. ⁸	MP	338	35	NA	16.6		54	21.9	
	VMP	344	71	NA	24.4	<0.001	68.5	30.2	0.21
Palumbo et al. ⁹	VMP	257	89	50	27.3		87	NR	
	VMPT-VT	254	81	59	NR	0.008	89	NR	0.77
Durie et al. ¹⁰	Rd	261	72	32	30		NA	64	
	VRd	264	82	43	43	0.0018	NA	75	0.025
Mateos et al. ¹¹	VMP	356	74	49.7	18.1		NA	NR	
	Dara-VMP	350	91	71.1	NR	<0.001	NA	NR	

NR indicates no response.

AE profile was manageable, and most patients did not require dose adjustment.¹⁴

Although ORR in the varied triplet induction regimens ranging from 90% to 100%, along with generally tolerable adverse effect profiles, the question of a need for a fourth drug arose. Would it deepen remissions and yield improvements in PFS/OS, and could it be done without significantly altering toxicity rates?

CYKLONE

In a phase Ib/II trial, 64 transplant-eligible patients received a combination of carfilzomib/cyclophosphamide/thalidomide/dexamethasone.¹⁵ The maximum tolerated dose of carfilzomib in this protocol was achieved at the 20/36 mg/m² level. The ORR was 91% with PFS and OS rates at 24 months of 76% and 96%, respectively. Adverse event rates were within acceptable parameters. Grade 3 or higher neutropenia and anemia rates were 23% and 20%. All peripheral neuropathy was grade 1, seen in 31% of patients, and attributed to thalidomide. All patients who attempted stem cell collection were successful. This regimen represents a highly efficacious approach with manageable AEs and given the pharmacokinetics and pharmacodynamics of the drug combination and represents an option for newly diagnosed MM patients with marrow and renal impairment.

EVOLUTION

The EVOLUTION trial sought to elucidate the risks and benefits of 3- and 4-drug combinations with lenalidomide (R), bortezomib (V), cyclophosphamide (C), and dexamethasone (D)¹⁶ (Table 2).

Although the study did not have the power for a robust comparison of the 4 different regimens, the data showed similar efficacies among the combinations. Notably, the VDCR regimen was associated with an increased rate of toxicity, specifically hematologic AEs. Rates of febrile neutropenia were low in all arms. Overall, the study did not show an advantage of a 4-drug regimen over its 3-drug counterpart. This may stem from the class of drugs available

for combination at the time of the trial. The next path would look toward incorporation of mAbs into the induction paradigm.

Elo-RVD

Elotuzumab has been utilized in the relapsed and refractory setting of myeloma in combination with lenalidomide and dexamethasone.¹⁷ In an open-label phase IIa study, Laubach¹⁸ evaluated the combination of Elo plus bortezomib, lenalidomide, and dexamethasone (Elo-RVD) in newly diagnosed MM patients. Patients received 4 cycles of Elo-RVD and then underwent stem cell mobilization. Following this, they could either proceed with autologous stem cell transplant (ASCT) or defer transplant and receive 4 more cycles of induction therapy. Following either ASCT or 8 cycles of induction chemotherapy, patients transitioned to risk-adapted maintenance with Elo-Rd or Elo-RVD (high-risk cytogenetics, International Staging System stage II or III). The ORR after 4 cycles was 100%, with 24% achieving a CR, 47% achieving a VGPR, and 29% achieving a partial response (PR). Seventy-one percent of patients achieved a VGPR or better.

The regimen was associated with an acceptable toxicity profile, and stem cell collection was successful with an average collection of 10.3×10^6 CD34 cells/kg. Further follow-up time is needed to appropriately assess the PFS and OS rates. Ultimately, further studies are needed to elucidate the role of Elo in the upfront setting.

Dara-KRd

The addition of Dara to the KRd regimen was recently evaluated in the newly diagnosed setting.¹⁹ The dosing incorporated Dara at 16 mg/kg weekly for cycles 1 and 2, every 2 weeks on cycles 3 to 6, and every 4 weeks thereafter. The carfilzomib was dosed in a similar way as the A.R.R.O.W. trial²⁰ at 20 mg/m² on day 1 and then increasing to 70 mg/m² on days 8 and 15 with subsequent cycles utilizing the 70-mg/m² dose on days 1, 8, and 15. The ORR was 100% with 43% stringent CR, 14% CR, 33% VGPR, and 10% PR. Responses were noted to deepen over time/therapy.

TABLE 2. EVOLUTION Trial Regimens

Regimen	Bortezomib	Dexamethasone	Cyclophosphamide	Lenalidomide	ORR, %	≥VGPR, %	CR, %	At Least 1 Grade 3 or above Hematological AE, %	AE Resulting in Discontinuation, %	Median CD34 ⁺ Cell Yield 10 ⁶ /kg, n (Range)
VDR	1.3 mg/m ² d 1,4,8,11	40 mg d 1,8,15		25 mg d 1–14	85	51	24	26	19	7.8 (2.2–25.9)
VDC	1.3 mg/m ² d 1,4,8,11	40 mg d 1,8,15	500 mg/m ² d 1,8		75	41	22	52	12	7.95 (3.1–17.6)
VDC-mod	1.3 mg/m ² d 1,4,8,11	40 mg d 1,8,15	500 mg/m ² d 1,8,15		100	53	47	29	6	7.75 (2.1–20)
VDCR	1.3 mg/m ² d 1,4,8,11	40 mg d 1,8,15	500 mg/m ² d 1,8	15 mg d 1–14	88	58	25	58	21	6.8 (0.3–21)

Left ventricular ejection fraction was monitored throughout the study without significant changes throughout therapy, except for 1 patient with a transient drop in left ventricular ejection fraction, who ultimately resumed therapy at a reduced dose of carfilzomib. The most common grade 3/4 treatment-emergent AEs included lymphopenia (14 [64%]), neutropenia (4 [18%]), diarrhea (4 [18%]), and pulmonary embolism (3 [14%]).

The trial yielded excellent responses with an acceptable AE profile. Head-to-head trials are needed to better evaluate the role of regimens, such as these, as compared with their non-mAb triplet counterparts. Minimal residual disease (MRD) analysis will be key in future studies as the benefit of the 4-drug approach may not be seen in significant improvements in ORR but in rates of MRD negativity.

UK NCRI MYELOMA XI TRIAL

The UK NCRI Myeloma XI trial is a large, phase III study comparing the induction quadruplet carfilzomib/cyclophosphamide/lenalidomide/dexamethasone to the triplet combinations: cytoxan/lenalidomide/dexamethasone or cytoxan/thalidomide/dexamethasone. There was additional pretransplant consolidation with PI triplet therapy for those with a suboptimal response. The patients in the triplet arms were then randomized to receive additional treatment based on initial response. Patients achieving a minor response or PR were randomized to receive CyBorD or nothing. Patients with stable disease or progressive disease all received sequential therapy with CyBorD. All patients receiving the quadruplet as well as the triplet patients who achieved a VGPR or better proceeded directly to transplant. The quadruplet was associated with a slightly higher rate of hematologic AEs; however, responses to treatment in this arm were both faster and deeper, with 92% of patients achieving a VGPR or better.²¹ Furthermore, there were no differences seen in mean CD34 selected stem cell harvests.

UPFRONT THERAPY FOR THE TRANSPLANT INELIGIBLE PATIENT

The transplant-ineligible population has, interestingly enough, had a fuller evaluation of the 3- versus 4-drug approach. The combination of bortezomib/melphalan/prednisone (VMP) was found to be superior to MP alone, in a large randomized study, in rates of CR, time to progression, and OS at 3 years.²² In a subsequent study, thalidomide was added to VMP and administered as the quadruplet of VMPT followed by velcade and thalidomide maintenance compared with VMP alone.

The 3-year PFS rate was 56% with VMPT compared with 41% with VMP. However, patients in the VMPT arm received maintenance therapy with bortezomib and thalidomide, whereas patients in the VMP arm did not receive any additional therapy beyond 9 months. Sensory neuropathy rates were not statistically different between the groups with rates of 8% and 5% in the VMPT and VMP arms, respectively. Of note, the CR rates were higher in the quadruplet at 38% compared with 24% in the triplet. This did not result in an improvement in 3-year OS rates. At the 3-year time mark, there was no difference seen in OS with rates of 89% with VMPT and 87% with VMP, respectively.

More recently, the standard VMP induction regimen was compared with Dara-VMP in the ALCYONE trial. The 18-month PFS rate was 71.6% in the Dara group and 50.2% in the control. The ORR was 90.9% in the quadruplet, as compared with 73.9% in the triplet. Daratumumab-VMP was also associated with a CR (or better) rate of 42.6% versus 24.4% with VMP. Furthermore, 22.3% of the patients in the Dara-VMP arm achieved MRD negativity. Hematologic AEs were comparable; however, the quadruplet was associated with higher rates of grade 3/4 infections,

TABLE 3. Clinical Trials Utilizing 4-Drug Regimens

Study Name	ClinicalTrials.gov Identifier	Drugs Utilized	Therapeutic Setting
Study of Bortezomib, Lenalidomide, Dexamethasone & Elotuzumab in Newly Diagnosed MM	NCT02375555	Bortezomib, dexamethasone, Elo, lenalidomide	Newly diagnosed MM
A Phase III Trial on the Effect of Elotuzumab in VRD Induction/Consolidation and Lenalidomide Maintenance in Patients With Newly Diagnosed Myeloma (GMMG-HD6)	NCT02495922	Bortezomib, dexamethasone, Elo, lenalidomide	Newly diagnosed MM
A Study of Elotuzumab With Pomalidomide, Bortezomib, and Dexamethasone in Relapsed Multiple Myeloma	NCT02718833	Bortezomib, dexamethasone, Elo, pomalidomide	Relapsed/refractory MM
Study Comparing Daratumumab, Lenalidomide, Bortezomib, and Dexamethasone (D-RVd) Versus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Subjects With Newly Diagnosed Multiple Myeloma	NCT02874742	Bortezomib, Dara, dexamethasone, lenalidomide	Newly diagnosed MM
A Study to Evaluate Dara-CyBorD in Previously Untreated and Relapsed Subjects With Multiple Myeloma	NCT02951819	Bortezomib, cyclophosphamide, Dara, dexamethasone	Newly diagnosed MM
Cyclophosphamide-Bortezomib-Dexamethasone (CyBorD) With Daratumumab (DARA) (CyBorD-Dara)	NCT02955810	Bortezomib, cyclophosphamide, Dara, dexamethasone	Newly diagnosed MM
Study of Initial Treatment With Elotuzumab, Carfilzomib, Lenalidomide and Dexamethasone in Multiple Myeloma	NCT02969837	Carfilzomib, dexamethasone, Elo, lenalidomide	Newly diagnosed MM
Ixazomib Citrate, Lenalidomide, Dexamethasone, and Daratumumab in Treating Patients With Newly Diagnosed Multiple Myeloma	NCT03012880	Dara, dexamethasone, ixazomib, lenalidomide	Newly diagnosed MM
A Study Of Daratumumab, Low-Dose Oral Dexamethasone and Cyclophosphamide With Or Without Pomalidomide (DCDP)	NCT03215524	Cyclophosphamide, Dara, pomalidomide, prednisone	Relapsed/refractory MM
A Study of VELCADE (Bortezomib) Melphalan-Prednisone (VMP) Compared to Daratumumab in Combination With VMP (D-VMP), in Participants With Previously Untreated Multiple Myeloma Who Are Ineligible for High-Dose Therapy (Asia Pacific Region)	NCT03217812	Bortezomib, Dara, melphalan, prednisone	Newly diagnosed MM
A Study of Combination Therapy With Venetoclax, Daratumumab and Dexamethasone (With and Without Bortezomib) in Subjects With Relapsed or Refractory Multiple Myeloma	NCT03314181	Bortezomib, Dara, dexamethasone, venetoclax	Relapsed/refractory MM
LCL-HEM-MYE-CRD-002: Carfilzomib-Revmid-Dexamethasone-Elotuzumab in Relapsed/Refractory Multiple Myeloma	NCT03361306	Carfilzomib, dexamethasone, Elo, lenalidomide	Relapsed/refractory MM
Daratumumab, Carfilzomib, Lenalidomide and Low Dose Dexamethasone (DKRd) in Newly Diagnosed, Multiple Myeloma	NCT03500445	Carfilzomib, Dara, dexamethasone, lenalidomide	Newly diagnosed MM
A Study of Carfilzomib, Lenalidomide, Dexamethasone and Daratumumab for Patients With Relapsed/Refractory Myeloma With Salvage Autologous Hematopoietic Cell Transplantation	NCT03556332	Carfilzomib, Dara, dexamethasone, lenalidomide	Relapsed/refractory MM, includes salvage ASCT
SELIBORDARA: Selinexor, Bortezomib and Daratumumab in Multiple Myeloma	NCT03589222	Bortezomib, Dara, dexamethasone, selinexor	Relapsed/refractory MM
Daratumumab, Ixazomib, Pomalidomide, and Dexamethasone as Salvage Therapy in Relapsed/Refractory Multiple Myeloma	NCT03590652	Dara, dexamethasone, ixazomib, pomalidomide	RELAPSED/refractory MM

Continued next page

TABLE 3. (Continued)

Study Name	ClinicalTrials.gov Identifier	Drugs Utilized	Therapeutic Setting
An Intensive Program With Quadruplet Induction and Consolidation Plus Tandem Autologous Stem Cell Transplantation in Newly Diagnosed High Risk Multiple Myeloma Patients (IFM 2018-04)	NCT03606577	Carfilzomib, Dara, dexamethasone, lenalidomide	Newly diagnosed MM
A Study Comparing Daratumumab, VELCADE (Bortezomib), Lenalidomide, and Dexamethasone (D-VRd) With VELCADE, Lenalidomide, and Dexamethasone (VRd) in Participants With Untreated Multiple Myeloma and for Whom Hematopoietic Stem Cell Transplant Is Not Planned as Initial Therapy	NCT03652064	Bortezomib, Dara, dexamethasone, lenalidomide	Newly diagnosed MM
Study Association of Lenalidomide, Ixazomib, Dexamethasone and Daratumumab in Newly Diagnosed Standard Risk Multiple Myeloma (IFM2018-01)	NCT03669445	Dara, dexamethasone, ixazomib, lenalidomide	Newly diagnosed MM
Daratumumab, Bortezomib, and Dexamethasone With or Without Venetoclax in Treating Patients With Relapsed or Refractory Multiple Myeloma	NCT03701321	Bortezomib, Dara, dexamethasone, venetoclax	Relapsed/refractory MM
Daratumumab, VELCADE (Bortezomib), Lenalidomide and Dexamethasone Compared to VELCADE, Lenalidomide and Dexamethasone in Subjects With Previously Untreated Multiple Myeloma (Perseus)	NCT03710603	Bortezomib, Dara, dexamethasone, lenalidomide	Newly diagnosed MM

23.1% versus 14.7%. Ultimately, because of the superiority of the quadruplet, Dara-VMP was approved by the US Food and Drug Administration on May 7, 2018.²³

RELAPSED AND REFRACTORY MYELOMA

Although the necessity for a 4-drug regimen is debatable in the upfront setting, there are patients with such aggressive and refractory disease in the relapsed setting who all but require this approach for disease control. Histone deacetylase inhibitors are not widely used in day-to-day myeloma therapy, and although they have not demonstrated single-agent activity, they have been studied in 4-drug combinations in refractory patients.

In a phase I study, the QUAD regimen (carfilzomib/vorinostat/lenalidomide/dexamethasone) was studied in a dose-escalated fashion in relapsed and refractory MM. No dose limiting toxicities were observed, and the maximum tolerated dose was not reached. The maximum administered dose was carfilzomib 20/27 mg/m², lenalidomide 25 mg, vorinostat 400 mg, and dexamethasone 40 mg. The ORR was 53%, with 12% of patients achieving a VGPR and 41% of patients achieving a PR. At the time of publication, the median follow-up was 10 months with a median PFS of 12 months and median OS of no response.²⁴

The VERUMM study evaluated that the combination of vorinostat/bortezomib/doxorubicin/dexamethasone was admitted to elderly patients with relapsed disease. The ORR and clinical benefit rate amounted to 67% and 94%, respectively. At a median follow-up of 30.8 months, the median PFS and OS were 9.6 and 33.8 months. There were no nonhematologic grade 4 toxicities, and the remaining grade 3/4 toxicities were low in number and manageable.

Small case report studies have evaluated a number of quadruplet regimens in the relapsed setting including carfilzomib/pomalidomide/cyclophosphamide/dexamethasone²⁵ and bortezomib/venetoclax/Dara/dexamethasone.²⁶ Additional anecdotal data of single-patient (off study) outcomes on 4-drug combinations exist throughout the myeloma community. This information is hard to integrate into clinical practice, given the small numbers and retrospective nature of the data sets.

ONGOING STUDIES/DISCUSSION

Below is a list of more than 20 trials currently listed on clinicaltrials.gov, all of which incorporate a quadruplet regimen either in the upfront or the relapsed/refractory setting. Whether 4-drug regimens are here to stay, there is certainly a desire to study them.

The relapsed setting has a strong argument for the utility of quadruplet regimens. In a landscape where the current dogma is that of an incurable disease with limited therapeutic options, drugs that synergize (and/or resensitize) with regimens that a patient may already be refractory to may offer a new chance of remission. Utilizing drugs such as histone deacetylase inhibitors (vorinostat and panobinostat) as well as nelfinavir in this setting may be able to extend duration of remissions in regimens where the tide is shifting.

From a transplant-ineligible standpoint, Dara-VMP clearly shows benefit and is being utilized as an induction regimen outside the United States. Within the United States, doublet regimens are far more common as induction therapy for this older and frailer group of patients.

Regarding the role of quadruplet induction in transplant-eligible patients, the jury is still out. Triplet-based induction regimens are associated with extremely high ORR, some approaching 100%. What has become clear is the importance of depth of response, especially in the upfront setting. There is evidence from the IFM2009 trial that patients achieving MRD negativity

following induction therapy had similar outcomes whether they went on to receive ASCT.²⁷ What follows from this is the potential for quadruplet regimens in the upfront settings to improve PFS and potentially OS via achieving deeper remissions without significant changes in ORR. Ultimately, this needs to be balanced by patient heterogeneity, tumor heterogeneity, toxicity profile, and cost.

Novel recombinations of previously refractory drugs also lend itself to the formation of quadruplet regimens in the refractory setting. The notion of combining drug A and drug B when the patient is already refractory to the individual drugs has become commonplace in the clinic. This was evaluated in the combination of Dara and pomalidomide in patients naive to both refractory to one (or the other) and refractory to both during disparate prior regimens. The ORRs were 89%, 49.9%, and 33.3%, respectively.²⁸ We can both combine previously used therapies in novel ways with or without the addition of a fourth drug. This approach is already used at the bedside but requires prospective analysis to better elucidate the true risk/benefit profile (Table 3).

As our ability to better understand the heterogeneity of myeloma improves, so will our knowledge of who needs a doublet, who needs a triplet, and who needs a quadruplet. As to whether 4-drug regimens are here to stay in myeloma, it appears so.

REFERENCES

- Gormley NJ, Ko CW, Deisseroth A, et al. FDA drug approval: elotuzumab in combination with lenalidomide and dexamethasone for the treatment of relapsed or refractory multiple myeloma. *Clin Cancer Res*. 2017;23:6759–6763.
- Bhatnagar V, Gormley NJ, Luo L, et al. FDA approval summary: daratumumab for treatment of multiple myeloma after one prior therapy. *Oncologist*. 2017;22:1347–1353.
- Harousseau JL, Attal M, Avet-Loiseau H, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. *J Clin Oncol*. 2010;28:4621–4629.
- Moreau P, Avet-Loiseau H, Facon T, et al. Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment before autologous stem cell transplantation in newly diagnosed multiple myeloma. *Blood*. 2011;118:5752–5758.
- Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet*. 2010;376:2075–2085.
- Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *Lancet Oncol*. 2010;11:29–37.
- Palumbo A, Bringhen S, Liberati AM, et al. Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial. *Blood*. 2008;112:3107–3114.
- Mateos MV, Richardson PG, Schlag R, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. *J Clin Oncol*. 2010;28:2259–2266.
- Palumbo A, Bringhen S, Rossi D, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. *J Clin Oncol*. 2010;28:5101–5109.
- Durie BG, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet*. 2017;389:519–527.
- Mateos MV, Dimopoulos MA, Cavo M, et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. *N Engl J Med*. 2018;378:518–528.
- Khan ML, Reeder CB, Kumar SK, et al. A comparison of lenalidomide/dexamethasone versus cyclophosphamide/lenalidomide/dexamethasone versus cyclophosphamide/bortezomib/dexamethasone in newly diagnosed multiple myeloma. *Br J Haematol*. 2012;156:326–333.
- Moreau P, Hulin C, Macro M, et al. VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial. *Blood*. 2016;127:2569–2574.
- Jakubowiak AJ, Dytfield D, Griffith KA, 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.
- Mikhael JR, Reeder CB, Libby EN, et al. Phase Ib/II trial of CYKLONE (cyclophosphamide, carfilzomib, thalidomide and dexamethasone) for newly diagnosed myeloma. *Br J Haematol*. 2015;169:219–227.
- Kumar S, Flinn I, Richardson PG, 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.
- Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med*. 2015;373:621–631.
- Laubach. An open-label, single arm, phase IIa study of bortezomib, lenalidomide, dexamethasone, and elotuzumab in newly diagnosed multiple myeloma. *J Clin Oncol*. 2017;(suppl; abstr 8002).
- Chari. Daratumumab (DARA) in combination with carfilzomib, lenalidomide, and dexamethasone (KRd) in patients with newly diagnosed multiple myeloma (MMY1001): updated results from an open-label, phase 1b study. *Blood*. 2017;130:3110.
- Moreau P, Mateos MV, Berenson JR, et al. Once weekly versus twice weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (A.R.R.O.W.): interim analysis results of a randomised, phase 3 study. *Lancet Oncol*. 2018;19:953–964.
- Pawlyn. Quadruplet vs sequential triplet induction therapy for myeloma patients: results of the Myeloma XI study. Presented at the European Hematology Association 2017 Annual Meeting Abstracts. Abstract: S407. 22nd Congress of EHA. June 22–25, 2017 Madrid, Spain.
- San Miguel. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med*. 2008;359:906–917.
- Janssen Announces DARZALEX® (daratumumab) U.S. FDA Approval for Newly Diagnosed Patients with Multiple Myeloma who are Transplant Ineligible. Available at: <https://www.jnj.com/media-center/press-releases/janssen-announces-darzalex-daratumumab-us-fda-approval-for-newly-diagnosed-patients-with-multiple-myeloma-who-are-transplant-ineligible>. Accessed January 21, 2019.
- Vesole DH, Bilotti E, Richter JR, et al. Phase I study of carfilzomib, lenalidomide, vorinostat, and dexamethasone in patients with relapsed and/or refractory multiple myeloma. *Br J Haematol*. 2015;171:52–59.
- Richter J, Biran N, Duma N, et al. Safety and tolerability of pomalidomide-based regimens (pomalidomide-carfilzomib-dexamethasone with or without cyclophosphamide) in relapsed/refractory multiple myeloma and severe renal dysfunction: a case series. *Hematol Oncol*. 2017;35:246–251.
- Rahbari KJ, Nosrati JD, Spector TM, et al. Venetoclax in combination with bortezomib, dexamethasone, and daratumumab for multiple myeloma. *Clin Lymphoma Myeloma Leuk*. 2018;18:e339–e343.
- Avet-Loiseau. Minimal residual disease in multiple myeloma: final analysis of the IFM2009 trial. *Blood*. 2017;130:435.
- Nooka. Clinical efficacy of daratumumab, pomalidomide and dexamethasone in relapsed, refractory myeloma patients: utility of retreatment with daratumumab among refractory patients. *Blood*. 2016;128:492.