

## Treatment of Newly Diagnosed Multiple Myeloma Based on Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART): Consensus Statement

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Multiple myeloma is a neoplastic plasma cell dyscrasia that on a yearly basis affects nearly 17,000 individuals and kills more than 11,000. Although no cure exists, many effective treatments are available that prolong survival and improve the quality of life of patients with this disease. The purpose of this consensus is to offer a simplified, evidence-based algorithm of decision making for patients with newly diagnosed myeloma. In cases in which evidence is lacking, our team of 18 Mayo Clinic myeloma experts reached a consensus on what therapy could generally be recommended. The focal point of our strategy revolves around risk stratification. Although a multitude of risk factors have been identified throughout the years, including age, tumor burden, renal function, lactate dehydrogenase,  $\beta_2$ -microglobulin, and serum albumin, our group has now recognized and endorsed a genetic stratification and patient functional status for treatment.

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CR = complete response; FISH = fluorescence in situ hybridization; HSCT = hematopoietic stem cell transplantation; IFM = Intergroupe Français du Myélome; IMiD = immunomodulatory drug; ISS = International Staging System; MP = melphalan and prednisone; MPT = melphalan, prednisone, and thalidomide; mSMART = Mayo Stratification of Myeloma and Risk-Adapted Therapy; OS = overall survival; PFS = progression-free survival; VAD = vincristine, doxorubicin (Adriamycin), and dexamethasone

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Multiple myeloma is a neoplastic plasma cell dyscrasia that on a yearly basis affects nearly 17,000 individuals and kills more than 11,000.<sup>1</sup> Survival of patients with multiple myeloma varies from months to decades.<sup>2,3</sup> Historically, no precise methods have been available to identify the subset of patients with newly diagnosed myeloma who are best served by standard intensity therapies, maintenance therapies, novel therapies, or more intensive regimens. Although the Durie-Salmon system has separated patients predominantly by tumor burden and renal function,<sup>4</sup> it has been supplanted by the International Staging System (ISS).<sup>5</sup> The ISS incorporates the more easily reproducible parameters of albumin and  $\beta_2$ -microglobulin, resulting in low-, intermediate-, and high-risk groups of patients with median overall survival (OS) times of 62, 45, and 29 months, respectively. Although the ISS is highly prognostic and important for comparing results across trials and providing a global estimate of outcome, for therapeutic purposes we favor a cytogenetics and proliferation-based model,<sup>6</sup> which appears to offer greater power and predictive value for risk stratification (Table 1).<sup>7-13</sup>

Several molecular classification systems have been proposed on the basis of gene expression profiling.<sup>14-17</sup> Although these systems may ultimately elucidate the pathogenesis of myeloma, they are not easily translated into routine clinical practice. In contrast, cytogenetic classification systems are readily applied in the clinic.

Nearly all patients with myeloma have abnormal chromosomes by fluorescence in situ hybridization (FISH), including deletions, aneuploidy, and translocations,<sup>18,19</sup> although abnormal karyotypes are seen in only 18% to 30% of cases using standard metaphase analysis.<sup>20</sup> This apparent discrepancy is explained by the generally low proliferative rate of myeloma cells and the requirement of obtaining plasma cells (and not just the rapidly dividing normal myeloid precursors) in metaphase to generate informative conventional cytogenetics.<sup>21-23</sup> Therefore,

[For editorial comment, see page 279](#)

TABLE 1. Genetic-Based Prognostic and Staging Systems in Patients With Newly Diagnosed Multiple Myeloma\*

Reference	No. of patients	Risk or stage	Patients (%)	Features	Median overall survival (mo)
Smadja et al, <sup>7</sup> 2001†	159	Low	35	$\beta_2M \leq 3$ mg/L and nonhypodiploid‡	52
		Intermediate	42	$\beta_2M > 3$ mg/L or hypodiploid‡	30
		High	23	$\beta_2M > 3$ mg/L and hypodiploid‡	11
Fonseca et al, <sup>8</sup> 2003	275	Low	39	Absence of F- $\Delta 13q$ , t(4;14), t(14;16), and F- $\Delta 17p13$	50
		Intermediate	37	F- $\Delta 13q$	42
		High	24	t(4;14), t(14;16), or $\Delta 17p13$	25
Konigsberg et al, <sup>9</sup> 2000	88	Low	36	No F- $\Delta 13q$ and $\beta_2M \leq 4$ mg/L	102
		Intermediate	40	F- $\Delta 13q$ or $\beta_2M > 4$ mg/L	46
		High	24	F- $\Delta 13q$ and $\beta_2M > 4$ mg/L	11
Tricot et al, <sup>10</sup> 1995§	147	Low	79	Absence of M- $\Delta 13q$ , and M- $\Delta 11q$	>48
		Intermediate	18	M- $\Delta 13q$ OR M- $\Delta 11q$	>50
		High	3	M- $\Delta 13q$ AND M- $\Delta 11q$	12
Facon et al, <sup>11</sup> 2001//	110	Low	20	No F- $\Delta 13q$ and $\beta_2M < 2.5$ mg/L	>111
		Intermediate	50	F- $\Delta 13q$ or $\beta_2M \geq 2.5$ mg/L	47
		High	30	F- $\Delta 13q$ and $\beta_2M \geq 2.5$ mg/L	25
Fassas et al, <sup>12</sup> 2002§	1475	Low	67	No karyotypic abnormality	51
		Intermediate	16	Not hypodiploid but karyotypic abnormality other than M- $\Delta 13q$	36
		High	17	Hypodiploid or M- $\Delta 13q$	19
Chiecchio et al, <sup>13</sup> 2006†	470	Low	53	No F- $\Delta 13q$	NR
		Intermediate	26	F- $\Delta 13q$ only	29
		High	18	F- $\Delta 13q$ + poor IgHt OR F- $\Delta p53$	20
		Very high	3	F- $\Delta 13q$ + poor IgHt AND F- $\Delta p53$	13

\*Prognostic categories were defined based on patients treated with standard-intensity chemotherapy unless stated otherwise.  $\beta_2M$  =  $\beta_2$ -microglobulin; F- $\Delta$  = fluorescence in situ hybridization deletion; poor IgHt = poor prognosis IgH translocation; M- $\Delta$  = metaphase cytogenetic deletion; NR = not reached.

†Patients received either standard chemotherapy or high-dose chemotherapy with transplantation.

‡Metaphase cytogenetics.

§Tandem transplantation study.

//High-dose melphalan, single transplantation, or tandem transplantation.

any abnormality in conventional cytogenetics identifies a group with a higher proliferative rate<sup>24</sup> and a particularly poor prognosis. There is excellent correlation between abnormal conventional cytogenetics and a high plasma cell proliferative rate.<sup>25,26</sup> Fonseca et al<sup>8</sup> have demonstrated that 3 distinct staging groups can be defined by the presence or absence of t(4;14)(p16.3;q32), t(14;16)(q32;q23), deletion 17p13, and deletion 13q by FISH (Table 1).

### PLOIDY STATUS

Overall, nonhyperdiploid myeloma is associated with more aggressive disease except for t(11;14)(q13;q32) (Table 1). This association has been demonstrated by flow cytometric methods<sup>27-29</sup> and metaphase cytogenetics.<sup>7,30-33</sup> There are strong associations among nonhyperdiploid myeloma, deletions of chromosome 13, and immunoglobulin heavy chain translocations.<sup>34</sup> In contrast, hyperdiploid myeloma, which is associated with good prognosis, is characterized by trisomies of chromosomes 3, 5, 6, 7, 9, 11, 15, 17, 19, and 21 by both metaphase cytogenetics<sup>22,32</sup> and FISH.<sup>35-37</sup>

### DELETIONS OF CHROMOSOME 13

As indicated in Table 1, monoallelic loss of chromosome 13 ( $\Delta 13$ ) or its long arm ( $\Delta 13q$ ), when determined by metaphase cytogenetics, is a powerful adverse prognostic factor in patients treated with standard chemotherapy<sup>9,38,39</sup> or high-dose chemotherapy and hematopoietic stem cell transplantation (HSCT).<sup>10,31,40-42</sup> Approximately 50% of patients newly diagnosed as having multiple myeloma have  $\Delta 13$  or  $\Delta 13q$  by FISH (F- $\Delta 13q$ ).<sup>11,26,38,43</sup> Patients with F- $\Delta 13q$  have a worse OS with standard chemotherapy,<sup>9,26,38</sup> high-dose therapy,<sup>11,44</sup> and interferon treatment.<sup>38</sup> The negative prognostic effect of F- $\Delta 13q$  is less than that for  $\Delta 13q$  by conventional cytogenetics (M- $\Delta 13q$ ), although it remains an independent prognostic factor. The poor prognosis associated with  $\Delta 13q$  may be because of other nonrandom, associated chromosomal abnormalities, such as immunoglobulin translocations and ploidy status.<sup>7,34,39</sup>

### IMMUNOGLOBULIN HEAVY CHAIN TRANSLOCATIONS

Up to 65% of patients with multiple myeloma have translocations that involve the heavy chain gene on chromosome

14. These translocations include illegitimate switch recombination of the variable regions of the immunoglobulin heavy chain gene at 14q32. Partners of the translocations into the immunoglobulin heavy chain switch region on chromosome 14 include chromosomes 11, 4, 6, and 16.<sup>45</sup> The t(11;14)(q13;q32) translocation is the most common translocation in multiple myeloma, occurring in approximately 20% of patients.<sup>22,34,46</sup> Most publications suggest that this translocation and the related t(6;14)(p21;q32)<sup>47</sup> are associated with a favorable or neutral outcome in patients with multiple myeloma.<sup>9,10</sup> In contrast, the t(4;14)(p16.3;q32) is present in 15% of patients,<sup>48-52</sup> and t(14;16)(q32;q23) is present in approximately 5% of patients.<sup>34,49</sup> Both convey a very poor prognosis (Table 1) and will be missed if FISH is not used to probe for their presence. The former translocation results in the up-regulation of fibroblast growth factor receptor 3 and in the hybrid transcript IgH/MMSET,<sup>48,49</sup> and the latter activates the c-maf proto-oncogene.<sup>49</sup>

#### DELETION OF 17P13 (P53)

Deletions of *p53* (locus *17p13*) as detected by FISH are present in 10% of patients with newly diagnosed myeloma<sup>8,53,54</sup> and confer a poorer survival.<sup>8,54</sup> Inactivating mutations are more common in human myeloma cell lines and in patients with a terminal phase of myeloma.<sup>55-59</sup>

#### PLASMA CELL LABELING INDEX

The plasma cell labeling index of bone marrow plasma cells, a slide-based immunofluorescent assay, is a reproducible and powerful prognostic factor in multiple myeloma.<sup>60-62</sup> An increased plasma cell labeling index predicts a short remission and survival but does not predict response to therapy. It is a helpful adjunct to a FISH myeloma panel.

#### RATIONALE FOR OUR RECOMMENDATIONS

Although investigators have proffered several genetic classification systems (Table 1), each of which includes different variables and cutoff points, no consensus exists regarding which system is best. Rather than promulgating any one specific prognostic system, we have focused our efforts on defining a composite high-risk group<sup>6,62</sup> that we believe should be managed differently from standard-risk patients. This approach is integral to the Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) (Figures 1 and 2; see also [www.mSMART.org](http://www.mSMART.org)).<sup>63</sup> The specific criteria given in Table 2<sup>62,64</sup> are used to classify patients into 2 distinct risk categories but are not intended to replace existing prognostic systems, and not all tests are required (but rather preferred) for any given patient. At a minimum,

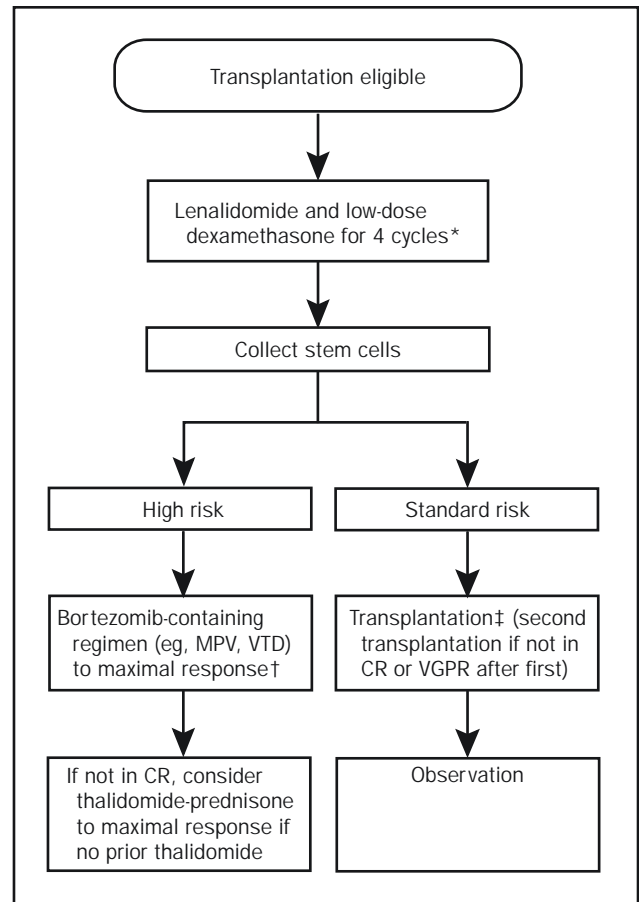


FIGURE 1. Nonstudy treatment algorithm for transplantation-eligible patients with newly diagnosed active myeloma. Many of the recommendations in this algorithm have not yet been supported by clinical trials; level of evidence is clearly indicated in the text. CR = complete response; MPV = melphalan, prednisone, and bortezomib; VGPR = very good partial response; VTD = bortezomib, thalidomide, and dexamethasone.

\*If no response after 2 cycles, consider bortezomib-containing regimen. †Potential allogeneic transplantation approaches considered in selected patients.

‡If transplantation deferred, continue induction to maximal response.

metaphase cytogenetics or FISH studies should be performed in addition to determinations of serum albumin,  $\beta_2$ -microglobulin, and lactate dehydrogenase levels. The ISS and the presence or absence of elevated lactate dehydrogenase levels will still retain prognostic importance, especially within the standard-risk group.

The purpose of this consensus is to offer a simplified, evidence-based (Appendix) algorithm of treatment decision making for patients with newly diagnosed myeloma. In cases in which evidence is lacking, our team of 18 Mayo Clinic myeloma experts reached a consensus on what therapy could generally be recommended. Our preferential use of oral therapies in instances in which no data were

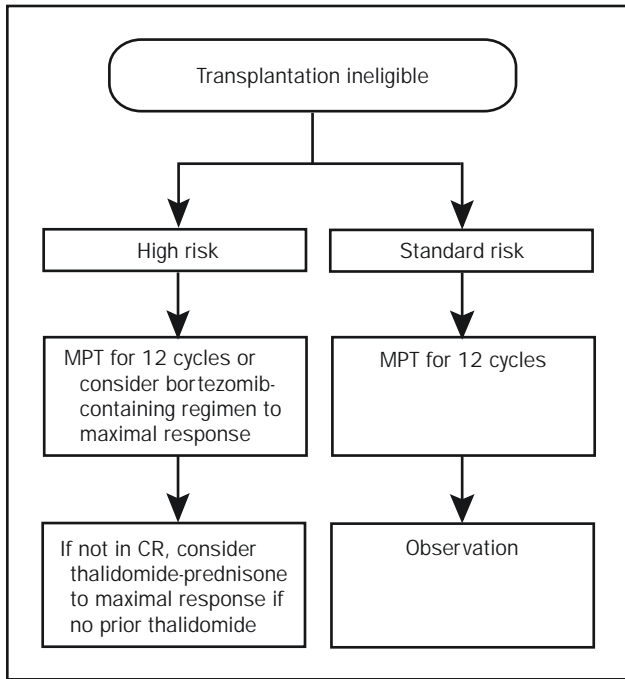


FIGURE 2. Nonstudy treatment algorithm for transplantation-ineligible patients with newly diagnosed active myeloma. Separating treatment by risk as shown in this algorithm has not yet been supported by clinical trials; level of evidence is clearly indicated in the text. CR = complete response; MPT = melphalan, prednisone, and thalidomide.

available to recommend immunomodulatory drugs (IMiDs) over proteasome inhibitors is largely a function of our referral practice pattern rather than a statement about efficacy.

**INDICATIONS FOR THERAPY FOR NEWLY DIAGNOSED MYELOMA**

**Guideline:** Treatment of myeloma should be initiated in all patients with symptomatic myeloma. However, care must be taken not to misclassify patients with smoldering multiple myeloma or monoclonal gammopathy of undetermined significance as having symptomatic myeloma (Table 2).

**Level of Evidence:** II

**Grade of Recommendation:** A

Approximately 15% of patients with multiple myeloma are recognized incidentally and without significant symptoms. These patients have smoldering (asymptomatic) multiple myeloma.<sup>64</sup> Patients with smoldering myeloma should be managed with observation alone, unless they are being enrolled in approved clinical trials. The rate of progression of smoldering myeloma to symptomatic disease is 10% per year for the first 5 years, 5% per year for the next 5 years, and 1.5% per year thereafter.<sup>65</sup> No survival advantage has been demonstrated by treating asymptomatic patients with myeloma.<sup>66-69</sup> In one study, 2 risk factors for progression were

TABLE 2. Criteria for Diagnosis of MGUS, SMM, and MM and Mayo Stratification of Myeloma and Risk-Adapted Therapy<sup>62,64,69\*</sup>

<b>MGUS</b>	
Serum monoclonal protein (<30 g/L)	
Bone marrow <10% plasma cells	
No evidence of other B-cell proliferative disorders	
No related organ or tissue impairment†‡	
<b>SMM (asymptomatic)</b>	
Serum monoclonal protein (≥30 g/L) and/or	
Bone marrow clonal plasma cells ≥10%	
No related organ or tissue impairment†	
<b>MM (active or symptomatic)</b>	
Monoclonal protein present in serum and/or urine	
Clonal bone marrow plasma cells or plasmacytoma	
Related organ or tissue impairment†	
<b>Mayo Stratification of Myeloma and Risk-Adapted Therapy</b> (for the purpose of selecting therapy)	
<b>High risk (~25% of patients)</b>	<b>Standard risk (~75% of patients)</b>
Presence of any of the following:	All other FISH or cytogenetic abnormalities, including:
FISH deletion 17p	Hyperdiploidy
FISH translocation 4;14	FISH translocation 11;14
FISH translocation 14;16	FISH translocation 6;14
Cytogenetic deletion 13q	
Cytogenetic hypodiploidy	
Plasma cell labeling index ≥3%	

\*FISH = fluorescence in situ hybridization; MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; SMM = smoldering multiple myeloma.

†The absence of CRAB (calcium level elevation [ >1 mg/dL above upper limit of normal], renal dysfunction [creatinine level >2 g/dL], anemia [hemoglobin level 2 g/dL below lower limit of normal], bone lesions [lytic lesions or osteoporosis with compression fracture] attributable to the plasma cell disorder).

‡The existence of immunoglobulin light chain amyloidosis or another paraneoplastic disorder attributable to the monoclonal gammopathy, such as a peripheral neuropathy, would be termed *monoclonal gammopathy associated with...*

identified: serum M protein level greater than 3 g/dL and IgA isotype, with median times to progression of greater than 48 months, 24 months, and 9 months, respectively, based on whether patients had none, one, or both risk factors.<sup>70</sup> Others have reported greater than 10% bone marrow plasmacytosis,<sup>71</sup> circulating plasma cells,<sup>72</sup> and myeloma cells that produce high levels of interleukin-1β<sup>73</sup> as risk factors for progression.

**TREATMENT OPTIONS**

Before 1999, the bifunctional alkylators, nitrosoureas, doxorubicin, and glucocorticoids were the primary agents shown to have single-agent activity against multiple myeloma in vivo.<sup>74</sup> These drugs along with vincristine, either singly or in combination, had been the mainstay of therapy. Until recently,<sup>75</sup> the higher response rates seen with regimens that combine multiple active agents as part of initial therapy had not resulted in improved OS rates.<sup>76</sup> With the advent of new active agents, such as thalidomide, bortezomib, and lenalidomide, therapeutic options have increased substan-

TABLE 3. Induction Regimens for Patients Ineligible for Hematopoietic Stem Cell Transplantation\*

Reference	Regimen	Phase	No. of patients	CR (%)	VGPR (%)	PR (%)	OR (%)	PFS (mo)	OS (mo)
Facon et al (IFM 95-01), <sup>77</sup> 2006	Dexamethasone	3	127	1	0	41	42	12	33
	Dexamethasone-interferon	3	121	1	0	42	43	15	32
	MP	3	122	1	0	40	41	21	34
	MD	3	118	3	0	67	70	23	40
Palumbo et al, <sup>78</sup> 2006	MP	3	126	2	10	36	48	~14	NR
	MPT	3	129	16	21	40	76	~25	NR
Facon et al (IFM 99-06), <sup>79</sup> 2005	MP	3	196	3	5	26	34	17	30
	MPT	3	125	14	37	33	84	29	NR
Ludwig et al, <sup>80</sup> 2005	Thalidomide-dexamethasone	3	125/2†	10	27	15	52	NA	NA
	MP	3	125/2†	3	12	20	35	NA	NA
Rajkumar et al, <sup>81</sup> 2006	Dexamethasone	3	235	NA	NA	NA	NA	NA	25
	Thalidomide-dexamethasone	3	235	NA	NA	NA	NA	NA	25
Dimopoulos et al, <sup>82</sup> 2006	MDT	2	50	10	0	62	72	21‡	28
Offidani et al, <sup>83</sup> 2006	ThaDD	2	50	34	24	30	88	57% at 3 y§	74% at 3 y
Mateos et al, <sup>84</sup> 2006	MPV	1/2	60	32	11	45	88	83% at 16 mo§	86% at 2 y
Hussein et al, <sup>85</sup> 2006	T-DVd	2	53	36	13	34	83	28	NR at 50 mo
Cluett et al, <sup>86</sup> 2005	Low-dose thalidomide, dexamethasone, and zoledronic acid	2	45	0	30	68	98	NA	68% at 2 y
Palumbo et al, <sup>87</sup> 2006	MPR	1/2	50	10	NA	60	70	NA	NA

\*CR = complete response; IFM = Intergroupe Français du Myélome; MD = melphalan and dexamethasone; MDT = melphalan, dexamethasone, and thalidomide; MP = melphalan and prednisone; MPR = melphalan, dexamethasone, and lenalidomide; MPT = melphalan, prednisone, and thalidomide; MPV = melphalan, dexamethasone, and bortezomib; NA = not available; NR = not reached; OR = overall response; OS = overall survival; PFS = progression-free survival; PR = partial response; T-DVd = thalidomide, pegylated doxorubicin, vincristine, and dexamethasone; ThaDD = thalidomide, pegylated doxorubicin, and dexamethasone; VGPR = very good partial response.

†A total of 125 patients divided between the 2 arms of the trial; the exact number of patients in each arm was not reported.

‡Time to progression.

§Event-free survival.

tially, and there is significant complexity in decision making, which involves assessment of risk status, eligibility for transplantation, and response to therapy (Tables 3 and 4). Although clinical trials are always preferred, Figures 1 and 2 outline the Mayo Clinic mSMART treatment algorithms for patients with newly diagnosed myeloma for whom clinical trials are unavailable. The goal of chemotherapy for myeloma is to prolong survival and when possible by choosing therapy that has the most favorable effect on quality of life.

### INITIAL THERAPY FOR STANDARD-RISK PATIENTS INELIGIBLE FOR STEM CELL TRANSPLANTATION

**Guideline:** Melphalan, prednisone, and thalidomide (MPT) for 12 cycles.

**Level of Evidence:** I-II

**Grade of Recommendation:** A

Until the report of improved OS for patients receiving MPT over melphalan and prednisone (MP) by Facon et al,<sup>75</sup> the standard induction therapy for elderly patients was MP. Response rates with MP are approximately 50%, with complete responses (CRs) seen in approximately 5% of patients.

Median OS with MP is approximately 3 years. A meta-analysis of 27 randomized trials showed no survival advantage with any chemotherapeutic regimen compared with MP.<sup>76</sup>

Recently, 2 randomized trials showed superior response rates and progression-free survival (PFS) using MPT compared with MP,<sup>75,78</sup> 1 of which has also demonstrated superior OS.<sup>75</sup>

Palumbo et al<sup>78</sup> randomized patients to either standard dose MP for 6 months or MP for 6 months followed by thalidomide indefinitely. Overall response rates were significantly higher with MPT than MP (76% vs 48%) as were the near-complete or CR rates (28% vs 7%) and the 2-year event-free survival rates (54% vs 27%;  $P=.0006$ ). A trend was seen toward an improved 3-year OS in favor of MPT (80% vs 64%). Two criticisms of this trial are that 6 months of MP is short of standard therapy and that this trial addresses a maintenance question rather than an induction question. These data alone were insufficient to guide the practice change but strongly suggested that the addition of thalidomide to MP can improve long-term outcome.

The Intergroupe Français du Myélome (IFM) 99-06 trial substantially bolsters the results of the trial by Palumbo et

TABLE 4. Induction Regimens Before Hematopoietic Stem Cell Transplantation\*

Reference	Regimen	Phase	No. of patients	CR (%)	VGPR (%)	PR (%)	OR (%)
Rajkumar et al, <sup>88</sup> 2006	Dexamethasone	3	104	0	NR	41	41
	Thalidomide-dexamethasone	3	99	4	NR	59	63
Rifkin et al, <sup>89</sup> 2006	VAD	3	95	0	NR	41	41
	DVD	3	97	3	NR	41	44
Dimopoulos et al, <sup>90</sup> 2003	VAD	3	127	13	NR	49	62
	DVD	3	132	13	NR	48	61
Goldschmidt et al, <sup>91</sup> 2005	VAD	3	406/2†	3	NR	60	63
	TAD	3	406/2†	7	NR	73	80
Barlogie et al, <sup>92</sup> 2006	TT2 no thalidomide	3	323	10	NR	30	40
	TT2 with thalidomide	3	345	19	NR	41	60
Rajkumar et al, <sup>93</sup> 2001	Thalidomide	2	16	0	NR	37	37
Rajkumar et al, <sup>94</sup> 2003	Thalidomide	2	29	0	NR	34	34
Weber et al, <sup>95</sup> 2003	Thalidomide	2	28	0	NR	36	36
Rajkumar et al, <sup>96</sup> 2002	Thalidomide-dexamethasone	2	50	0	NR	64	64
Weber et al, <sup>95</sup> 2003	Thalidomide-dexamethasone	2	40	16	NR	56	72
Sidra et al, <sup>97</sup> 2006	CDT	2	15	0	27	60	87
Rajkumar et al, <sup>98</sup> 2005	Rev-dexamethasone	2	34	6	32	53	91
Niesvizky et al, <sup>99</sup> 2006	BiRD	2	40	25	18	53	95
Jagannath et al, <sup>100,101</sup> 2005	Bortezomib	2	32	3	9	28	40
Anderson et al, <sup>102</sup> 2006	Bortezomib with or without dexamethasone	2	32	6	19	63	88
	Bortezomib	2	60	10	NR	28	38
Harousseau et al, <sup>103</sup> 2005	Bortezomib-dexamethasone	2	53	20	NR	47	67
Wang et al, <sup>104</sup> 2005	VTD	2	36	19	NR	73	92
Hussein et al, <sup>105</sup> 2002	DVD	2	33	12	NR	55	67
Hassoun et al, <sup>106</sup> 2006	AD and TD	2	45	16	20	49	85
Zervas et al, <sup>107</sup> 2004	T-DVD	2	39	10	NR	64	74
Oakervee et al, <sup>108</sup> 2005	PAD	2	21	24	NR	71	95
Popat et al, <sup>109</sup> 2005	Low-dose PAD	2	19	11	28	50	89
Badros et al, <sup>110</sup> 2005	VDT-PACE	1/2	11	9	9	92	100
Barlogie et al, <sup>111</sup> 2006	TT1	2	231	12	NR	51	63

\*AD = doxorubicin (Adriamycin) and dexamethasone; BiRD = Biaxin, Revlimid, and dexamethasone (clarithromycin, lenalidomide, and dexamethasone); CDT = cyclophosphamide, dexamethasone, and thalidomide; CR = complete response; DVD = pegylated doxorubicin, vincristine, and dexamethasone; NR = not reported; OR = overall response; PAD = bortezomib, doxorubicin, and dexamethasone; PR = partial response; Rev = Revlimid (lenalidomide); TAD = thalidomide, doxorubicin, and dexamethasone; TD = thalidomide and dexamethasone; T-DVD = thalidomide, pegylated doxorubicin, vincristine, and dexamethasone; TT1 = Total Therapy 1; TT2 = Total Therapy 2 (a complex anthracycline-containing multiagent chemotherapy regimen); VAD = vincristine, doxorubicin, and dexamethasone; VDT-PACE = bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide; VGPR = very good partial response; VTD = bortezomib, thalidomide, and dexamethasone.

†A total of 406 patients divided between the 2 arms of the trial; the exact number of patients in each arm was not reported.

al. Although the results of this trial have been published only in abstract form,<sup>75</sup> its results are compelling enough and consistent with the published report from Palumbo et al that we concluded that they mandate a change in clinical practice. In the IFM 99-06 study, 436 patients were randomized to 12 cycles of either MP or MPT or to 2 sequential miniautologous peripheral blood stem cell transplantations. The MPT regimen consisted of melphalan, 0.25 mg/kg orally on days 1 to 4, prednisone, 2 mg/kg orally on days 1 to 4, and thalidomide, 100 to 400 mg orally on days 1 to 28, repeated every 6 weeks for 12 cycles. Higher response rates and longer PFS were seen for the MPT compared with either the MP or sequential miniautologous peripheral blood stem

cell transplantation groups, with respective PFS times of 29, 17, and 19 months. With a median follow-up of 32 months, a significant survival advantage was found for the patients in the MPT arm, with respective OS times not reached at 56, 30, and 39 months.<sup>75</sup> One weakness of this study is that no data are provided regarding the percentage of patients in the nonthalidomide arm who received thalidomide regimens as salvage.

A cautionary note is that, although MPT performed better than MP in both trials with regard to efficacy end points, it is associated with a consistently higher toxicity profile, although lower 4-month mortality rates.<sup>75,78</sup> In the study by Palumbo et al,<sup>78</sup> the respective percentages of patients having

grade 3 to 4 adverse events were as follows: at least 1 event, 48% vs 25% ( $P=.0002$ ); thrombosis or embolism, 12% vs 2%; peripheral neuropathy, 10% vs 1%; infections, 10% vs 2%; and gastrointestinal events, 6% vs 1%. After 13 of 65 patients in the MPT arm had thromboembolic events without prophylaxis, the final 64 received enoxaparin; in this subsequent group, only 2 thromboembolic events occurred, notably after discontinued use of enoxaparin.

As indicated in Table 3,<sup>77-87</sup> several active novel combinations are being tested in patients ineligible for transplantation, but none has yet been shown to produce superior survival over MP or MPT. The combination of bortezomib with melphalan and prednisone appears particularly active, and large phase 3 trial results are awaited. Given the apparent ability of bortezomib to negate or at least favorably modify high-risk genetics as risk factors,<sup>84</sup> this regimen could be considered now for patients in the high-risk genetic class.

#### INITIAL THERAPY FOR HIGH-RISK PATIENTS INELIGIBLE FOR STEM CELL TRANSPLANTATION

**Guideline:** MPT for 12 cycles; as an alternative, consider a bortezomib-containing regimen to maximal response.

**Level of evidence:** III (for MPT); III-IV (for considering bortezomib-based regimen)

**Grade of Recommendation:** D

The consensus recommendation and rationale for MPT are the same as for standard-risk patients. Neither MP nor MPT trial provides information about the high-risk subgroup. On the basis of the prevalence of cytogenetic abnormalities in myeloma, approximately 25% of patients in these studies are likely to be high risk. No data from either trial indicate that this subgroup did not achieve the same benefit as patients with standard-risk disease; conversely, it is clear that the outcome for high-risk myeloma is poor with standard chemotherapy.

The panel recognizes, however, that several studies in post hoc analyses suggest that bortezomib may overcome the adverse prognostic impact of  $\Delta 13$ <sup>84,112-114</sup> and  $t(4;14)$ .<sup>84,112</sup> For this reason, consideration of a bortezomib-containing regimen, such as bortezomib, melphalan, and prednisone, is also a viable treatment option.<sup>84</sup> In a post hoc subgroup analysis of outcomes of elderly patients treated with bortezomib, melphalan, and prednisone, Mateos et al<sup>84</sup> examined differential outcomes of the 33 patients who had deletion 13 FISH analysis performed. Thirteen patients had the abnormality. All responded, but no data were provided about the relative PFS or OS of these same patients. Patients with deletion 13 are typically no less likely to respond to therapy, but duration of response and OS rates are consistently lower with standard alkylator-based therapy<sup>38</sup> and with high-dose chemotherapy with HSCT.<sup>115,116</sup>

#### MAINTENANCE THERAPY FOR PATIENTS INELIGIBLE FOR STEM CELL TRANSPLANTATION

**Guideline for Standard-Risk Patients:** No maintenance except in the context of a clinical trial for standard-risk patients.

**Level of Evidence:** II

**Grade of Recommendation:** B

**Guideline for High-Risk Patients:** If not in CR, consider maintenance therapy with thalidomide and prednisone until best response if no prior use of thalidomide.

**Level of Evidence:** V

**Grade of Recommendation:** D

Strategies for maintenance therapy can be divided into 2 broad categories: (1) continued initial therapy (such as MP) until progression or (2) initiation of a maintenance agent after completion of initial therapy. The former strategy was prevalent until recognition of the risk of developing alkylator-induced myelodysplastic syndromes and leukemia.<sup>117-121</sup> The latter strategy has predominantly applied immune modulators, including prednisone, interferon, cellular therapies, and more recently thalidomide and lenalidomide.

#### ALKYLATORS

Several randomized studies established that alkylator-based maintenance therapy does not produce a survival benefit.<sup>66,122-129</sup> In general, patients not receiving maintenance therapy had similar to slightly shorter remission duration than those receiving maintenance therapy<sup>66,125-128,130</sup> but had higher rates of second remission.<sup>127,130</sup> Some studies have shown a trend toward longer survival in the former group.<sup>122-124</sup> Alkylator unmaintained remissions tend to last approximately 12 months.<sup>125</sup>

#### CORTICOSTEROIDS

The two most important randomized studies deal with corticosteroids as maintenance therapy.<sup>131,132</sup> None justifies a recommendation of corticosteroids as a standard maintenance regimen for all patients. The Southwest Oncology Group trial 9210 compared prednisone at 10 mg every other day to prednisone at 50 mg every other day in patients who had responded to 6 to 12 months of a vincristine, doxorubicin (Adriamycin), and dexamethasone (VAD)-based program, that is, a corticosteroid-intensive program. From the time of randomization to the 2 different alternate-day prednisone schedules, the median PFS for the higher-dose prednisone arm was 14 months compared with 5 months for the lower dose ( $P=.003$ ). Also, survival was marginally better at 37 and 26 months ( $P=.05$ ).<sup>131</sup> Although the more dose-intensive corticosteroid maintenance strategy provided a longer PFS in corticosteroid-responsive patients, these data cannot be generalized.

An earlier randomized study, which compared dexamethasone maintenance to interferon maintenance after induction with melphalan and dexamethasone, demonstrated equivalence to inferiority of dexamethasone compared with interferon. Patients received maintenance treatment with interferon alfa (3 MU [million units] 3 times a week) or dexamethasone (20 mg/m<sup>2</sup> orally daily for 4 days repeated monthly) until relapse. Remission duration was identical (10 months); however, significantly more patients responded on reinstitution of the melphalan and dexamethasone therapy at disease relapse in the interferon group than in the dexamethasone group (82% vs 44%;  $P=.001$ ).<sup>132</sup>

#### INTERFERON ALFA

The initial positive findings for interferon alfa as maintenance therapy were reported by Mandelli et al<sup>133</sup> in 1990. Subsequent studies yielded divergent results. Ludwig and Fritz<sup>134</sup> analyzed 1615 patients in 13 maintenance trials; the Myeloma Trialists' Collaborative Group<sup>135</sup> used the individual data of 1543 patients enrolled in 12 randomized trials. Results were similar in that the first group found a 4.4-month prolongation of relapse-free survival ( $P<.01$ ) and a 7.0-month increase in OS ( $P<.01$ ).<sup>134</sup> The latter group reported a 3-year PFS of 27 vs 19 months ( $P<.00001$ ) in favor of the interferon maintenance group. However, only a marginal improvement in OS (4 months) was noted ( $P=.04$ ).<sup>135</sup> Of note, *in vitro*, interferon alfa has been shown to stimulate the myeloma cells of some patients,<sup>136</sup> and in a retrospective subgroup analysis of a large randomized Eastern Cooperative Oncology Group trial, patients with deletion 13 who received interferon alfa actually had worse survival than their counterparts who did not receive interferon.<sup>38</sup>

#### MAINTENANCE THERAPY CONCLUSIONS FOR PATIENTS INELIGIBLE FOR STEM CELL TRANSPLANTATION

For standard-risk patients, no therapy has yet been shown to prolong survival in a clinically important manner to justify associated adverse effects. Moreover, no data are available to support maintenance after MPT as initial therapy. Three randomized trials ongoing in the United States are testing thalidomide-prednisone, thalidomide-dexamethasone, and lenalidomide as maintenance therapy; however, all 3 trials are in the posttransplantation setting. The consensus recommendation for standard-risk patients is observation, but participation in clinical trials should be encouraged.

For high-risk patients, the risk of relapse is high even after high-dose therapy, with median PFS of approximately 6 to 9 months and median OS of 2 years.<sup>7,10-13,31,40-42,137-139</sup> In a recent randomized trial, a significant improvement in PFS and OS was noted with thalidomide.<sup>140</sup> Similarly, a South-

west Oncology Group randomized trial suggested a similar benefit with prednisone.<sup>131</sup> Other studies also suggest improvement in PFS with corticosteroid maintenance therapy.<sup>141</sup> Although these studies had limitations and were conducted in different settings, our consensus is that high-risk patients ineligible for transplantation who do not obtain a CR should be offered maintenance therapy given the high risk of recurrence and early data that suggest a clinical benefit with maintenance approaches in the absence of a CR with prior therapy. Maintenance thalidomide and prednisone therapy is feasible, has been reported, and is preferred until data emerge based on other maintenance approaches.<sup>78</sup>

#### INDUCTION THERAPY FOR PATIENTS ELIGIBLE FOR TRANSPLANTATION

**Guideline for Standard-Risk Patients:** Lenalidomide and low-dose dexamethasone.

**Level of Evidence:** II-III

**Grade of Recommendation:** B

**Guideline for High-Risk Patients:** Lenalidomide and low-dose dexamethasone.

**Level of Evidence:** II-III

**Grade of Recommendation:** B

In general, for patients eligible for stem cell transplantation, non-alkylator-based induction therapies are preferred for approximately 4 months before stem cell transplantation. The goal of induction is to promptly alleviate symptoms, reduce or reverse end-organ damage, and safely achieve maximal tumor reduction before stem cell harvest. During induction therapy, important logistical issues, such as insurance approval for harvest and possible transplantation, should be addressed so that the transition from induction to consolidation is seamless.

Several induction regimens (Table 4)<sup>88-111</sup> have been studied in this setting. Comparative trials are limited, and hence recommendations are based on nonrandomized data. However, an important point about these regimens is that so far no one has demonstrated that any pretransplantation induction regimen—regardless of how high its response rate—improves PFS or OS. Currently, the only evidence-based relevant outcomes are toxicity and early death. Table 5 gives the early death rates associated with several regimens. On the basis of the low early death rates seen with bortezomib with or without dexamethasone and lenalidomide plus low-dose dexamethasone, these 2 options are among the most feasible, but any recommendation is limited by the absence of long-term outcome data. In our practice in the nontrial setting, we preferentially use the latter regimen because of its convenience of administration in patients without renal failure. For patients with renal failure, bortezomib-based regimens are favored.

**VAD REGIMENS**

VAD and VAD-like regimens have commonly been used as induction therapy before stem cell collection and transplantation. These regimens include vincristine-pegylated liposomal doxorubicin-dexamethasone,<sup>105</sup> VAD,<sup>144</sup> vincristine-doxorubicin-methylprednisolone,<sup>145</sup> and cyclophosphamide-vincristine-doxorubicin-methylprednisolone.<sup>145</sup> Response rates in previously untreated patients are 50% to 84%.<sup>146-155</sup> The CR rate of cyclophosphamide-vincristine-doxorubicin-methylprednisolone is higher than that of vincristine-doxorubicin-methylprednisolone alone, but survival is not different.<sup>149</sup> Two randomized trials comparing vincristine-pegylated liposomal doxorubicin-dexamethasone to VAD, using either standard high-dose dexamethasone<sup>90</sup> or attenuated doses of dexamethasone,<sup>89</sup> have been completed. Results were comparable between arms with regard to response rates: 42% in the attenuated dexamethasone trial<sup>89</sup> and 61% in the standard dose dexamethasone trial.<sup>90</sup> More alopecia occurred in the nonliposomal doxorubicin arms and more palmar-plantar erythrodyesthesia in the liposomal doxorubicin arms.

**DEXAMETHASONE**

The response rate of single-agent high-dose dexamethasone is approximately 43%,<sup>156</sup> which is only 15% lower than for VAD. Better tolerability and convenience prompted myeloma experts to use single-agent dexamethasone in lieu of VAD for induction therapy in patients destined for stem cell collection. This strategy has been used successfully, resulting in adequate collections of peripheral blood stem cells with no apparent adverse effects on complete remission rates or PFS in several single-arm studies.<sup>157,158</sup> Nevertheless, given the modest response rates and the associated treatment-related morbidity together with the advent of other oral therapies, single-agent dexamethasone has been losing favor as induction therapy.

**THALIDOMIDE-DEXAMETHASONE**

The combination of thalidomide and dexamethasone results in response rates of 63% to 72%.<sup>81,95,96</sup> The thalidomide-dexamethasone combination has been compared with dexamethasone alone in 2 separate randomized trials.<sup>81</sup> In the smaller of the 2 trials (n=207), the overall response rate of thalidomide-dexamethasone was significantly higher than with dexamethasone alone (63% vs 41%); however, toxicity was greater using the combination, with grade 4 to 5 toxicity of 45% vs 21% ( $P<.001$ ).<sup>88</sup> In the second, larger trial (n=470), time to progression was significantly better in the combination arm (17.4 months; 95% confidence interval, 8.1 months to not reached vs 6.4 months; 95% confidence interval, 5.6 to 7.4 months). Grade 3 to 4 adverse events were higher using the combination: deep venous thrombosis and

TABLE 5. Initial Therapy and Early Mortality\*

Regimen	RR (%)	Deaths (%)
Dexamethasone (E1A00) <sup>88</sup>	41	11
Dexamethasone with or without interferon (IFM 95-01) <sup>77</sup>	41	10.5
MP (IFM 99-06) <sup>75</sup>	40	8
Thalidomide-dexamethasone (E1A00) <sup>88</sup>	63	7
Rev-dexamethasone (E4A03) <sup>142</sup>	Unknown	4.9
MPT (IFM 99-06) <sup>75</sup>	81	3
Rev and low-dose dexamethasone (E4A03) <sup>142</sup>	Unknown	0.5
Bortezomib <sup>100</sup>	40	0
Bortezomib and dexamethasone <sup>143</sup>	66	0

\*IFM = Intergroupe Français du Myélome; MP = melphalan and prednisone; MPT = melphalan, prednisone, and thalidomide; Rev = lenalidomide; RR = response rate.

pulmonary embolism, 15.4% vs 4.3%; cerebral ischemia, 3.4% vs 1.3%; myocardial infarction, 4.7% vs 1.3%; and peripheral neuropathy, 3.8% vs 0.4%.<sup>81</sup> This combination is commonly used as induction therapy in the months before stem cell collection because of its high response rates and its ease of administration, using only oral medications. The risk of thrombosis and other adverse effects make the combination less convenient than originally thought.

**BORTEZOMIB BASED**

Thirty-eight percent to 40% of patients with newly diagnosed myeloma will respond to single-agent bortezomib.<sup>100,102,159</sup> The addition of dexamethasone results in an overall response rate of 67% to 88%.<sup>100,143</sup> Several combinations have been explored for induction therapy. Oakervee et al<sup>108</sup> treated 21 previously untreated patients with bortezomib, doxorubicin, and dexamethasone. Ninety-five percent of patients achieved at least a partial response, including a CR in 24%. Fifteen grade 3 to 4 adverse events occurred in 12 patients, with the most common serious adverse events including infections (n=7) and herpes zoster (n=3). Grade 3 to 4 peripheral neuropathy, postural hypotension, nausea and vomiting, atrial fibrillation, and hyperglycemia each occurred in 1 patient. All but one patient proceeded to stem cell collection and transplantation. Although no cardiac toxicity was observed, cardiac biomarkers screening for subtle toxic effects was not performed.

Wang et al<sup>104</sup> treated 36 previously untreated patients with thalidomide, escalating doses of bortezomib, and dexamethasone. All patients received full anticoagulation. The overall response rate was 92%, including a 19% CR rate. Bortezomib doses greater than 1.3 mg/m<sup>2</sup> did not seem to add any value.

**LENALIDOMIDE-DEXAMETHASONE**

Lenalidomide plus dexamethasone yields high overall response rates of 91%,<sup>98</sup> with CRs in 18% and very good

TABLE 6. Adverse Events With Lenalidomide-Dexamethasone Combinations From E4A03<sup>142\*</sup>

Toxic effect	Dexamethasone (%)	
	High-dose (n=223)	Low-dose (n=222)
Cardiac ischemia (grade $\geq 3$ )	2.7	0.5
Hyperglycemia (grade $\geq 3$ )	5.8	1.8
Infection or pneumonitis (grade $\geq 3$ )	18.8	9.0
Neuropathy (grade $\geq 3$ )	0.9	0.9
Thromboembolism (grade $\geq 3$ )	18.4	5.4
Any nonhemotoxic effect (grade $\geq 3$ )	53.4	36.0
Any toxic effect (grade $\geq 4$ )	22.0	12.6
Death (grade 5)	4.5	1.4

\*High-dose dexamethasone was 40 mg orally on days 1 to 4, 9 to 12, and 17 to 20 every 28 days. Low-dose dexamethasone was 40 mg orally on days 1, 8, 15, and 22 every 28 days.

partial responses in 38% when used as induction therapy for patients with newly diagnosed myeloma.<sup>98,160</sup> Of note, in that Mayo Clinic–led trial, dexamethasone was administered in typical pulsed (high-dose) fashion (40 mg on days 1-4, 9-12, 17-20) for only 4 cycles and decreased to low dose (40 mg on days 1-4 each month) thereafter. The response rates seen in the Mayo trial are not surprising given the high response rates (60%) observed using this combination in the relapsed, refractory setting in 2 large randomized trials.<sup>161,162</sup>

The Eastern Cooperative Oncology Group E4A03 randomized trial compared lenalidomide and standard dose dexamethasone (40 mg on days 1-4, 9-12, and 17-20) to lenalidomide and low-dose dexamethasone (40 mg on days 1, 8, 15, and 22). Preliminary data from this trial show that the low-dose dexamethasone arm has substantially lower rates of serious adverse events, including deep venous thrombosis, compared with lenalidomide plus high-dose dexamethasone (Table 6).<sup>142,163</sup> Furthermore, compared with data on other IMiD-based regimens tested in recent randomized trials, lenalidomide plus low-dose dexamethasone has the lowest mortality rate in the first 4 months, a critical period in patients considering early stem cell transplantation as consolidation (Table 5).

Lenalidomide-dexamethasone is a highly effective regimen in patients with newly diagnosed myeloma, with response rates exceeding 90%. In addition, the regimen is orally administered. Although no response data are available from the E4A03 trial, no data have demonstrated that superior response rates from induction translate into better long-term outcome after transplantation. On the basis of single-agent activity rates of lenalidomide and dexamethasone, the response rate with lenalidomide plus low-dose dexamethasone is not likely to be lower than that observed with the current Food and Drug Administration–approved induction therapy—thalidomide-dexamethasone. On the other hand, the low 4-month mortality rate with this regimen compared with either thalidomide-dexamethasone or lenalidomide

plus high-dose dexamethasone is striking. In addition, another major advantage of lenalidomide plus low-dose dexamethasone is the markedly lower rate of deep venous thrombosis,<sup>163</sup> which allows aspirin alone as thromboprophylaxis. On the basis of these factors, we recommend lenalidomide plus low-dose dexamethasone as standard induction therapy for patients (both standard risk and high risk) with newly diagnosed myeloma who are eligible for transplantation.

#### TIMING OF STEM CELL COLLECTION IN PATIENTS ELIGIBLE FOR STEM CELL TRANSPLANTATION

**Guideline for Patients:** All standard-risk patients who are candidates for HSCT should have their hematopoietic stem cells collected for future use within 4 to 6 months of starting therapy for active myeloma.

**Level of Evidence:** III

**Grade of Recommendation:** B

Although controversy exists regarding whether high-risk patients should undergo HSCT, all patients younger than 65 years without other significant comorbidities should have their stem cells collected within 4 to 6 months of starting therapy for active myeloma. Hematopoietic stem cells should be collected before the patient is exposed to cumulative doses of alkylating agents<sup>164,165</sup> because prolonged melphalan exposure leads to an impaired harvest of peripheral blood stem cells.<sup>166,167</sup> After 4 to 6 cycles of vincristine-melphalan-cyclophosphamide-prednisone with vincristine-carmustine-doxorubicin-prednisone, a regimen containing low doses of melphalan, sufficient stem cells could not be collected for transplantation in approximately 10% of patients.<sup>168</sup> In contrast, successful stem cell collection is achieved in 95% to 100% of patients with multiple myeloma treated with VAD before mobilization with high-dose cyclophosphamide.<sup>169</sup>

#### CONSOLIDATION THERAPY FOR PATIENTS ELIGIBLE FOR STEM CELL TRANSPLANTATION

**Guideline for Standard-Risk Patients:** Early autologous HSCT, followed by a second HSCT if the patient does not achieve a very good partial response or better with the first HSCT.

**Level of Evidence:** I

**Grade of Recommendation:** B

**Guideline for High-Risk Patients:** After stem cell collection and banking sufficient for 2 transplantations, cross over to a bortezomib-containing regimen, such as bortezomib, melphalan, and prednisone. In younger patients, an allogeneic option could also be considered.

**Level of Evidence:** V

**Grade of Recommendation:** D

TABLE 7. Conventional Chemotherapy vs Single Autologous Hematopoietic Stem Cell Transplantation: Randomized Trials\*

Reference	No. of patients	CR/VGPR (%)		PFS (mo)		OS (mo)		SCT (%)	
		CCT	ASCT	CCT	ASCT	CCT	ASCT	CCT	ASCT
IFM 90 <sup>168,176</sup>	200	13	38†	18	28†	44	57†	9	74
MRC7 <sup>170</sup>	401	8	44†	20	32†	42	54†	15	75
MAG91 <sup>172</sup>	190	4	6	19	25†	48	48	22	75
MAG90 <sup>173</sup>	185	57	20	13	39	64	65	78	98
PETHMA <sup>175</sup>	164	11	30†	33	42	61	66	18	90
S9321 <sup>174</sup>	516	17	15	14% at 7 y	17% at 7 y	38% at 7 y	38% at 7 y	34	82
MMSG <sup>171‡</sup>	194	6	25†	16	28†	42	≥58†	39	92
HOVON-24 <sup>177§</sup>	303	13	28†	23	24†	50	55	...	...

\*ASCT = autologous stem cell transplantation; CCT = conventional chemotherapy; CR/VGPR = complete response or very good partial response; HOVON = Dutch-Belgian Hemato-Oncology Cooperative Group; IFM = Intergroupe Français du Myélome; MAG = Myélome Autogreffe; MMSG = Italian Multiple Myeloma Study Group; MRC = Medical Research Council; ORR = any response greater than or equal to a partial response; PETHMA = Programa para el Estudio de la Terapéutica en Hemopatía Maligna; PFS = progression-free survival; OS = overall survival; SCT = patients known to have undergone an autologous hematopoietic stem cell transplantation.

†Statistically significant.

‡Transplantation arm is 2 low-dose (melphalan, 100 mg/m<sup>2</sup>) autologous stem cell transplantations.

§Often included in "double transplantation" tables because both arms received melphalan, 70 mg/m<sup>2</sup> for 2 doses, without stem cell support as induction therapy.

#### AUTOLOGOUS STEM CELL TRANSPLANTATION

The preponderance of randomized data supports the role of autologous HSCT for patients younger than 65 years.<sup>168-171</sup> Although HSCT is not curative, event-free survival and OS were improved in 3<sup>168,170,171</sup> of the 7 published randomized controlled trials that addressed this issue<sup>172-175</sup> (Table 7). Three of the 4 negative studies are largely early vs delayed transplantation trials, and the fourth negative study excluded from randomization those patients who did not respond to induction therapy.<sup>175</sup> Response rates with HSCT are 75% to 90%, and CR rates are 20% to 40%.<sup>168,170,175</sup>

Despite the fact that conventional chemotherapy vs HSCT trials have demonstrated that the timing of transplantation is not important with regard to OS, the current guidelines recommend early HSCT in standard-risk patients for 2 reasons: quality-of-life issues and the double-transplantation literature. Of the 3 trials that address the early vs delayed transplantation strategy,<sup>175-177</sup> the Myélome Autogreffe 90 trial evaluated the time without systemic therapy and found that it was longer in the early than the delayed autologous HSCT group, potentially providing better quality of life for the early transplantation group. Another important consideration in young patients who opt to collect and store stem cells

is the cumulative risk of myelodysplastic syndrome and acute leukemia posed by alkylator therapy.

#### SINGLE VS DOUBLE TRANSPLANTATION

The strategy of double transplantation has only been studied formally up front. Two of 3 randomized trials that compared single to double autologous stem cell transplantation demonstrated improvement in event-free survival and OS<sup>178-181</sup> (Table 8). In the largest and most mature study, by 4 years of follow-up, a survival benefit was detected that favored the double-transplantation group.<sup>178</sup> Although the response rate was not significantly different between the 2 groups (CR and very good partial response, 42% in the single-transplantation arm vs 50% in the double-transplantation group;  $P=.15$ ), both event-free survival (25 vs 30 months) and OS (48 vs 58 months) were improved in the double-transplantation arm. The respective 7-year overall (21% vs 42%) and event-free (10% vs 20%) survivals also significantly favored the double-transplantation group. In an unplanned subgroup analysis, the authors found that patients who benefited most from the tandem transplantation were those who did not achieve a very good partial response or better after their first transplantation.

TABLE 8. Single vs Double Hematopoietic Stem Cell Transplantation: Randomized Trials\*

Reference	No. of patients	Follow-up (mo)	Event-free survival (mo)			Overall survival (%)		
			Single	Double	<i>P</i> value	Single	Double	<i>P</i> value
IFM 94 <sup>178</sup>	403	75	25	30	.03	48	58	.01
Bologna 96 <sup>179</sup>	228	~48	21	31	.001	44 at 6 y	63 at 6 y	NS
MAG 95 <sup>181</sup>	193	27	41	43	NS	27	22	NS
			events	events		deaths	deaths	

\*IFM = Intergroupe Français du Myélome; MAG = Myélome Autogreffe; NS = not significant.

Cavo et al<sup>179</sup> made similar observations in preliminary data, including the benefit of second transplantation being limited to patients who do not achieve a very good partial response or better after their first transplantation.

#### CONSOLIDATION WITH NOVEL THERAPY

To date, no data are available on the approach of consolidative chemotherapy outside the transplantation setting. However, several regimens appear promising and deserve consideration in this setting. Two such regimens are bortezomib, thalidomide, and dexamethasone and melphalan, prednisone, and bortezomib. The bortezomib, thalidomide, and dexamethasone combination has resulted in high overall (55%-92%) and CR (19%-43%) rates in both the relapsed<sup>182,183</sup> and newly diagnosed<sup>104</sup> settings. The melphalan, prednisone, and bortezomib combination is also an active regimen.<sup>84</sup> In a phase 1/2 trial of 60 elderly patients, after exclusion of the 3 early deaths and 4 other early withdrawals from their response analysis, the authors found that the response rate was 88% overall, including 32% CRs, 11% very good partial responses, and 45% partial responses. The 16-month event-free survival and OS were 83% and 90%, respectively.

#### ALLOGENEIC TRANSPLANTATION

Allogeneic transplantation can lead to CR rates of 22% to 67%, including molecular remissions in approximately one third<sup>184-186</sup> and prolonged disease-free survival in approximately one quarter to one third of patients.<sup>174,186,187</sup> The high treatment-related mortality (10%-63%) and significant toxic effects from graft-vs-host disease have limited the role of this procedure in the treatment of myeloma.<sup>186,188,189</sup> In a small single-center study of 37 patients with myeloma who underwent myeloablative allogeneic stem cell transplantation and had a median follow-up of 108 months, the 5-year OS, PFS, and event-free survival were 40%, 54%, and 24%, respectively, despite a 50% treatment-related mortality and a median OS of 28 months.<sup>190</sup> Outcomes were similar for the allogeneic stem cell transplantation treatment arm in the S9321 Intergroup study.<sup>174</sup>

In another effort to reduce allogeneic transplantation-related mortality, nonmyeloablative, reduced intensity, or mini stem cell transplantation regimens have been studied in patients with multiple myeloma. The principle behind this approach is to harness the improved CR rate and relapse-free mortality seen with a standard full allogeneic transplantation while eliminating the high treatment-related mortality rates. Initial trials that evaluated this approach included relapsed or refractory patients. Such patients were thought to account at least in part for the poor outcomes. It also became apparent that this approach was less useful in patients who had significant residual tumor

burden at the time of the nonmyeloablative transplantation, which led to the concept of a planned autologous stem cell transplantation followed a couple of months later with a reduced-intensity allogeneic stem cell transplantation. The initial studies had treatment-related mortalities that approached 25%; the 3-year OS and PFS rates were 41% and 21%, respectively.<sup>191</sup> Poor OS was associated with chemoresistant disease, more than 1 prior transplantation, and absence of chronic graft-vs-host disease. Using the planned tandem autologous and nonmyeloablative allogeneic stem cell transplantation approach, outcomes have been better, with treatment-related mortalities of 15% and 2-year OSs approaching 75%.<sup>192-195</sup>

Published data are available from only one randomized trial that addresses allogeneic stem cell transplantation in high-risk patients.<sup>115</sup> The high-risk group in this trial was of slightly lower risk than what our group defines as high risk because these authors defined high risk as the presence of deletion 13 by FISH and of a  $\beta_2$ -microglobulin level greater than 3 mg/L. On the basis of biological randomization, patients were allocated to either double autologous stem cell transplantation or autologous stem cell transplantation followed by a reduced-intensity allogeneic stem cell transplantation. Although patients fared better than expected in both arms, with median OSs of 41 and 35 months, respectively, no significant difference was found between the 2 arms, with a median follow-up of 24 months. The major criticisms of this study have been that (1) the criteria used to select high-risk disease did not select for the highest-risk patients and (2) the reduced-intensity conditioning used may have been too immunosuppressive, thereby abrogating the graft vs myeloma effect.

#### CONSOLIDATION THERAPY CONCLUSIONS

On the basis of currently available data, we recommend early autologous transplantation for standard-risk patients eligible to undergo stem cell transplantation, with a second transplantation offered to those who did not experience a very good partial response or better with the first transplantation. If such patients are unwilling to undergo stem cell transplantation, we recommend continuing induction therapy to maximal response. In the Mayo trial of lenalidomide-dexamethasone, 14 (67%) of 21 patients not proceeding to stem cell transplantation achieved a complete or very good partial response by continuing the induction regimen; overall 2-year PFS and OS rates in this trial were 74% and 91%, respectively.

In high-risk patients, we prefer nontransplantation consolidation approaches instead of transplantation. The rationale for this recommendation is that despite single or double HSCT, the median OS of high-risk patients is only 2 years.<sup>7,10-13,137,196</sup> Therefore, the benefit with intensive

therapy in this patient population is too low compared with the accompanying morbidity to recommend this approach early in the disease course. However, we continue to recommend early stem cell collection with the option for transplantation for 2 reasons. First, although OS after transplantation is consistently poorer in high-risk patients who have undergone transplantation than in their standard-risk counterparts, no data have shown that the high-risk patients do not derive a benefit from these intensive strategies; such strategies must be available as an option at the time of relapse. Second, conditioning regimens better than melphalan at 200 mg/m<sup>2</sup> are likely to be developed in the future.

High-quality evidence is lacking to support any single regimen as standard for nontransplantation consolidation. However, as discussed earlier, retrospective evidence is mounting that bortezomib may at least partially overcome the adverse prognostic influence of deletion 13 and t(4;14).<sup>84,112-114</sup> On the basis of these data, we recommend that bortezomib-based therapy be used as consolidation in high-risk patients with myeloma who are ineligible for stem cell transplantation. In addition, given the markedly adverse prognosis with standard therapy, we recommend that, in selected younger patients with high-risk myeloma, allogeneic stem cell transplantation approaches continue to be considered as an alternative.

#### STEM CELL TRANSPLANTATION IN ELDERLY PATIENTS AND PATIENTS WITH RENAL FAILURE UNDERGOING HEMODIALYSIS

**Guideline for Elderly Patients:** For standard-risk elderly patients (65-75 years old) without other significant comorbidities, high-dose chemotherapy with stem cell support is a legitimate option.

**Level of Evidence:** III

**Grade of Recommendation:** B

Age older than 65 years alone is not a contraindication for transplantation, although no randomized data are available to prove or disprove its utility in this age group.<sup>197,198</sup> Reduced-dose melphalan conditioning (ie, melphalan, 100 mg/m<sup>2</sup>), even if applied in the context of a double transplantation, is inferior to MPT.<sup>75</sup> Doses of 140 to 200 mg/m<sup>2</sup> should be used as conditioning.

**Guideline for Patients Undergoing Hemodialysis:** Allogeneic stem cell transplantation is not recommended.

**Level of Evidence:** III

**Grade of Recommendation:** C

Patients with renal failure, including those undergoing dialysis, can successfully undergo HSCT with melphalan, 140 mg/m<sup>2</sup>, with response rates and PFS similar to those in patients without renal failure, and a small proportion will even have reversal of their renal failure. Treatment-related

morbidity is higher,<sup>199</sup> and their OS is inferior to their dialysis-independent counterparts.<sup>200,201</sup>

#### MAINTENANCE THERAPY AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION

**Guideline for Standard-Risk Patients:** No maintenance except in the context of a clinical trial for standard-risk patients.

**Level of Evidence:** V

**Grade of Recommendation:** C

After transplantation, the current standard is bisphosphonates and observation. Data are limited regarding the efficacy of interferon alfa and thalidomide; therefore, their use cannot be recommended after HSCT off study.<sup>202,203</sup>

#### INTERFERON ALFA

In one small randomized trial of 85 patients, a survival advantage was found at 54 months in favor of the interferon alfa arm (33% vs 12% alive), but this difference did not persist with longer follow-up.<sup>202</sup> The benefit of interferon alfa was also supported by a study from the European Group for Blood and Marrow Transplantation registry. In this retrospective review of nearly 900 patients, just more than half of the patients received interferon alfa. The 2 groups were poorly matched, with the interferon-treated patients being of significantly lower risk.<sup>203</sup> Overall survival was better in the patients who received interferon (78 vs 47 months;  $P=.007$ ). Paradoxically, the partial response group had a better OS than the CR group, and there was a greater survival benefit for patients who achieved a partial response (97 vs 46 months for interferon vs no interferon;  $P=.03$ ) rather than CR (64 vs 51 months;  $P=.1$ ).

#### THALIDOMIDE

Continued use of thalidomide and prednisone is feasible, although its role after transplantation has not yet been clarified,<sup>141,204</sup> and continued study is required. The 2 completed trials that analyzed this issue are the IFM 99-02<sup>140</sup> and Total Therapy 2.<sup>92</sup>

The IFM 99-02 evaluated the value of maintenance thalidomide vs no thalidomide in low-risk patients with myeloma who had undergone tandem allogeneic stem cell transplantation.<sup>140</sup> Although the 3-year event-free survival (36% vs 52%;  $P<.009$ ) and the 4-year OS (75% vs 87%;  $P=.04$ ) favored the thalidomide maintenance arm, this trial has several caveats. First, median follow-up was only 39 months. Second, only 65% of the patients in the no maintenance arm actually received thalidomide at relapse. Third, fewer of the patients in the no maintenance group received modern salvage with either lenalidomide or bortezomib at relapse than did the maintenance group (15% vs 38%).

TABLE 9. Risk of Immunomodulatory Drug–Associated Thromboembolism\*

Reference	No. of patients	Regimen	Prophylaxis	% with thromboembolism
Zangari et al, <sup>205</sup> 2004	134	TT2	No	14
	87	TT2 and thalidomide	No	34
	35	TT2 and thalidomide	Low-dose warfarin	31
	62	TT2	Enoxaparin, 40 mg/d	15
	68	TT2 and thalidomide	Enoxaparin, 40 mg/d	15
Baz et al, <sup>206</sup> 2005	19	T-DVd	No	58
	26	T-DVd	Late aspirin	15
	58	T-DVd	Aspirin	19
Rajkumar et al, <sup>98</sup> 2005	34	Lenalidomide-dexamethasone	Aspirin	0
Palumbo et al, <sup>78</sup> 2006	65	MPT	No	17
	64	MPT	Enoxaparin, 40 mg/d	3
Palumbo et al, <sup>87</sup> 2006	50	MPR	Aspirin	2
Rajkumar et al, <sup>88</sup> 2006	102	Thalidomide-dexamethasone	No	17
	102	Dexamethasone	No	3
Rajkumar et al, <sup>163</sup> 2006	132	Lenalidomide-dexamethasone	No	18
	134	Lenalidomide and low-dose dexamethasone	No	4
Knight et al, <sup>207</sup> 2006	87	Lenalidomide-dexamethasone and erythropoietin	No	23
	83	Lenalidomide-dexamethasone	No	5
	67	Dexamethasone and erythropoietin	No	7
	103	Dexamethasone	No	1

\*MPR = melphalan, dexamethasone, and lenalidomide; MPT = melphalan, prednisone, and thalidomide; T-DVd = thalidomide, pegylated doxorubicin, vincristine, and dexamethasone; TT2 = total therapy 2 (a complex anthracycline-containing multiagent chemotherapy regimen).

With such a modest survival benefit, it is possible that this finding will not survive the test of time.

Total Therapy 2 was a complex regimen in which all patients received intensive induction, tandem transplantation, and consolidative chemotherapy. There was randomization; however, patients were randomized to receive either thalidomide throughout their treatment course (including maintenance) or no thalidomide.<sup>92</sup> Because of the intensity of the program, it is difficult to make sweeping generalizations about the role thalidomide plays as maintenance therapy, but there are a few instructive points. Although response rates and event-free survival rates were significantly better in the group receiving thalidomide, the OS rates were no different. This trial exemplifies the danger of placing too much emphasis on event-free survival and PFS end points in the context of maintenance trials. The question always looms of whether salvage therapy will be as good as maintenance therapy. These are questions for the current decade.

#### MAINTENANCE THERAPY FOR HIGH-RISK PATIENTS AFTER BORTEZOMIB-BASED CONSOLIDATION THERAPY

**Guideline:** If patients are not in CR, consider maintenance therapy with thalidomide and prednisone until best response if no prior use of thalidomide.

**Level of Evidence:** V

**Grade of Recommendation:** D

Data on maintenance strategies in high-risk patients have been discussed earlier in the section on patients ineligible for transplantation. The risk of relapse is high in this patient population, and our consensus is that high-risk patients not in CR with consolidation therapy should be offered maintenance therapy given the high risk of recurrence and early data that suggest a clinical benefit with maintenance approaches.

#### MANAGING THROMBOTIC RISK IN PATIENTS RECEIVING THALIDOMIDE AND LENALIDOMIDE-BASED THERAPY

**Guideline for Single-Agent Thalidomide or Lenalidomide:** No anticoagulant recommended.

**Level of Evidence:** III

**Grade of Recommendation:** A

**Guideline for Thalidomide or Lenalidomide When Given in Combination With a Low-Intensity Corticosteroid:** Aspirin, 325 mg orally daily.

**Level of Evidence:** III

**Grade of Recommendation:** B

**Guideline for Thalidomide or Lenalidomide When Given in Combination With High-Dose Dexamethasone, Doxorubicin, Liposomal Doxorubicin, or Erythropoietin:** Prophylactic low-molecular-weight heparin (equivalent of enoxaparin, 40 mg subcutaneously daily) or full-dose warfarin to a therapeutic international normalized ratio of 2 to 3.

**Level of Evidence: V****Grade of Recommendation: D**

Thrombosis is an important complication in patients undergoing treatment with IMiDs (thalidomide or lenalidomide). As single agents, there does not appear to be any heightened risk; however, concomitant chemotherapy,<sup>78</sup> especially anthracyclines,<sup>205,206</sup> high-dose corticosteroids,<sup>88,98,163</sup> and erythropoietin,<sup>207</sup> appears to increase the risk of thrombosis to as high as 58% (Table 9). Prophylactic low-molecular-weight heparin (eg, enoxaparin, 40 mg daily)<sup>78,205</sup> abrogates that risk. Daily aspirin also appears to be protective in the lower-risk setting.<sup>87,88,207</sup> Low-dose warfarin is not protective. Although full anticoagulation with full-dose warfarin is commonly recommended, no trial data are available to substantiate this recommendation; the concern with warfarin anticoagulation is the difficulty of maintaining a therapeutic international normalized ratio while cycling the IMiDs, corticosteroids, and other chemotherapeutic agents. It is for this reason that the current recommendation for thromboembolism protection in intermediate-risk patients is either aspirin or warfarin. The risk of bleeding when using any of the thromboembolism protective agents must be weighed against the risk of bleeding in any given patient.

APPENDIX. Levels of Evidence and Grade of Evidence for Recommendations

Level	Type of evidence
I	Evidence from meta-analysis of multiple, well-designed, controlled studies; randomized trials with low false-positive and low false-negative errors (high power)
II	Evidence from at least 1 well-designed experimental study; randomized trials with high false-positive and/or negative errors (low power)
III	Evidence from well-designed, quasiexperimental studies, such as nonrandomized, controlled single-group, prepost, cohort, time, or matched case-control series
IV	Evidence from well-designed, nonexperimental studies, such as comparative and correlational descriptive and case studies
V	Evidence from case reports and clinical examples
Grade	Grade for recommendation
A	Evidence of type I or consistent findings from multiple studies of types II, III, or IV
B	Evidence of types II, III, or IV, and findings are generally consistent
C	Evidence of types II, III, or IV, but findings are inconsistent
D	Little or no systematic empirical evidence

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