

ANNUAL CLINICAL UPDATES IN HEMATOLOGICAL MALIGNANCIES:
A CONTINUING MEDICAL EDUCATION SERIES

Multiple myeloma: 2011 update on diagnosis, risk-stratification, and management

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Disease overview: Multiple myeloma is malignant plasma-cell disorder that accounts for ~10% of all hematologic malignancies.

Diagnosis: The diagnosis requires (1) 10% or more clonal plasma cells on bone marrow examination or a biopsy-proven plasmacytoma plus (2) evidence of end-organ damage felt to be related to the underlying plasma cell disorder.

Risk stratification: Patients with 17p deletion, t(4;14), t(14;16), t(14;20), and karyotypic deletion 13 or hypodiploidy are considered to have high-risk myeloma. All others are considered to have standard-risk disease.

Risk-adapted therapy: Standard-risk patients are treated with nonalkylator-based therapy such as lenalidomide plus low-dose dexamethasone (Rd) followed by autologous stem-cell transplantation (ASCT). If patients are tolerating the induction regimen treatment well, an alternative strategy is to continue initial therapy after stem-cell collection, reserving ASCT for first relapse. High-risk patients are treated with a bortezomib-based induction followed by ASCT and then bortezomib-based maintenance. Patients not eligible for ASCT can be treated with Rd for standard risk disease or a bortezomib-based regimen if high-risk features are present. To reduce toxicity, when using bortezomib, the once-weekly dose is preferred; similarly, when using dexamethasone, the low-dose approach (40 mg once a week) is preferred, unless there is a need for rapid disease control.

Management of refractory disease: Patients with indolent relapse can be treated first with lenalidomide, bortezomib, or alkylators plus low-dose corticosteroids. Patients with more aggressive relapse often require therapy with a combination of multiple active agents. The most promising new agents in development are pomalidomide and carfilizomib. *Am. J. Hematol.* 86:57–65, 2011. © 2010 Wiley-Liss, Inc.

Disease Overview

Multiple myeloma accounts for 1% of all cancers and ~10% of all hematologic malignancies [1,2]. Each year, over 20,000 new cases are diagnosed in the United States [3]. Contrary to the popular belief, the annual *age-adjusted* incidence in the United States has remained stable for decades at approximately four per 100,000 [4]. Multiple myeloma is slightly more common in men than in women and is twice as common in African-Americans compared to Caucasians [5]. The median age of patients at the time of diagnosis is about 65 years [6].

Unlike other malignancies that metastasize to bone, the osteolytic bone lesions in myeloma exhibit no new bone formation. Bone disease is the main cause of morbidity and can be detected on routine skeletal radiographs, magnetic resonance imaging (MRI), or fluorodeoxyglucose positron emission tomography/computed tomographic scans (PET-CT) [7]. True extramedullary lesions and extramedullary expansion of bone lesions can also occur. Other major clinical manifestations are anemia, hypercalcemia, renal failure, and an increased risk of infections.

It is now known clear that almost all patients with myeloma evolve from an asymptomatic premalignant stage termed monoclonal gammopathy of undetermined significance (MGUS) [8,9]. MGUS is present in over 3% of the population above the age of 50 and progresses to myeloma or related malignancy at a rate of 1% per year [10,11]. In some patients, an intermediate asymptomatic but more advanced premalignant stage referred to as smoldering multiple myeloma (SMM) can be recognized clinically [12,13]. SMM progressed to myeloma at a rate of ~10% per year over the first 5 years following diagnosis, 3% per year over the next 5 years, and 1.5% per year thereafter.

Diagnosis

The diagnosis of myeloma requires (1) 10% or more clonal plasma cells on bone marrow examination or a biopsy

proven plasmacytoma and (2) evidence of end-organ damage (hypercalcemia, renal insufficiency, anemia, or bone lesions) that is felt to be related to the underlying plasma cell disorder (Table I) [27]. When multiple myeloma is suspected clinically, patients should be tested for the presence of M proteins using a combination of tests that should include a serum protein electrophoresis, serum immunofixation, and the serum-free light chain (FLC) assay [28]. Approximately 2% of patients with multiple myeloma have true nonsecretory disease and have no evidence of an M protein on any of the above studies [6].

Bone marrow studies at the time of initial diagnosis should include conventional karyotyping to detect hypodiploidy and deletion 13, and fluorescent in situ hybridization designed to detect t(11;14), t(4;14), t(14;16), t(6;14), t(14;20), hyperdiploidy, and deletion 17p (see Risk-Stratification below) [29–31]. Gene expression profiling if available can provide additional prognostic value [32]. Serum Cross-Laps to measure carboxy-terminal collagen crosslinks may be useful in assessing bone turnover and to determine adequacy of bisphosphonate therapy [33,34]. Although plain radiographs of the skeleton are typically required to assess the extent of bone disease, PET-CT and MRI scans are

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TABLE 1. Diagnostic Criteria for Plasma Cell Disorders

Disorder	Disease definition	References
Monoclonal gammopathy of undetermined significance (MGUS)	All three criteria must be met: ● Serum monoclonal protein <3 g/dL ● Clonal bone marrow plasma cells <10% ● Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to the plasma cell-proliferative disorder; or in the case of IgM MGUS, no evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder.	14
Smoldering multiple myeloma (also referred to as asymptomatic multiple myeloma)	Both criteria must be met: ● Serum monoclonal protein (IgG or IgA) ≥ 3 g/dL and/or clonal bone marrow plasma cells $\geq 10\%$. ● Absence of end-organ damage such as lytic bone lesions, anemia, hypercalcemia, or renal failure that can be attributed to a plasma cell proliferative disorder	14
Multiple myeloma	All three criteria must be met except as noted: ● Clonal bone marrow plasma cells $\geq 10\%$ ● Presence of serum and/or urinary monoclonal protein (except in patients with true nonsecretory multiple myeloma) and ● Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically ○ Hypercalcemia: serum calcium ≥ 11.5 mg/dL or ○ Renal insufficiency: Serum creatinine >1.73 mmol/L (or >2 mg/dL) or estimated creatinine clearance less than 40 mL/min ○ Anemia: normochromic, normocytic with a hemoglobin value of >2 g/dL below the lower limit of normal or a hemoglobin value <10 g/dL ○ Bone lesions: lytic lesions, severe osteopenia, or pathologic fractures	14, 15
IgM monoclonal gammopathy of undetermined significance (IgM MGUS)	All three criteria must be met: ● Serum IgM monoclonal protein <3 g/dL ● Bone marrow lymphoplasmacytic infiltration <10% and ● No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder.	16–20
Smoldering Waldenström's macroglobulinemia (also referred to as indolent or asymptomatic Waldenström's macroglobulinemia)	Both criteria must be met: ● Serum IgM monoclonal protein ≥ 3 g/dL and/or bone marrow lymphoplasmacytic infiltration $\geq 10\%$ and ● No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder.	16–20
Waldenström's macroglobulinemia	All criteria must be met: ● IgM monoclonal gammopathy (regardless of the size of the M protein) and ● $\geq 10\%$ bone marrow lymphoplasmacytic infiltration (usually intertrabecular) by small lymphocytes that exhibit plasmacytoid or plasma cell differentiation and a typical immunophenotype (e.g., surface IgM+, CD5+/-, CD10-, CD19+, CD20+, and CD23-) that satisfactorily excludes other lymphoproliferative disorders including chronic lymphocytic leukemia and mantle cell lymphoma. ● Evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder.	16–20
Light-chain MGUS	All criteria must be met: ● Abnormal FLC ratio (<0.26 or >1.65) ● Increased level of the appropriate involved light chain (increased kappa FLC in patients with ratio > 1.65 and increased lambda FLC in patients with ratio < 0.26) ● No immunoglobulin heavy chain expression on immunofixation	21
Solitary plasmacytoma	All four criteria must be met: ● Biopsy proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells ● Normal bone marrow with no evidence of clonal plasma cells ● Normal skeletal survey and MRI of spine and pelvis (except for the primary solitary lesion) ● Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) that can be attributed to a lympho-plasma cell proliferative disorder	22,23
Systemic AL amyloidosis	All four criteria must be met: ● Presence of an amyloid-related systemic syndrome (such as renal, liver, heart, gastrointestinal tract, or peripheral nerve involvement) ● Positive amyloid staining by Congo red in any tissue (e.g., fat aspirate, bone marrow, or organ biopsy) ● Evidence that amyloid is light-chain related established by direct examination of the amyloid [possibly using mass spectrometry (MS)-based proteomic analysis, or immunoelectron microscopy; note that immunohistochemistry results to type amyloid may be unreliable] and ● Evidence of a monoclonal plasma cell proliferative disorder (serum or urine M protein, abnormal free light chain ratio, or clonal plasma cells in the bone marrow). Note: Approximately 2–3% of patients with AL amyloidosis will not meet the requirement for evidence of a monoclonal plasma cell disorder listed above; the diagnosis of AL amyloidosis must be made with caution in these patients.	24
POEMS syndrome	All four criteria must be met: ● Polyneuropathy ● Monoclonal plasma cell proliferative disorder (almost always <i>lambda</i>) ● Any one of the following three other major criteria: 1. Sclerotic bone lesions 2. Castleman's disease 3. Elevated levels of vascular endothelial growth factor (VEGF)^a ● Any one of the following six Minor Criteria 1. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) 2. Extravascular volume overload (edema, pleural effusion, or ascites) 3. Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, and pancreatic)^b 4. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomas, plethora, acrocyanosis, flushing, and white nails) 5. Papilledema 6. Thrombocytosis/polycythemia Note: Not every patient meeting the above criteria will have POEMS syndrome; the features should have a temporal relationship to each other and no other attributable cause. Anemia and/or thrombocytopenia are distinctively unusual in this syndrome unless Castleman disease is present.	25,26

^a The source data do not define an optimal cut-off value for considering elevated VEGF level as a major criterion. We suggest that VEGF measured in the serum or plasma should be at least three to fourfold higher than the normal reference range for the laboratory that is doing the testing to be considered a major criteria.

^b To consider endocrinopathy as a minor criterion, an endocrine disorder other than diabetes or hypothyroidism is required, because these two disorders are common in the general population.

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more sensitive and are indicated when symptomatic areas show no abnormality on routine radiographs [35].

The M protein is monitored by serum and urine protein electrophoresis to assess treatment response. The serum FLC assay can be used to monitor patients who lack a measurable M protein [36]. Response to therapy is assessed using the International Myeloma Working Group uniform response criteria [37].

Risk Stratification

Although staging using the Durie–Salmon staging [38] or the International Staging System [39,40] provide prognostic information for counseling, it is not useful for making therapeutic choices. On the other hand, a risk-stratification model that relies on a number of independent molecular cytogenetic markers is useful for both counseling and therapeutic decision making [41]. At the Mayo Clinic, newly diagnosed myeloma is stratified into standard-risk and high-risk disease using the Mayo stratification for myeloma and risk-adapted therapy classification (Table II) [29,31]. Patients with standard risk myeloma have a median survival of 6–7 years while those with high-risk disease have a me-

dian survival of less than 2–3 years despite tandem autologous stem-cell transplantation (ASCT) [2].

Risk-Adapted Therapy

Overall survival in myeloma has improved significantly in the last decade [42,43] with the emergence of thalidomide [44], bortezomib [45,46], and lenalidomide [47,48]. Bortezomib is a first-in-class proteasome inhibitor [49–51]; the mechanism of action of thalidomide and lenalidomide is unclear but both drugs possess immunomodulatory properties [52].

The approach to treatment of symptomatic newly diagnosed multiple myeloma is outlined in Figure 1 and is dictated by eligibility for ASCT and risk-stratification [53,54]. The major regimens used for therapy and the data to support their use are listed in Tables III and IV. There is an ongoing “cure versus control” debate on whether we should treat myeloma with an aggressive multidrug strategy targeting complete response (CR) or a sequential disease control approach in which CR while desirable is not pursued as a specific treatment goal [78]. Based on recent data, high-risk patients require a CR for long-term survival and hence clearly need an aggressive strategy [79]. On the other hand, standard-risk patients have similar overall survival regardless of whether CR is achieved or not and therefore have the option of pursuing either an aggressive or a gentler sequential approach.

Options for initial treatment in patients eligible for ASCT

Typically, patients are treated with approximately two to four cycles of induction therapy before stem-cell harvest [80]. After harvest, patients can either undergo frontline ASCT or resume induction therapy delaying ASCT until first relapse.

Thalidomide-dexamethasone. In a randomized trial, [55] the best response within four cycles of therapy was significantly higher with TD compared to dexamethasone alone; 63% versus 41%, respectively, $P = 0.0017$. In a subsequent randomized, double-blind, placebo-controlled

TABLE II. Risk-Stratification of Myeloma Using Fluorescent In Situ Hybridization Studies and Conventional Karyotyping

A. Standard-risk ^a
1. Hyperdiploidy
2. t (11;14)
3. t (6;14)
B. High-risk ^b
1. 17p deletion
2. t (4;14)
3. t (14;16)
4. t (14;20)
5. Deletion 13 or hypodiploidy by conventional karyotyping

^a None of the high-risk features can be present.

^b Any one high risk feature is sufficient to classify patient as high-risk.

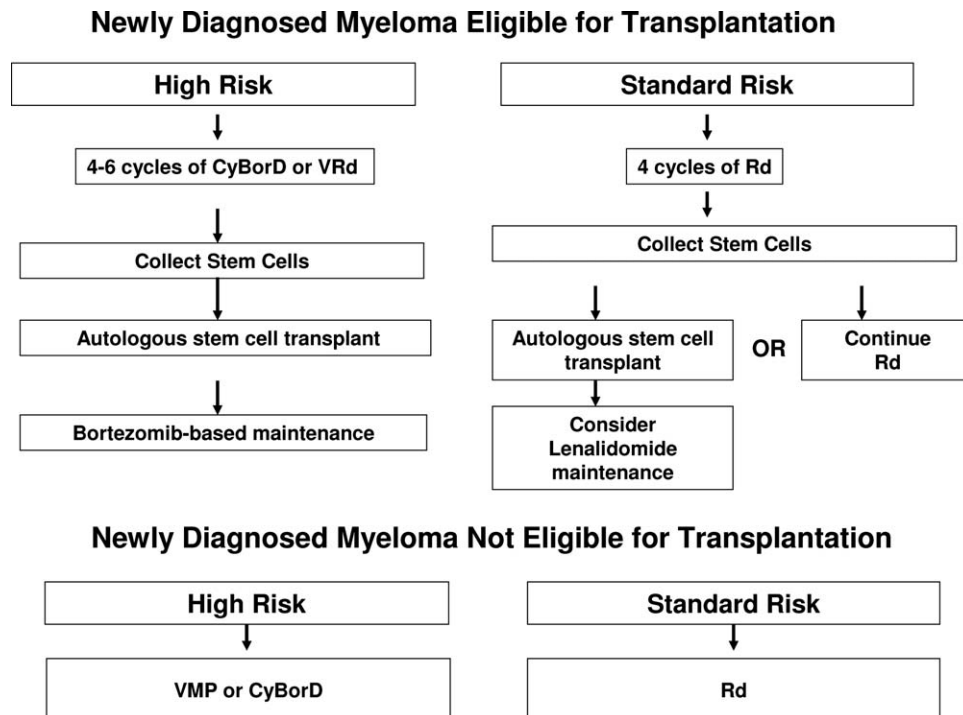


Figure 1. Approach to the treatment of newly diagnosed myeloma in patients eligible for transplantation (A) and not eligible for transplantation (B). Abbreviations: Rd, lenalidomide plus low-dose dexamethasone; VMP, bortezomib, melphalan, prednisone; Dex, dexamethasone; CR, complete response; VGPR, very good partial response; CyBorD, cyclophosphamide, bortezomib, dexamethasone.

TABLE III. Major Treatment Regimens in Multiple Myeloma

Regimen	Usual dosing schedule ^a
Melphalan–Prednisone (7-day schedule) [1]	Melphalan 8–10 mg oral days 1–7 Prednisone 60 mg/day oral days 1–7 Repeated every 6 weeks
Thalidomide–Dexamethasone [55,56] ^b	Thalidomide 200 mg oral days 1–28 Dexamethasone 40 mg oral days 1, 8, 15, and 22 Repeated every 4 weeks
Lenalidomide–Dexamethasone [57]	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 [58] ^b	Bortezomib 1.3 mg/m ² intravenous days 1, 8, 15, and 22 Dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1, 8, 15, and 22) Repeated every 4 weeks
Melphalan–Prednisone–Thalidomide [59,60]	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) 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 [61–63] ^b	Bortezomib 1.3 mg/m ² intravenous days 1, 8, 15, and 22 Melphalan 9 mg/m ² oral days 1–4 Prednisone 60 mg/m ² oral days 1–4 Repeated every 35 days
Bortezomib–Thalidomide–Dexamethasone [64,65] ^b	Bortezomib 1.3 mg/m ² intravenous days 1, 8, 15, and 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, and 22) Repeated every 4 weeks × 4 cycles as pretransplant induction therapy
Cyclophosphamide–Bortezomib–Dexamethasone (CyBorD) [66,67] ^b	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, and 22 Dexamethasone 40 mg orally on days on days 1, 8, 15, and 22 Repeated every 4 weeks ^c
Bortezomib–Lenalidomide–Dexamethasone [67,68] ^b	Bortezomib 1.3 mg/m ² intravenous days 1, 8, and 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, and 22) Repeated every 3 weeks ^d

^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 based on 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 done in total therapy protocols [67,70].

study, TD was associated with better time to progression (TTP) compared to dexamethasone alone [56]. However, TD is inferior in terms of activity and toxicity compared to 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. Patients receiving thalidomide-based regimens require DVT prophylaxis with aspirin, low-molecular weight heparin, or coumadin [81,82].

Lenalidomide-low-dose dexamethasone (Rd). Lenalidomide plus high-dose dexamethasone (RD) is active in newly diagnosed myeloma [47,83,84]. A recent randomized trial found that Rd, which used a lower dose of dexamethasone (40 mg once weekly), has less toxicity and better overall survival than lenalidomide plus high-dose dexamethasone [57]. Rd may impair collection of peripheral blood stem cells for transplant in some patients when mobilized with granulocyte stimulating factor (G-CSF) alone [85,86]. Thus, patients over the age of 65 and those who have received more than four cycles of Rd stem cells must be mobilized with either cyclophosphamide plus G-CSF or with plerixafor [80,87]. Rd carries the risk of DVT, and all patients require antithrombotic prophylaxis with aspirin; low-molecular weight heparin or coumadin is needed in patients at high risk of DVT [81,82].

Bortezomib-dexamethasone (VD). Bortezomib, alone and in combination with dexamethasone (Rd), has shown the activity in newly diagnosed myeloma [58,88–90]. Harousseau and colleagues compared VD versus vincristine, adriamycin, and dexamethasone (VAD) as pretransplant induction therapy [71]. Postinduction very good partial

response (VGPR) was superior with VD compared to VAD, 38% versus 15%, respectively. This translated into superior VGPR post-transplant, 54% versus 37%, respectively. However, progression-free survival (PFS) improvement was modest, 36 months versus 30 months, respectively, and did not reach statistical significance. No overall survival benefit is apparent so far. The major drawback of VD is the risk of neurotoxicity early in the disease course. The neuropathy with bortezomib can occur abruptly and can be significantly debilitating in a subset of patients. Recent studies show that reducing the dose of bortezomib to once a week show similar efficacy with significantly lower risk of neurotoxicity [91]. Unlike lenalidomide, bortezomib does not appear to have any adverse effect on stem-cell mobilization [92].

Multidrug combinations. Bortezomib–thalidomide–dexamethasone (VTD) results in better response rates and PFS compared to TD or VD in preliminary results from randomized trials [64,72,73]. Similarly, bortezomib, lenalidomide, and dexamethasone (VRd) produce high overall and CR rates when used in the treatment of newly diagnosed multiple myeloma [68]. A Southwest Oncology Group randomized trial is currently comparing VRd to Rd in the United States. A three-drug combination of cyclophosphamide, bortezomib, and dexamethasone (CyBorD) is a lower cost option compared to VTD or VRd and has shown significant activity in newly diagnosed multiple myeloma [66]. Although results with all these three-drug combinations (VTD, VRd, and CyBorD) show that we can improve response rates and PFS compared to two-drug combinations (Rd and VD), there are no data on whether the early incorporation of the third drug results in prolongation of overall survival, and what detrimental effect adding the third

TABLE IV. 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 years)	P value for progression-free survival	3-year overall survival rate (%) ^a	Overall survival (median in years)	P value for overall survival
Rajkumar et al. [57]	Rd	223	81	50	19.1		75	NR	
	Rd	222	70	40	25.3	0.026	74	NR	0.47
Harousseau et al. [71]	VAD	242	63	15	30		77	NR	
	VD	240	79	38	36	0.06	81	NR	0.46
Cavo et al. [64, 72]	TD	238	80	31	NR		N/A	N/A	
	VTD	236	93	62	NR	0.009	N/A	N/A	
Moreau et al. [73]	VD	99	81	35	N/A		N/A	N/A	
	VTD	100	90	51	N/A		N/A	N/A	
Facon et al. [59]	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		66	51.6	
Hulin et al. [60]	MP + Placebo	116	31	7	18.5	<0.001	40	29.1	<0.001
	MPT	113	62	21	24.1	0.001	55	44	0.028
Wijermans et al. [74]	MP	168	45	10	9		43	31	
	MPT	165	66	27	13	<0.001	55	40	0.05
Palumbo et al. [75]	MP	164	48	11	14.5		65	47.6	
	MPT	167	69	29	21.8	0.004	65	45	0.79
Waage et al. [76]	MP + Placebo	175	33	7	14		43	32	
	MPT	182	34	23	15	NS	43	29	0.16
San Miguel et al. [61, 77] ^b	MP	331	35	8	16.6		54	43	
	VMP	337	71	41	24	<0.001	69	NR	<0.001

^a Estimated from survival curves when not reported.^b Progression-free survival not reported, and numbers indicate time to progression.

Abbreviations: MP, melphalan plus prednisone; MPT, melphalan plus prednisone plus thalidomide; VMP, bortezomib plus melphalan plus prednisone; Rd, lenalidomide plus dexamethasone; VTD, bortezomib, thalidomide, dexamethasone; N/A, not available; NS, not significant; CR, complete response; VGPR, very good partial response.

drug has on quality of life, especially given the neurotoxicity associated with bortezomib and thalidomide. Besides these regimens, another option is multiagent combination chemotherapy, such as VDT-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide) [69,70]. VDT-PACE is particularly useful in patients with very aggressive disease such as plasma cell leukemia or multiple extramedullary plasmacytomas. Several other regimens have been tested in newly diagnosed multiple myeloma, but there are no clear data from randomized controlled trials that they have an effect on long-term endpoints compared to the regimens discussed earlier.

Recommendations. Unfortunately, the various options for treatment discussed earlier have not been compared in adequately powered clinical trials with relevant end-points to determine the best treatment strategy.

- In low-risk patients, I favor Rd as initial therapy for 4 months, followed by stem-cell harvest and ASCT. In patients who are tolerating and responding well, it is equally reasonable to continue Rd after stem-cell collection, reserving ASCT for first relapse. With such a strategy, Rd dose is reduced as much as possible or stopped after 1 year.
- In high-risk patients, I favor CyBorD or VRd as initial therapy for four cycles followed by ASCT and then maintenance with a bortezomib-based regimen.
- In patients presenting with acute renal failure suspected to be secondary to light-chain cast nephropathy, I prefer VTD as initial therapy in conjunction with plasma exchange. Plasma exchange is continued daily until the serum FLC levels are less than 50 mg/dL and then repeated as needed till VTD is fully effective.
- In patients presenting with plasma-cell leukemia or multiple extramedullary plasmacytomas, I prefer VDT-PACE as initial therapy followed by ASCT and then maintenance with a bortezomib-based regimen.
- Once weekly bortezomib is preferred in most patients for initial therapy, unless there is felt to be an urgent need for rapid disease control [93].
- Dexamethasone 40 mg once a week (low-dose dexamethasone) is preferred in most patients for initial therapy, unless there is an urgent need felt for rapid disease control.

Options for initial treatment in patients not eligible for ASCT

In patients with newly diagnosed multiple myeloma who are considered ineligible for ASCT due to age or other comorbidities, the major options at present are either melphalan-based combination therapies or Rd [94]. With melphalan-based therapy patients are usually treated for a fixed duration of time (9–18 months) and then observed. With Rd, it is unclear whether treatment should continue until relapse or be stopped after a fixed duration of therapy.

Melphalan, prednisone, thalidomide (MPT). Four randomized studies have shown that melphalan, prednisone, and thalidomide MPT improve response rates compared to MP [59,60,74,76,95]. Four of these trials have shown a significant prolongation of PFS with MPT, [59,60,74,95], and an OS advantage has been observed in the two Intergroupe Francophone du Myelome trials and in the trial by Wijermans et al. [59,60,74,76,95] (Table IV). A recent meta-analysis of these five studies shows a clear superiority of MPT in terms of PFS, and a trend toward improved survival [96]. Grade 3–4 adverse events occur in ~ 55% of patients treated with MPT, compared to 22% with

MP [95]. As with Thal/Dex, there is a significant (20%) risk of DVT with MPT in the absence of thromboprophylaxis.

Bortezomib, melphalan, and prednisone (VMP). In a large phase III trial, VMP had a significantly superior response rate compared to MP (71% vs. 35%, $P < 0.001$) [61]. TTP and overall survival were also significantly superior with VMP compared to MP, and there was a suggestion that bortezomib can overcome some high-risk cytogenetic features [77]. Neuropathy is a significant risk with VMP therapy; grade 3 neuropathy occurred in 13% of patients versus 0% with MP [61]. The risk of neuropathy can be greatly decreased by using a once-weekly schedule of bortezomib [62,63].

Lenalidomide plus low-dose dexamethasone (Rd). Rd is an attractive option for the treatment of elderly patients with newly diagnosed myeloma because of its excellent tolerability, convenience, and efficacy. The 3-year overall survival rate with Rd in patients 70 and older who did not receive ASCT is 70% [97] and is comparable to results with MPT and VMP. An ongoing phase III trial is currently comparing MPT versus Rd for 18 months versus Rd until progression.

Other regimens. Melphalan plus prednisone (MP) may still have a role in elderly patients who do not have access to Rd in whom therapy with MPT or VMP is not considered safe or feasible [98,99]. The addition of lenalidomide to MP (MPR) does not seem to improve PFS compared to MP alone [100]. An ECOG randomized trial (E1A06) is currently comparing MPR to MPT.

Recommendations. Unfortunately, the various options for treatment discussed earlier have not been compared in adequately powered clinical trials with relevant end-points to determine the best treatment strategy.

- In standard-risk patients, I favor Rd as initial therapy. Dexamethasone dose is reduced as much as possible after the first 4–6 months and possibly discontinued after the first year. For frail patients, dexamethasone may be started at 20 mg once a week.
- In high-risk patients, I favor VMP or CyBorD as initial therapy for ~1 year followed by a lower intensity maintenance schedule of bortezomib.

Role of hematopoietic stem-cell transplantation

Autologous stem-cell transplantation. ASCT improves CR rates and prolongs median OS in multiple myeloma by ~12 months [101–104]. Importantly, three randomized trials show that survival is similar whether ASCT is done early (immediately following four cycles of induction therapy) or delayed (at the time of relapse as salvage therapy) [105–107]. In a Spanish randomized trial, patients responding to induction therapy failed to benefit from ASCT trial, suggesting that the greatest benefit from ASCT is among those with disease refractory to induction therapy [108]. Two randomized trials have found benefit with tandem (double) versus single ASCT, with the benefit primarily seen in patients failing to achieve CR or VGPR with the first ASCT [109,110]. Two other randomized trials have yet to show significant improvement in OS with double ASCT [111,112].

Allogeneic transplantation. The role of allogeneic and nonmyeloablative–allogeneic transplantation in myeloma is controversial and remains investigational. The TRM (10–20%) and high-GVHD rates even with nonmyeloablative allogeneic transplantation are unacceptably high [113].

Recommendations

- ASCT should be considered in all eligible patients. But in standard-risk patients responding well to therapy,

ASCT can be delayed until first relapse provided stem cells are harvested early in the disease course.

- Tandem ASCT is considered only if patients fail to achieve a VGPR with the first ASCT. With modern induction regimens, such patients are a small minority, and, even in this circumstance, patients can be probably treated with maintenance therapy rather than tandem ASCT.
- At present, allogeneic transplantation should primarily be considered only in the context of clinical trials in multiple myeloma.

Post-transplant maintenance therapy

There is confusion about whether post-transplant strategies should be referred to as “consolidation” or “maintenance,” but these distinctions are semantic and do not distract from the main questions: should we administer post-transplant therapy? Who should receive such therapy? Thalidomide has shown modest PFS and survival benefit as maintenance therapy in two randomized trials [114,115]. More recently, two randomized studies have shown better PFS with lenalidomide as post-ASCT maintenance therapy [116,117]. However, patients in the control arm of these trials lacked uniform access to the active drug (thalidomide or lenalidomide) at relapse, and it is not clear whether the PFS improvement will be neutralized, because patients in the control arm can always initiate the same therapy at the time of first relapse.

Although not studied well, bortezomib-based maintenance approaches may be important in high-risk patients.

Recommendations

- At this point, it is not clear whether all patients should receive maintenance therapy post-ASCT with either thalidomide or lenalidomide, but results of the maintenance trials must be discussed with the patient, along with the pros and cons of maintenance versus therapy at first relapse.
- I recommend observation alone for most patients post-transplant except those who fail to achieve VGPR (candidates for lenalidomide maintenance) and those with high-risk disease (candidates for bortezomib-based maintenance).

Treatment of relapsed multiple myeloma

Almost all patients with multiple myeloma eventually relapse. The remission duration in relapsed myeloma decreases with each regimen [118]. The median PFS and overall survival in patients with relapsed myeloma refractory to lenalidomide and bortezomib is poor, with median times of 5 and 9 months, respectively [119]. Alkylators, corticosteroids, and thalidomide are all known options for therapy. Other options are discussed below.

Bortezomib and lenalidomide-based regimens.

Approximately one-third of patients with relapsed refractory myeloma respond to bortezomib therapy, with an average response duration of 1 year [45,46,120]. Similarly, two large phase III trials have shown superior TTP with lenalidomide (25 mg oral days 1–21 every 28 days) plus Rd compared to placebo plus Rd in relapsed multiple myeloma [121,122]. Bortezomib and immunomodulatory drugs (thalidomide or lenalidomide) can be combined effectively into highly active combination regimens: VTD and VRd. In a study of 85 patients with refractory myeloma treated with VTD, 63% achieved PR including 22% near CR [123]. Similarly, VRd has shown significant activity in relapsed, refractory myeloma with a PR rate of 67%, including 24% near CR or better [124].

Liposomal doxorubicin. A phase III randomized trial found that median TTP was superior with bortezomib plus pegylated liposomal doxorubicin compared to bortezomib alone, 9.3 months versus 6.5 months, respectively, $P < 0.001$ [125]. Survival at 15 months was also superior, 76% compared to 65%, respectively, $P = 0.03$. Based on this study, liposomal doxorubicin appears to have modest activity in relapsed myeloma, and this combination can be considered in patients not responding to VD or in patients with aggressive relapse.

Emerging options. Pomalidomide appears to have significant activity in relapsed refractory myeloma, even in patients failing lenalidomide [126]. Another emerging option is carfilzomib, a novel keto-epoxide tetrapeptide proteasome that has shown single agent activity in relapsed refractory multiple myeloma [127]. The most promising agents being investigated besides pomalidomide and carfilzomib are the histone deacetylase inhibitors (vorinostat and panabinoestat) and the anti-CS-1 antibody, elotuzumab.

Recommendations

- Patients who have cryopreserved stem cells early in the disease course should consider ASCT as salvage therapy at first relapse [128].
- If relapse occurs more than 6 months after stopping therapy, the initial treatment regimen that successfully controlled the myeloma initially can be reinstituted when possible.
- Patients who have an indolent relapse can often be treated first with lenalidomide, bortezomib, or alkylators plus low-dose corticosteroids. These patients present with asymptomatic increases in serum and urine monoclonal protein levels, progressive anemia, or a few small lytic bone lesions.
- Patients with more aggressive relapse often require therapy with a combination of active agents, e.g., VTD, VRd, CyBORd, or VDT-PACE.
- The duration of therapy has not been well addressed in relapsed myeloma, and, in some regimens, such as those employing bortezomib or alkylators, it may be reasonable to stop therapy once a stable plateau has been reached in order to minimize risks of serious toxicity.

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