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Supplement Article

IV. Initial treatment of multiple myeloma

S. Vincent Rajkumar*

Division of Hematology, Mayo Clinic, Rochester, MN, USA

**Correspondence to:*
S. Vincent Rajkumar, Division of Hematology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA.
E-mail: rajkumar.vincent@mayo.edu

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Introduction

The initial treatment of myeloma is rapidly evolving as newer and newer regimens are tested in phase II and III trials [1,2]. Over 20 modern regimens have been reported to be highly effective in a variety of recent trials [3]. Separating 'promising' results that should be interpreted as merely hypothesis that need further testing from those that provide clear evidence of clinical benefit requiring a change in practice is challenging. Part of this conundrum is driven by different standards used by experts to adjudicate what constitutes 'evidence'. Part of this is driven by regulatory pressures and cost. A large part of the variance in interpretation of data and ensuing recommendations is however dictated by competing philosophies on the approach to the treatment of myeloma.

In evaluating the available data and to make recommendations for initial therapy of the disease, certain key tenets can be used as universal guiding principles. First, although rational ideas such as the potential benefits of eradicating all myeloma cells are intuitive and attractive, it is prudent to wait for empiric evidence of clinical benefit. Numerous apparently rational strategies in medicine have been shown eventually to produce no benefit, or even harm to patients. Second, it is important to have a clear definition of clinical benefit. In myeloma, clinical benefit is not based on changes in surrogate markers, but rather on proof of prolongation or life or improvement in quality of life. Third, proof requires convincing data from randomized trials, not small uncontrolled studies. Finally, when there is no clear winner on the basis of the above three criteria, the default position should be to choose the least toxic, least expensive option.

Although there are empiric data showing clear survival benefit from randomized trials with a few modern regimens such as melphalan, prednisone, thalidomide (MPT) and bortezomib, melphalan, prednisone (VMP), these come from trials in which these regimens were compared with old historical ones such as melphalan, prednisone (MP). Similar results from randomized trials comparing two or more modern regimens with each other are scarce. Several modern regimens have not been compared with each other, and even among those that have been tested head-to-head in phase III trials, no data are yet available. Hence, currently, the guiding principle to choose among modern regimens is 'first do no harm', in other words, choosing regimens that are the least toxic and expensive in the absence of clear and convincing evidence that a more aggressive or expensive regimen provides clinical benefit. The choice is driven by balancing risks and benefits, and by factoring in patient preferences as well. There is an alternative approach: choose the most 'effective' regimen on the basis of rational thinking or surrogate data, but although this should be a standard strategy for designing the next set of trials, it is a less optimal approach for deciding standard of care in clinical practice.

Risk stratification

The choice of initial therapy is influenced to a considerable extent on the anticipated prognosis since this is an important determinant of the extent of risk that a patient is willing to undertake, and the type of risk one can recommend outside of a clinical trial setting. At the Mayo Clinic, newly diagnosed myeloma is stratified into standard, intermediate, and high risk disease using the Mayo stratification for myeloma and risk-adapted therapy classification (mSMART) [4]. Patients with translocations t(14;16) and t(14;20) and deletion of chromosome 17p (del 17p) are considered to have high risk myeloma. Patients with t(4;14) have intermediate risk myeloma. All others including trisomies t(11;14) and t(6;14) are considered standard risk. The presence of trisomies in patients with high and intermediate risk myeloma ameliorates the excess risk. Patients with standard risk myeloma have a median overall survival (OS) in excess of 6–7 years, whereas those with high risk disease have a median OS of less than 2–3 years despite tandem autologous stem cell transplantation (ASCT) [1].

The major regimens used for therapy and the key trials with these regimens are listed in Tables 1 and 2 [3]. The value of complete response (CR) as a therapeutic goal in standard risk patients remains unproven, but studies employing rigorous landmark analysis at various time points suggest that high risk patients require a CR for long-term survival and hence need an aggressive strategy to achieve that goal [5].

Initial treatment in patients eligible for ASCT

Patients eligible for ASCT are treated with approximately four cycles of induction therapy followed by stem cell harvest. After harvest, patients typically undergo frontline ASCT; however, cryopreservation of stem cells and delaying ASCT until first relapse may be an equally effective option for standard risk patients. In such instances, induction therapy is continued after harvest for an additional 8–14 months. Although thalidomide plus dexamethasone (TD) is approved for the treatment of newly diagnosed myeloma [6], it is inferior in terms of activity and toxicity compared with lenalidomide-based regimens and is not recommended as the standard frontline therapy except in countries where lenalidomide is not available for initial therapy and in patients with acute renal failure where it can be used effectively in combination with bortezomib.

Table 1. Major treatment regimens in multiple myeloma

Regimen	Usual dosing schedule[a]
Thalidomide–dexamethasone[b] [6]	Thalidomide 200 mg oral days 1–28 Dexamethasone 40 mg oral days 1, 8, 15, 22 Repeated every 4 weeks
Lenalidomide–dexamethasone [7]	Lenalidomide 25 mg oral days 1–21 every 28 days Dexamethasone 40 mg oral days 1, 8, 15, 22 every 28 days Repeated every 4 weeks
Bortezomib–dex[b] [15]	Bortezomib 1.3 mg/m^2 intravenous days 1, 8, 15, 22 Dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22) Repeated every 4 weeks
Melphalan–prednisone-thalidomide [13]	Melphalan 0.25 mg/kg oral days 1–4 (use 0.20 mg/kg/day oral days 1–4 in patients over the age of 75 years) Prednisone 2 mg/kg oral days 1–4 Thalidomide 100–200 mg oral days 1–28 (use 100 mg dose in patients >75) Repeated every 6 weeks
Bortezomib–melphalan–prednisone[b] [14]	Bortezomib 1.3 mg/m^2 intravenous days 1, 8, 15, 22 Melphalan 9 mg/m^2 oral days 1–4 Prednisone 60 mg/m^2 oral days 1 to 4 Repeated every 35 days
Bortezomib–thalidomide–dexamethasone[b] [10]	Bortezomib 1.3 mg/m^2 intravenous days 1, 8, 15, 22 Thalidomide 100–200 mg oral days 1–21 Dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22) Repeated every 4 weeks × 4 cycles as pre-transplant induction therapy
Bortezomib–cyclophosphamide–dexamethasone[b] (VCD) [12]	Cyclophosphamide 300 mg/m^2 orally on days 1, 8, 15 and 22 Bortezomib 1.3 mg/m^2 intravenously on days 1, 8, 15, 22 Dexamethasone 40 mg orally on days 1, 8, 15, 22 Repeated every 4 weeks[c]
Bortezomib–lenalidomide–dexamethasone[b] [12]	Bortezomib 1.3 mg/m^2 intravenous days 1, 8, 15 Lenalidomide 25 mg oral days 1–14 Dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22) Repeated every 3 weeks[d]

Source: Modified from [3].
[a]All doses need to be adjusted for performance status, renal function, blood counts, and other toxicities.
[b]Doses of dexamethasone and/or bortezomib reduced on the basis of subsequent data showing lower toxicity and similar efficacy with reduced doses.
[c]Omit day 22 dose if counts are low or when the regimen is used as maintenance therapy; when used as maintenance therapy for high risk patients, delays can be instituted between cycles.
[d]Omit day 15 dose if counts are low or when the regimen is used as maintenance therapy; when used as maintenance therapy for high risk patients, lenalidomide dose may be decreased to 10–15 mg per day, and delays can be instituted between cycles as carried out in total therapy protocols.

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Table 2. Results of selected 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 (%)[a]	Overall survival (median in months)	*P* value for overall survival
Rajkumar *et al.* [7]	RD	223	81	50	19.1		75	NR	
	Rd	222	70	40	25.3	0.026	74	NR	0.47
Harousseau *et al.* [8]	VAD	242	63	15	30		77	NR	
	VD	240	79	38	36	0.06	81	NR	0.46
Cavo *et al.* [10]	TD	238	79	28	40		84	NR	
	VTD	236	93	62	NR	0.006	86	NR	0.3
Facon *et al.* [13]	MP	196	35	7	17.8		48	33.2	
	Mel 100	126	65	43	19.4		52	38.3	
	MPT	125	76	47	27.5	<0.001	66	51.6	<0.001
San Miguel *et al.*[b] [14]	MP	331	35	8	16.6		54	43	
	VMP	337	71	41	24	<0.001	69	NR	<0.001

Source: Modified from [3].
MP, melphalan plus prednisone; MPT, melphalan plus prednisone plus thalidomide; VMP, bortezomib plus melphalan plus prednisone; Rd, lenalidomide plus dexamethasone; TD, thalidomide plus dexamethasone; VTD, bortezomib, thalidomide, dexamethasone; CR, complete response; VGPR, very good partial response.
[a]Estimated from survival curves when not reported.
[b]Progression free survival not reported; numbers indicate time to progression.

Lenalidomide–low dose dexamethasone (Rd)

Rd (lenalidomide plus low dose dexamethasone) is an active regimen in newly diagnosed myeloma [7]. Stem cell collection with granulocyte stimulating factor (G-CSF) alone may be impaired with Rd induction. Older patients (>65 years) and those who have received more than four cycles of Rd must be mobilized with cyclophosphamide plus G-CSF or plerixafor. All patients treated with Rd require antithrombosis prophylaxis. Aspirin is adequate for most patients, but in patients who are at higher risk of thrombosis, either low molecular weight heparin or coumadin is needed.

Bortezomib-containing regimens

Bortezomib plus dexamethasone (VD) produces better response rates compared with vincristine, adriamycin, dexamethasone (VAD) as pre-transplant induction therapy [8]. However, progression free survival (PFS) improvement is modest, 36 months versus 30 months, respectively; no overall survival benefit is apparent so far. Studies have evaluated several three-drug regimens that add an additional active agent to the VD regimen. The most common of such triplet regimens containing bortezomib are bortezomib–cyclophosphamide–dexamethasone (VCD), bortezomib–thalidomide–dexamethasone (VTD), bortezomib–lenalidomide–dexamethasone (VRD), and bortezomib–adriamycin–dexamethasone (PAD) [9]. In randomized trials, VTD has shown better response rates and PFS compared with TD [10] and VD [11]. PAD has shown superiority over TD in randomized trials. Results from randomized trials are not available for VRD and VCD. Nevertheless, these two regimens are commonly used in clinical practice on the basis of promising results from phase II studies. VCD does not add either cost or toxicity to the VD regimen. In fact, it typically has less neuropathy than VD because the addition of cyclophosphamide allows for weekly rather than twice weekly administration of bortezomib. VCD can also be considered as a minor modification of the VMP regimen, which has been tested extensively in phase III studies. In a phase II randomized trial, VCD had similar activity compared with VRD [12]. It is harder to justify VRD for all patients at this time because there are no phase III data and it doubles the cost of regimens such as Rd, VD, or VCD.

Approach to therapy

Figure 1 outlines an approach to therapy on the basis of underlying risk status and clinical presentation. There are no data comparing these bortezomib-based combinations with Rd to determine relative superiority in terms of overall survival or quality of life. Thus, in standard risk patients, either Rd or a bortezomib-based regimen such as VCD or PAD or VTD is reasonable. Among the bortezomib-

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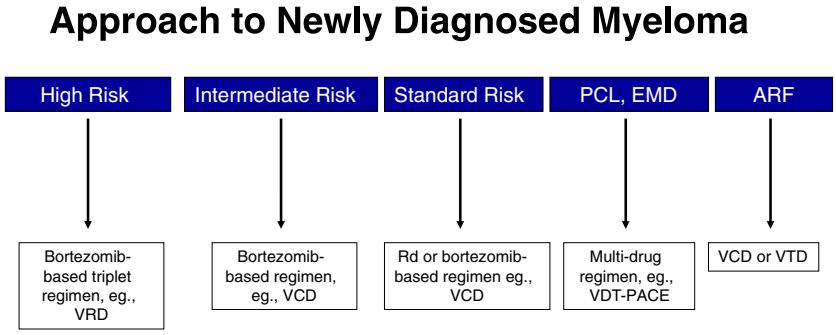

Figure 1. Approach to the treatment of newly diagnosed myeloma. Rd, lenalidomide plus low-dose dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; VRD, bortezomib, lenalidomide, dexamethasone; VTD, bortezomib, thalidomide, dexamethasone; PCL, plasma cell leukaemia; EMD, extramedullary disease; ARF, acute renal failure due to light chain cast nephropathy

based regimens, VCD is preferred on the basis of toxicity, cost, and convenience. In contrast, in intermediate risk patients with the t4;14 translocation, bortezomib-based regimens are needed as initial therapy because they appear to overcome the adverse prognostic effect of this translocation to some extent. In high-risk patients, regimens associated with the higher rates of CR are preferred, and depending on availability, VRD or other triplet regimen is reasonable.

The neurotoxicity of bortezomib can be greatly diminished by administering bortezomib using a once weekly schedule and by administering the drug subcutaneously. Unless there is a need for rapid disease control, twice weekly intravenous administration is best avoided.

In some special circumstances, additional modifications are needed for initial therapy (Figure 1). For example, in patients with renal failure, triplets such as VTD and VCD are preferred because they can be administered safely and have a high chance of reducing the light chain secretion rapidly. Similarly, patients with aggressive disease such as plasma cell leukaemia or multiple extramedullary plasmacytomas need multi-drug regimens such as VDT-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide).

Initial treatment in patients not eligible for ASCT

The initial regimens used to treat multiple myeloma in patients who are not candidates for ASCT because of age or other comorbidities include Rd and VCD used for patients eligible for ASCT [1]. In addition, melphalan-containing regimens that have been the mainstay of therapy for these patients for decades are additional options for initial therapy. However, in recent years, melphalan-based regimens are being increasingly avoided as frontline therapy, especially in the USA where the upper age limit for ASCT is flexible. The 3-year overall survival rate with Rd in patients 70 years and older who did not receive ASCT is 70%, which is comparable with the results with MPT and VMP. Results of a phase III trial comparing MPT versus Rd are not yet available.

For most patients treated without ASCT, initial therapy is typically administered for a fixed duration of approximately 9–18 months. In the case of Rd, which lends itself to long-term therapy, it is unclear whether treatment should continue until relapse or be stopped after a fixed duration. Maintenance therapy should be considered for intermediate and high risk patients.

Melphalan, prednisone, thalidomide

Six randomized studies have compared MPT versus MP, and a survival advantage has been observed in three trials [13]. MPT is associated with a grade 3–4 toxicity rate of over 50% and a DVT risk of 20%.

Bortezomib, melphalan, prednisone

VMP is associated with better survival compared with MP [14]. Bortezomib–thalidomide–prednisone is not superior to VMP. Neuropathy is a significant risk with VMP when bortezomib is administered in a twice weekly schedule. However, this rate can be decreased by administering bortezomib using a once weekly schedule. The VCD regimen used in patients who are candidates for ASCT can be considered as a minor modification of the VMP regimen, in which cyclophosphamide is used as the alkylating agent in place of melphalan.

Bortezomib, melphalan, prednisone, thalidomide

Preliminary results suggest superior survival with bortezomib, melphalan, prednisone, thalidomide (VMPT) compared 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 the initial 9 months. Thus, it is difficult to determine whether the survival benefit is due to the addition of the fourth drug or to the addition of maintenance.

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Approach to therapy

Figure 1 outlines an approach to therapy on the basis of underlying risk status and clinical presentation. There are no data comparing melphalan containing regimens (VMP, MPT) to regimens such as Rd and other bortezomib-based combinations (e.g. VCD and VTD) discussed for patients who are candidates for ASCT. In standard risk patients, Rd-, MPT-, or bortezomib-based regimens such as VMP or VCD are all reasonable options. Among the various bortezomib-based regimens, VCD is preferred on the basis of toxicity, cost, and convenience. In contrast, in intermediate risk patients, bortezomib-based regimens such as VMP or VCD are needed as initial therapy. In high risk patients, regimens such as VRD or a similar triplet regimen that produces high CR rates is reasonable.

TD is inferior to MP and is not recommended in elderly patients. The melphalan, prednisone, lenalidomide (MPR) regimen does not improve PFS or overall survival compared with MP and is therefore not recommended.

Future directions

As newer and newer drugs emerge, the array of options available for the treatment of newly diagnosed myeloma will continue to increase. There will be a constant need to choose regimens in clinical practice without clear data showing clinical benefit of one regimen from the other. In such circumstances, it is imperative to use a risk-adapted strategy that takes into account cost and toxicity and resist the temptation to choose regimens with the most impressive surrogate endpoint data. Promising regimens with impressive response rates in single arm trials such as carfilzomib, lenalidomide, dexamethasone (CRD) are best left for comparative phase III trials. It is only through rigorous testing of competing strategies and regimens in randomized trials can we be assured of progress.

Conflict of interest

The author has no competing interest.

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