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Treatment of Newly Diagnosed Myeloma: Bortezomib-based Triplet

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Abstract

In this paper we review the options for the treatment of newly diagnosed myeloma in a patient who is a candidate for autologous stem cell transplantation. Bortezomib, lenalidomide, dexamethasone (VRD) has been studied in two randomized trials as first line therapy. In one of these trials, VRD demonstrated improved overall survival compared with lenalidomide plus dexamethasone (Rd). By contrast, phase III data with overall survival differences are not available for other bortezomib containing regimens compared with modern lenalidomide containing regimens. Carfilzomib-lenalidomide-dexamethasone (KRD) is an alternative promising regimen but has only been evaluated in small phase II studies in the frontline setting. More data are needed before this regimen can be recommended to standard risk patients with newly diagnosed myeloma. A phase III trial comparing VRD and KRD is ongoing.

The treatment of multiple myeloma (MM) is rapidly evolving with the approval of multiple new drugs.[1] Several others have shown activity and are expected to enter the market soon.[2] The rapid expansion in the number of treatment combinations that are possible pose a major dilemma for treating physicians: Should therapy be administered based on the best randomized data available? Or should treatments be chosen based on the most promising regimen in preliminary phase II trials? The clinical vignette presented describes a patient with newly diagnosed MM, with normal cytogenetics. Our recommendation in this patient is bortezomib-lenalidomide-dexamethasone (VRD) therapy based on the best randomized data available to date. The rationale for our choice is discussed below.

MM is a clonal plasma cell malignancy characterized by several primary and secondary cytogenetic abnormalities.[3] Almost all patients with MM will have one of the primary cytogenetic abnormalities (trisomies or immunoglobulin heavy chain translocations). The prevalence of secondary cytogenetic abnormalities such as deletion 17p or gain 1q is

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variable. The type of cytogenetic abnormalities detected in MM has a major influence on response to therapy and prognosis. In order to have high sensitivity in detecting cytogenetic abnormalities by cytoplasmic immunoglobulin (cIg) fluorescent in situ hybridization (FISH) it is important to have an adequate set of probes.[4] The probes used at Mayo Clinic for newly diagnosed MM are: 1p36.3(TP73), 1q21(gain), 3cen (D3Z1), 7cen (D7Z1), 8q24 (3'MYC, 5'MYC), 9cen (D9Z1), 15cen (D15Z4), 11q13 (CCND1-XT), 13q14 (RB1), 13q34 (LAMP1), 14q32 (IGH-XT), 14q32 (5'IGH,3'IGH), 17p13.1 (p53), and 17cen (D17Z1). Additional probes are then used as needed to detect t(4;14), t(6;14), t(14;16), t(14;20) translocations, and other abnormalities based on the results of the initial screen. Patients are considered to have high risk disease if FISH studies demonstrate one of the following abnormalities: t(14;16), t(14;20), or loss of p53 gene locus [del(17p) or monosomy 17].

The first step in the treatment of newly diagnosed MM is to determine eligibility for autologous stem cell transplantation and risk-stratification. Based on age, the patient will be considered a candidate for ASCT. The lack of cytogenetic abnormalities in this patient must be considered as the result of an inadequate probe set; it does not automatically indicate standard risk MM. Nevertheless for purposes of discussion we consider this as a patient without known high risk features.

So what are the major treatment options for this patient? Common regimens that have been tested in randomized trials in the treatment of newly diagnosed MM are listed in Table 1.[5–8] These include lenalidomide plus low dose dexamethasone (Rd), bortezomib-cyclophosphamide-dexamethasone (VCD; also commonly referred to as CyBorD), bortezomib- thalidomide-dexamethasone (VTD), and bortezomib-lenalidomide-dexamethasone (VRD).

What is our rationale for choosing VRD among the options discussed above? VRD is highly active and well tolerated with a response rate of 80–100%.[9] Complete responses are seen in 40–50% of patients. More importantly, it is the only modern triple therapy that has shown a clear overall survival advantage in a randomized trial. In the Southwest Oncology Group (SWOG) phase III trial conducted in the United States, progression free survival (PFS) and overall survival were significantly longer with VRD compared with Rd (Table 1).[6] The absolute overall survival results with VRD are impressive; the median overall survival in the SWOG randomized trial was 75 months. By contrast, studies have shown superior response rates and progression free survival with VTD compared with other doublet regimens, but no significant differences in overall survival were noted.[10,11] VCD had lower response rates compared with VTD in a recent randomized trial.[7]

We therefore consider VRD the standard of care in this patient, as it is the only modern regimen that has been rigorously evaluated in a randomized controlled trial, and has shown a clear survival advantage in newly diagnosed myeloma. Moreover, VRD also has the benefit of having been field tested in this setting, as observed in another large randomized trial conducted by Attal and colleagues.[8] Therefore, the safety of this regimen in the real world is not in doubt. By initiating therapy with VRD, which carries a median survival in excess of 6 years, it will provide a standard-risk patient ample opportunity to be treated with other novel regimens at the time of relapse. At which point it is likely we may have more options than

those available today, particularly with the arrival of monoclonal antibodies such as daratumumab.

In initial studies, one of the main problems with bortezomib-containing regimens was the incidence of peripheral neuropathy. However, recent studies show that the neurotoxicity of bortezomib can be greatly diminished by administering bortezomib once a week instead of twice-weekly,[12,13] and by administering the drug subcutaneously instead of via the intravenous route.[14] The once-weekly subcutaneous bortezomib schedule has made serious neuropathy an uncommon problem, and has made regimens such as VCD and VRD much more tolerable.

What about carfilzomib-lenalidomide-dexamethasone (KRD)? Two phase II trials have reported excellent results with KRD in newly diagnosed multiple myeloma.[15,16] However, there are no data from phase III trials in the newly diagnosed setting. It would be premature to recommend this regimen to a young patient who has no high risk features. Doing so would be based on a hopeful reliance on phase II data and expert opinion. As Prasad and colleagues have shown, such an approach may turn out to be useless or harmful. We need to be patient and wait for randomized data to merge.[17] A randomized trial in the United States (referred to as the Endurance trial) is currently ongoing comparing VRD versus KRD as initial therapy. If experts proceed to deliver clinical care outside of a trial setting with promising regimens before phase III data are available, how will we be able to accrue randomized trials and get the truth? With carfilzomib, there is a greater need for us to be careful.[18] A small but significant number of patients develop cardiac dysfunction and/or severe dyspnea. The drug is more cumbersome to administer, requiring 6 infusions per month, and this can affect quality of life. It is also twice as expensive compared with bortezomib; true cost effectiveness comparisons cannot be done accurately without randomized trials.[19] For us to justify a less well-studied, riskier, more cumbersome and expensive regimen, we need more than the mere promise of small phase II trials.

In summary, VRD is the standard of care for this patient. More data on safety and efficacy of KRD are needed before this regimen can be recommended in newly diagnosed multiple myeloma, except perhaps in young patients with high risk cytogenetics. In this small subset of MM one could argue that the potential promise of KRD may outweigh the risks of waiting for phase III data.

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Table 1

Results of Recent Randomized Studies in Newly Diagnosed Myeloma

Trial	Regimen	No. of patients	Overall response rate (%)	CR plus VGPR (%)	Progression-free survival (Median in months)	P value for progression free survival	3 year overall survival rate (%)*	Overall survival (Median in months)*	P value for overall survival
Rajkumar et al[5]	RD	223	81	50	19		75	NR	
	Rd	222	70	40	25	0.026	74	NR	0.47
Durie et al[6]	Rd	232	72	32	30	0.004	75	64	0.002
	VRd	242	82	44	43		85	75	
Moreau et al[7]	VCD	170	84	66	N/A		N/A	N/A	N/A
	VTD	170	92	77	N/A	N/A	N/A	N/A	
Attal et al[8]	VRD	350	N/A	46% CR	NR; 48% @3 years		88% at 3 years	NR	0.25
	VRD-ASCT	350	N/A	58% CR	NR; 61% at 3 years	<0.001	88% at 3 years	NR	

*Estimated from survival curves when not reported

**Progression free survival not reported, numbers indicate time to progression

†Rd until progression versus MPT

Abbreviations: VTD, bortezomib, thalidomide, dexamethasone; VRD, bortezomib, lenalidomide plus dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; N/A, not available; NR, not reported; CR, complete response; VGPR, very good partial response.

Modified from Rajkumar SV, Kumar S. Multiple Myeloma: Diagnosis and Treatment. Mayo Clin Proc 2016;91:101–119