European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma

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ABSTRACT

Multiple myeloma management has undergone profound changes in the past thanks to advances in our understanding of the disease biology and improvements in treatment and supportive care approaches. This article presents recommendations of the European Myeloma Network for newly diagnosed patients based on the GRADE system for level of evidence. All patients with symptomatic disease should undergo risk stratification to classify patients for International Staging System stage (level of evidence: 1A) and for cytogenetically defined high- *versus* standard-risk groups (2B). Novel-agent-based induction and up-front autologous stem cell transplantation in medically fit patients remains the standard of care (1A). Induction therapy should include a triple combination of bortezomib, with either adriamycin or thalidomide and dexamethasone (1A), or with cyclophosphamide and dexamethasone (2B). Currently, allogeneic stem cell transplantation may be considered for young patients with high-risk disease and preferably in the context of a clinical trial (2B). Thalidomide (1B) or lenalidomide (1A) maintenance increases progression-free survival and possibly overall survival (2B). Bortezomib-based regimens are a valuable consolidation option, especially for patients who failed excellent response after autologous stem cell transplantation (2A). Bortezomib-melphalan-prednisone or melphalan-prednisone-thalidomide are the standards of care for transplant-ineligible patients (1A). Melphalan-prednisone-lenalidomide with lenalidomide maintenance increases progression-free survival, but overall survival data are needed. New data from the phase III study (MM-020/IFM 07-01) of lenalidomide-low-dose dexamethasone reached its primary end point of a statistically significant improvement in progression-free survival as compared to melphalan-prednisone-thalidomide and provides further evidence for the efficacy of lenalidomide-low-dose dexamethasone in transplant-ineligible patients (2B).

Introduction

The outcome for patients with multiple myeloma (MM) has improved substantially over the past 20 years due to several therapeutic advances. High-dose therapy (HDT) with autologous stem cell transplantation (ASCT) was developed in the 1980s and is currently considered the standard front-line treatment for younger and fit patients.[1-3] The introduction of novel agents, thalidomide, lenalidomide, bortezomib, but also the availability of various others, such as 3rd-generation immunomodulatory drugs (IMiDs; pomalidomide), novel proteasome inhibitors, including carfilzomib, ixazomib and oprozomib, antibodies, such as elotuzumab (target: CS1), daratumumab and SAR650984 (CD38), siltuximab (IL-6), tabalumab (BAFF), denosumab (RANKL), romosozumab (sclerostin), Bruton tyrosine kinase, heat shock protein inhibitors and other innovative phase I/II agents have changed or will alter the therapeutic scenario in several ways.[4-7] Moreover, cereblon (CRBN) has been identified as a possible biomarker for the assessment of clinical efficacy of IMiDs, although this is still a subject of controversy and CRBN testing needs to be standardized.[8,9] The predictive role of CRBN was assessed in the HOVON/GMMG trial, where higher CRBN expression was associated with better survival and clinical efficacy of thalidomide.[9] Novel agents have been incorporated as induction regimens with the objective of increasing the response prior to ASCT, and as consoli-

 doi:10.3324/haematol.2013.099358
Manuscript received on October 8, 2013. Manuscript accepted on December 4, 2013.
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dation or maintenance treatment to increase the depth of response and prolong the duration of response. The current goal of ASCT with inclusion of novel agents is improvement in quality of response, extension of progression-free survival (PFS) and, importantly, overall survival (OS).[10] Some experts even consider MM a potentially curable disease, challenging this approach with earlier treatment, more intensive therapy approaches, risk-adapted strategies and use of serial biological examinations guiding treatment decisions.[3,11] This 'cure *versus* control' debate on whether MM patients should be treated with an intensive multi-drug strategy targeting complete response (CR), or a sequential disease control approach that emphasizes quality of life (QoL), toxicity avoidance and OS has not been solved and may be different for the various molecular MM subtypes.[12] International initiatives and collaborations under the auspices of the European Myeloma Network (EMN), the International Myeloma Working Group (IMWG) and others co-operate in large trials translating insights from innovative trials into clinical practice. The EMN reviewed all available evidence and provides below recommendations for the management of newly diagnosed MM.

Methodology

These recommendations were developed by an interdisciplinary panel of clinical experts on MM based on evidence of published data including randomized clinical studies, meta-analyses, systematic reviews and other available published clinical studies through August 2013. Expert consensus was used to suggest recommendations where there were no sufficient data. Grades of recommendations were assigned using the GRADE criteria (Table 1). The recommendations were circulated among each panel member who made their comments, while the recommendations were also discussed in the EMN Trialist meeting (Baveno, Italy, 15-16 September 2013). The manuscript subsequently underwent two rounds of revision until the EMN experts reached a consensus.

Diagnosis of symptomatic myeloma

It is important to establish a diagnosis of symptomatic MM requiring therapy. MM always arises from an asymptomatic precursor condition, either monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma (SMM).[13,14] Patients with MGUS and SMM should be followed carefully for the development of myeloma-related organ or tissue impairment (ROTI), the most common being hypercalcemia, renal failure, anemia and bone disease (CRAB). It is critical that the clinician determines whether symptoms are related to the MM, since there are numerous examples of false attribution of symptoms to MM, when in fact other conditions account for hypercalcemia, such as primary hyperparathyroidism or anemia secondary to iron-deficiency.[15] MGUS with renal impairment (RI) has been recognized as an independent entity and named 'monoclonal gammopathy of renal significance' (MGRS).[16] Similar to MGRS, small PC clones, although not fulfilling the criteria of MM, can give rise to clinically relevant extrarenal organ damage, that should be diagnosed and treated early and appropriately, e.g. AL-amyloidosis, light chain deposition disease, POEMS syndrome, cold hemagglutinine disease or sleromyxedema.[17] Since a critical determinant of survival in most malignancies is early detection, the timely diagnosis and treatment in MM is currently being explored. Nevertheless, early detection is not applicable to MM, because there is no current definition of 'early myeloma'. Because of this, treatment protocols do not adapt therapy on the basis of tumor burden, but rather on that of CRAB criteria, reflecting substantial disease burden that is considered more difficult to eradicate than lower tumor burden. MM is consistently preceded by a precursor state, rendering the effects of early intervention testable; namely, whether MM will evolve. Early intervention is currently not recommended outside a clinical trial, because subjects with myeloma precursor diseases do not all develop overt MM. Notably, the distinction between SMM and MM is not based on clear biological differences, and there is a significant overlap. Determination of end-organ damage often requires subjective interpretation of insensitive modalities, such as skeletal surveys. Therefore, most tertiary institutions use more sensitive tests, e.g. whole-body computed tomography (CT) or magnetic resonance imaging (MRI). Alternate proposals are to classify cases of MM with limited organ damage and SMM with the highest risk of progression as 'early myeloma'. However, this concept requires reliable biological tools to distinguish cases of SMM that are 'MGUS-like' *versus* those that are more 'MM-like'. Two groups have retrospectively identified variables that identify SMM patients at the highest risk of progression, but neither identified with any certainty subjects who will progress to MM.[18] In addition, risk stratification models for SMM have a low concordance rate with each other.[19] Therefore, without precise tools for patient selection, the decision for early intervention concentrates on the perceived assessment of risk *versus* benefit. The Spanish MM-group has recently shown that HR SMM patients may benefit from early therapy with lenalidomide as induction and subsequent maintenance therapy *versus* observation,[20] intruguing results which need to be confirmed in subsequent trials. Future well-designed correlative studies are needed to assess the advantages and disadvantages of early treatment, including long-term adverse effects or selection of more aggressive clones followed by non-responsive disease (Figure 1).[11,21]

The standard investigative workup for patients with suspected MM has been underlined by the IMWG report recommending measurement of the monoclonal protein, serum-free light chain assay, bone marrow (BM) aspiration and/or biopsy along with demonstration of clonality of PCs, FISH-cytogenetics with evaluation of del17p, t(4;14) and t(14;16) as mandatory abnormalities and of amp1q21 and del1p as optional parameters. The skeletal survey (with more sensitive imaging *via* CT, MRI and positron emission tomography (PET)) provides valuable diagnostic and prognostic information, both at initial diagnosis and at relapse.[22]

Prognosis and current risk factors

Prognosis in MM is based on both the ISS and chromosomal abnormalities (Table 2). The ISS is a simplified staging system incorporating beta (β)2-microglobulin and serum albumin, and reflects tumor burden, renal function and host fitness. Additionally, BM karyotype, translocations, chromosome number and gene expression profiling have prognostic value.[23] Currently, no specific therapies for particular molecular MM subgroups can be recommended based on results of prospective clinical trials, albeit two groups are pursuing this approach.[24,25] Risk stratification has skillfully been described by the IMWG consensus panel.[26]

Recommendation: All patients should undergo risk stratifi-

Table 1. Grade recommendations for grading levels of evidence.

Grade			
1	Evidence strongly suggests that the benefit of the procedure outweighs potential risks or risks of the procedure outweighs potential benefits	A	Consistent evidence from systemic reviews of high-quality randomized studies or from high-quality randomized studies or from high-quality observational studies
2	Evidence suggests the benefit and risk of a procedure is finely balanced or uncertain	B	Evidence from randomized and observational studies with important methodological flaws
		C	Evidence from randomized and observational studies with major methodological flaws or other sources of evidence (e.g. case series)

Table 2. Prognostic factors in MM.

Prognostic determinant	Standard-risk	High-risk*	Therapy implication
Host factors	- KPS>70% - Normal renal function - Normal organ function - No impairment in GA - FCI 0, CCI 0	- KPS<70% - Renal failure (eGFR<30) - Other organ impairment - GA reduced - Advanced age	HR pts typically require a decrease in treatment intensity
Tumor burden	Durie & Salmon stage I+II	Durie & Salmon stage III	Limited; some stage I pts require no therapy (SMM), and some require radiation only (if solitary bone lesion)
Tumor biology - (disease aggressiveness)	Hyperdiploidy, t(11;14), t(6;14) - ISS I+II	- t(4;14), t(14;16), t(14;20), 17p-, 1q/del1p - High LDH - ISS III - High PC proliferation rate - Presentation as PCL - Extramedullary disease - HR signature on GEP	Treatment of high-risk patients remains unsatisfactory, but bortezomib appears to overcome some HR features

*Adapted and modified with kind permission of Rajkumar Blood 2011.[12] KPS: Karnofsky Performance Status; GA: geriatric assessment; FCI: Freiburg Comorbidity Index; CCI: Charlson Comorbidity Index; eGFR: estimated glomerular filtration rate; HR: high-risk; SMM: smoldering MM; ISS: International Staging System; PC: plasma cell; PCL: plasma cell leukemia; GEP: gene expression profiling.; *Some HR features, such as t(4;14) or del17p, or renal impairment are overcome by bortezomib.*

cation to classify patients for ISS stage (1A) and also for cytogenetically defined HR *versus* SR groups, i.e. by FISH (2B). Retrospective analyses suggest that incorporation of bortezomib into the ASCT sequence may translate into extended PFS, and possibly OS, for patients who carry t(4;14) and/or del(17p) (2B).[27-29]

Recommended approach to initial therapy

The current paradigm for treatment of newly diagnosed MM is divided into three phases: induction, consolidation, and maintenance. The approach to each phase of therapy is individualized based on the features of the disease, age, comorbidities and personal preferences. Patients with renal failure (RF) from myeloma should start induction as soon as possible with bortezomib and dexamethasone-based regimens. In addition, MM patients with RF should avoid nephrotoxic drugs and maintain euvolemia. The role of mechanical removal of free light chains by plasmapheresis or high cut-off dialysis in the management of myeloma-related RF remains unclear, and is currently assessed in clinical trials in conjunction with chemotherapy. Several studies revealed significant activity of rapidly acting bortezomib-based regimens, such as bortezomib-doxorubicin-dexamethasone (PAD), bortezomib-melphalan-prednisone (VMP) or bortezomib-melphalan-prednisone-thalidomide followed by bortezomib-thalidomide (VMPT-VT)). Both latter combinations were tested in untreated patients with RI: RI reversed in 16 of 63 (25%) patients receiving VMPT-VT *versus* 31 of 77 (40%) with VMP, suggesting that the multi-drug combination VMPT-VT had no advantage in RI reversal over VMP, although it was superior with normal RF and moderate RI.[30] Moreover, analgesia and bisphosphonates for painful bone lesions should be started. Consultation with an orthopedic oncologist for bone lesions at HR of fracture may be needed along with local radiotherapy to promptly ameliorate localized bone pain. Hypercalcemia should be managed with intravenous fluids and bisphosphonates.

Recommendations for patients who are eligible for HDT and ASCT

Induction regimens usually contain 3 of the 4 classes of drugs: corticosteroids, IMiDs, proteasome inhibitors and alkylating agents (Table 3).[31] The goal of induction therapy is to reduce the myeloma burden, improve symptoms and allow for successful stem cell collection. Patients who are transplant candidates should not receive prolonged (>4-6 cycles) induction in order to ease stem cell harvest. Induction therapy can be considered as either two-or three-drug induction regimens. Although the three-drug induc-

Table 3. Induction regimens.

	Regimen	CR rate (%)	Common toxicities (>10%)
Transplant eligible	PAD	11	PNP, infection
	VTD	33	PNP, infection, gastrointestinal events
	VCD	22 (47)*	Thombocytopenia, neutropenia, anemia
	RVD	29	Lymphopenia
	Rd	24	Neutropenia, venous thrombosis
Transplant ineligible	VMP	24	Neutropenia, thrombocytopenia, anemia, PNP
	MPT	13	Neutropenia, venous thrombosis, PNP, infection
	MPR	16	Neutropenia, anemia, thrombocytopenia, infection

*PAD: bortezomib, doxorubicin, dexamethasone; VTD: bortezomib, thalidomide, dexamethasone; VCD: bortezomib, cyclophosphamide, dexamethasone; RVD: lenalidomide, bortezomib, dexamethasone; Rd: lenalidomide, low-dose dexamethasone; VMP: bortezomib, melphalan, prednisone; MPT: melphalan, prednisone, thalidomide, MPR: melphalan, prednisone, lenalidomide; CR: complete response; PNP: peripheral neuropathy; *VCD-mod.*[31]

tion regimens result in higher response rates, they are also accompanied by increased toxicity. In general, VD, VTD, PAD or others can be used as initial therapy for 3 or 4 cycles followed by stem cell harvest and ASCT (Table 3 and Figure 2).[31,32] Four-drug combinations, as tested in the EVOLUTION trial with bortezomib (V), dexamethasone (D), lenalidomide (R) or cyclophosphamide (C) as VDC, VDR and VDCR, have yielded similar PFS and OS, but four-drug combinations induced more side effects, so that VDR and VCD were the preferred regimens for clinical practice.[31]

In patients who respond well and tolerate induction, initial therapy may be continued after stem cell collection, reserving ASCT for first relapse. This high efficacy of novel agents has, indeed, led some groups to investigate these agents upfront without ASCT: Len/Dex yielded similar survival rates at two years compared to Len/Dex and ASCT in a non-randomized ECOG-trial,[33] although it had a number of shortcomings. This non-randomized comparative study included 290 patients who received IMiD-based initial therapy and early (n=173, 60%) or delayed (n=112, 40%) SCT. Both transplant options resulted in excellent survival regardless of the timing of transplantation (Table 4),[29,34-41] but the inherent important limitations of these options requires that they be carefully discussed with ASCT candidates.[42] In another non-randomized phase II trial of lenalidomide-bortezomib-dexamethasone (RVD) induction, in which the choice of ASCT was left to the physician and patient, no difference in outcome was seen between the two approaches. However, since the choice of transplant was not prospective, also this study has to be interpreted with caution.[43] Interestingly, the MRC-group has demonstrated that 42-58% of patients become minimal residual disease (MRD)-negative after ASCT and additional consolidation, arguing in favor of ASCT with an approximately 3-fold increase in MRD negativity,[44] and suggesting that ASCT may only be postponed in those few patients achieving MRD-negativity with induction alone. Moreover, this study showed that MRD-negativity is different to IF-negative (IF-) CR, since 14.5% of patients achieving IF-CR after ASCT had detectable MRD.[44] Since CR achievement has been shown to correlate with OS, efforts to achieve MRD-negativity will continue and will fuel the search for the best approach from among different consolidation/maintenance strategies.[44] Currently, there are only limited data of prospective studies comparing conventional chemotherapy plus novel agents to ASCT. The GIMEMA performed one prominent trial with 402 MM patients who received 4 cycles of Len/Dex (Rd) induction and were randomized to either 6 cycles of MPR or tandem-ASCT. This study reported a significantly improved PFS, but has not yet reported OS in the ASCT arm.[45] Other ongoing trials are investigating the same burning issue, i.e. EMN, Intergroupe Francophone du Myelome (IFM), German Study Group MM (DSMM).

Interestingly, although OS is equivalent, regardless of whether ASCT is performed early or at the time of relapse,[46] early transplantation is associated with improved time without symptoms, treatment and treatment-related adverse events and thus may often be preferred.[46] Also of note, long-term follow up after ASCT was reported by the Spanish MM group with a median follow up of 153 months (12.8 years): 344 patients transplanted between 1989 and 1998 achieved an OS of 35% in CR patients at 12 years, 22% in nearCR and 16% in VGPR and PR patients, suggesting that long-term MM control is attainable with ASCT and that in some patients with excellent response, even a cure can be obtained.[47] That ASCT is a valid therapeutic option also in relapsed MM has also been shown in 200 patients undergoing retransplantation over a period of 15 years: PFS and OS were 15 and 42 months after ASCT, respectively, and factors associated with improved survival were an initial PFS of over 18 months after up-front ASCT, bortezomib- or lenalidomide-containing reinduction, response to reinduction and ISS stage I before ASCT.[48] Ongoing large co-operative trials comparing effective induction combinations with and without ASCT are awaited and will clarify whether the timing of ASCT is relevant for survival, e.g. randomized trials of RVD or Len/Dex induction, with or without initial ASCT (European Myeloma Network (clinicaltrials.gov identifier:01208766), IFM together with a US consortium (*Clinicaltrials.gov identifier:01208662*), DSMM XIII (*Clinicaltrials.gov identifier:01090089*).

Recommendation: novel-agent-based induction and up-front ASCT in medically fit patients lead to sustained remission and continues to be the standard of care in this patient cohort (1A). Current trials are investigating the role of novel agent combinations without up-front ASCT *versus* single- or tandem-ASCT. Induction therapy needs to include a triple combination of bortezomib with either adriamycin or thalidomide and dexamethasone (PAD or VTD; 1A), or with cyclophosphamide and dexamethasone (VCD; 2B).

Allogeneic transplantation

The role of allogeneic transplantation (allo-SCT) remains controversial due to the TRM (10-20%) and graft-*versus*-host disease (GvHD) rates even with non-myeloablative regimens. Therefore, allo-SCT is considered investigational

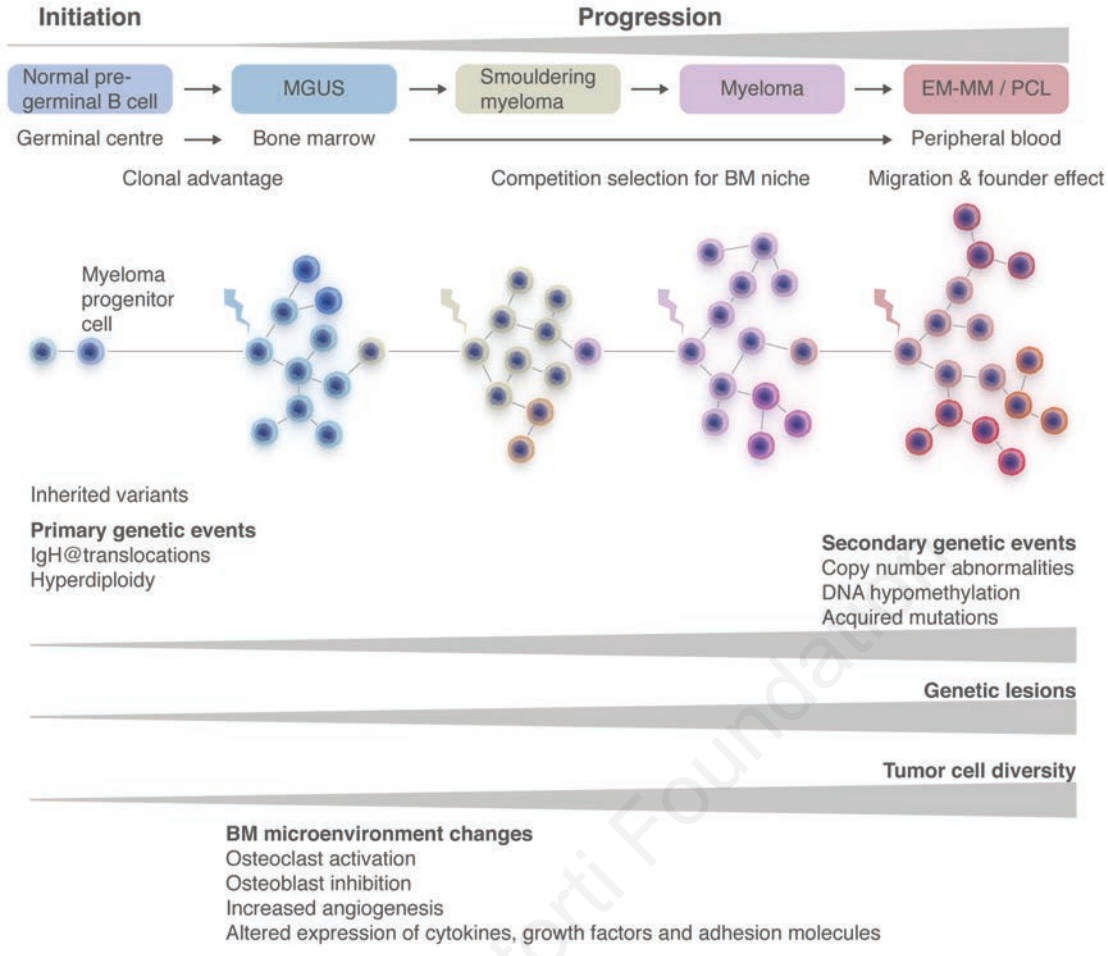

Figure 1. Initiation and progression of MM. MGUS is an indolent, asymptomatic condition and pre-malignant precursor form of MM, that may progress into SMM and symptomatic myeloma, and eventually (with a more aggressive disease courses - into extramedullary disease), such as plasma cell leukemia (PCL). During this disease progression, genetic events may accumulate with tumor diversity and genetic lesions increasing, these events evolving through clonal selection. *Adapted with kind permission of G. Morgan.*[21]

and actively pursued in clinical trials (DSMM, HOVON, GIMEMA, PETHEMA, EBMT, CIBMTR). Long-term follow up with 96 months from the European Group for Blood and Marrow Transplantation Non-Myeloablative Allogeneic stem cell transplantation in MM (EBMT-NMAM200) study has recently been published: this trial prospectively compared tandem-autologous/reduced intensity (RIC) allogeneic transplantation (auto/RICallo) to ASCT alone in 357 patients up to the age of 69 years. Patients with HLA-identical siblings were allocated to auto/RICallo (n=108) and those without to ASCT (n=249). At 96 months, PFS and OS were 22% and 49% *versus* 12% (P=0.027) and 36% (P=0.03) with auto/RICallo and ASCT, respectively. In patients with del(13) abnormalities, corresponding PFS and OS were 21% and 47% *versus* 5% (P=0.026) and 31% (P=0.154), respectively, suggesting that auto/RICallo can overcome the impact of del(13), although longer 5-year follow up is needed for the correct interpretation of the value of auto/RICallo.[49] Recent results from the CIBMTR analysis assessing allo-SCT in 1207 MM patients showed projected 5-year PFS and OS of 14% (95%CI: 9-20%) and 29% (95%CI: 23-35%), respectively; lower than in the EBMT-NMAM200 trial. Multivariate risk factors adversely affecting OS were increasing age, longer interval from diagnosis to transplantation and unrelated donor grafts.[50] Even though the number of allo-SCT has increased at the EBMT centers, primarily in advanced/refractory disease, most patients are not currently enrolled in prospective trials. As for newly diagnosed patients, recent findings raise the question of whether allografting, performed early in the course of the disease, may benefit the very HR MM population where poor outcomes are observed even after the introduction of new drugs. In particular, young patients with ISS II and III associated with del 1p/1q gain, t(4;14), del(17p) or t(14;16), in whom projected 4-year PFS and OS do not exceed 11% and 33%, respectively,[51] may potentially benefit from allo-SCT.

Recommendation: currently, allo-SCT may be considered for young patients with HR disease who are willing to accept the TRM and investigational nature of this therapy for a chance of a better long-term survival (2B). Carefully designed studies with long-term follow up are important to prove that allo-SCT should not be abandoned in MM.[49]

Consolidation and maintenance therapy following induction therapy or transplant

A series of studies has explored the role of maintenance therapy, both following conventional chemotherapy and

Table 4. Results of large recent randomized studies in newly diagnosed myeloma.

Trial	Regimen	N. of pts	ORR (%)	CR + VGPR (%)	PFS (median in months)	*P* for PFS	3-y OS (%)	OS (median in months)	*P* for OS
Facon 2007[34]	MP	196	35	7	17.8		48	33.2	
	Mel 100	126	65	43	19.4	<0.001	52	38.3	<0.001
	MPT	125	76	47	27.5	66	51.6		
Sonneveld 2012[35]	VAD	414	54	14	28	0.002	5y:55	NR at 66	0.07
	PAD	413	78	42	35		61	months	
Harousseau 2010[36]	VAD	242	63	15	30	0.06	77	NR	0.48
	VD	240	79	38	36		81	NR	
Moreau 2011[37]	VD	99	81	35	N/A		N/A	N/A	
	VTD	100	90	51	N/A		N/A	N/A	
Cavo 2012[29]	TD	238	87	31	32	0.042	88	NR	0.39
	VTD	236	96	63	NR		90	NR	
Rosinol 2012[38]	TD	127	33	29	28.2	0.01	65*	n.g.	NS
	VTD	130	25	60	56.2		74*		
	VBMCP/VBAD/B	129	39	36	35.5		70*		
Rajkumar	RD	223	81	50	19.1	0.026	75	NR0.47	
2010[33]	Rd	222	70	40	25.3		74	NR	
2011[39]	MP	873	28	9	14.9	<0.001	63.7#	32.70.004	
	MPT	807	34	25	20.3		68.8#	39.3	
Hulin 2009[40]	MP-placebo	116	31	7	18.5	0.001	40	29.1	0.028
	MPT	113	62	21	24.1		55	44	
Mateos 2010[41]	MP	331	35	8	16.6	<0.001	54	43<0.001	
	VMP	337	71	41	24		69	NR	

*N/A: not available; NR: not reached; n.g.: not given; *estimated overall survival at 4 years from randomization; #2-year overall survival.*

following ASCT. Earlier experiences with chemotherapy were disappointing, the benefit of corticosteroids as single-drug maintenance was questionable and meta-analyses of interferon-α have shown positive effects but at the cost of problems of tolerability.[1] Thalidomide has been shown to increase PFS after conventional therapy and ASCT. However, results have shown high rates of discontinuation due to toxicity and in HR MM has been described as detrimental in some studies:[52] the MRC study assessed thalidomide maintenance in 820 newly diagnosed patients and determined that the median PFS was significantly longer with thalidomide (*P*<0.001), whereas OS was similar with and without maintenance (*P*=0.40). Patients with favorable interphase FISH (iFISH) showed improved PFS (*P*=0.004) and trend toward a late survival benefit, whereas patients with adverse iFISH showed no PFS benefit and worse OS (*P*=0.009).[53] Similar results were reported from the Canadian group in 332 patients receiving TD *ver;sus* no consolidation with improvement of the duration of disease control, but worsening of patient reported QoL and no detectable OS benefit with TD.[54]

Randomized controlled trials of maintenance lenalidomide following conventional therapy or ASCT have also been performed: in the randomized MM015 trial using MPR-R, MPR or MP, PFS was improved with 31 *versus* 14 and 13 months, respectively.[55] The IFM and CALGB performed the ASCT trials with lenalidomide maintenance compared to placebo.[56,57] Both trials demonstrated a doubling of the PFS from approximately two to four years; the CALGB trial also demonstrated an OS benefit. However, the risk of second primary malignancies (SPMs) increased approximately 2-fold in the lenalidomide maintenance arm, although absolute event rates remained fairly small (~8%), and, despite the inclusion of SPMs as events, lenalidomide maintenance still resulted in improved EFS. Currently discussed issues of these trials are that patients in the control arm lacked uniform access to the active drug (thalidomide or lenalidomide) at relapse, and it is unclear whether the PFS improvement will be neutralized, since patients in the control arm can initiate the same therapy at the time of first relapse. Moreover, thalidomide might also potentiate solid SPMs, suggesting an IMiD class effect associated with melphalan exposure.[58] Currently, the issue of SPMs is under investigation to determine disease-, therapy- and patient-specific risks, and we are waiting for the OS benefit in all three maintenance trials to mature before routine lenalidomide is recommended.

Bortezomib administered every other week post ASCT has been shown to induce better OS than thalidomide maintenance,[35] and this is currently being assessed in various trials (Nordic Myeloma Study Group, DSMM, IFM). Patients with del(17p13) benefited most from the bortezomib-containing treatment before and after ASCT, suggesting that long-term administration of bortezomib may be recommended for patients with del(17p13).[28] Bortezomib consolidation after ASCT has also been analyzed in 370 patients randomized to 20 doses of bortezomib *versus* no consolidation showing an improved PFS of 27 *versus* 20 months (*P*=0.05). Although no difference in OS was observed, this study suggests that consolidation may be beneficial in patients not achieving at least VGPR, but not with more than VGPR after ASCT.[59] In a randomized, phase III study, comparing bortezomib-thalidomide-dexamethasone (VTD) *versus* thalidomide-dexamethasone

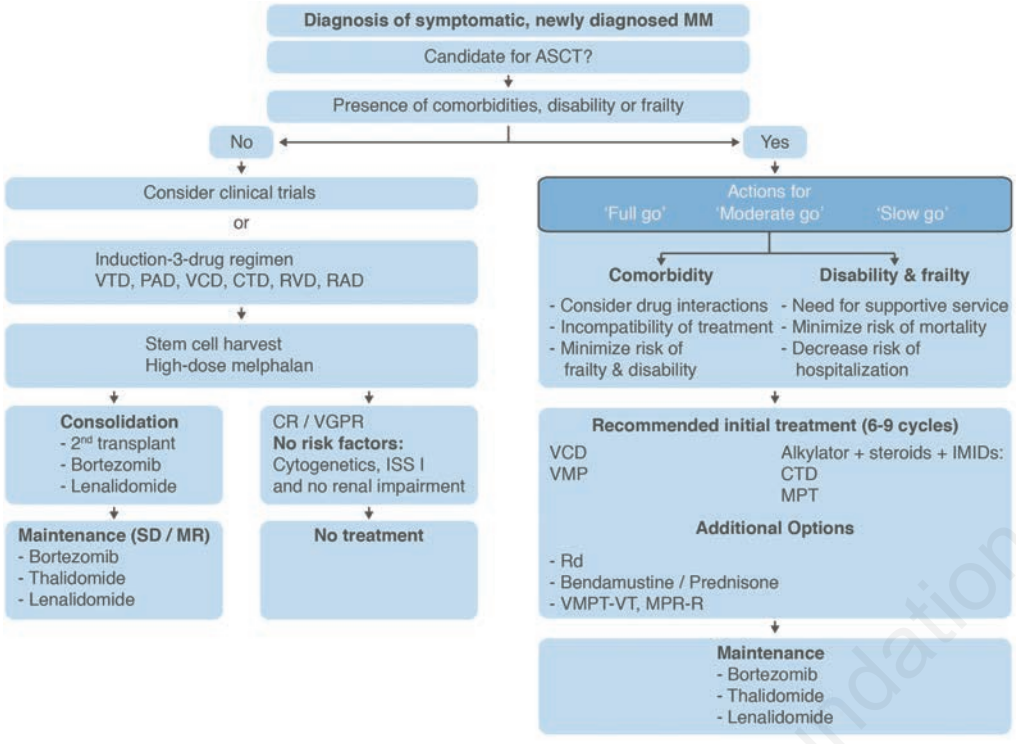

Figure 2. The initiation of most suitable and well-tolerable treatment in symptomatic, newly diagnosed MM patients involves the consideration of various factors, including whether this patient is a candidate for ASCT and presents with comorbidities, disability and frailty. In relation to these issues, either a 3-drug induction regimen, stem cell collection and ASCT may be considered, or with frailty, initial treatment according to 'full-go', 'moderate-go' or 'slow-go' protocols. 'Full go' patients are defined as those without risk factors of advanced age >75 years, moderate or severe frailty (patients needing help for household tasks and personal care) and comorbidities (FCI = 0), 'moderate-go' with at least one of these risks and 'slow-go' with at least two or more of these risk factors. Intermediate assessment of response (if in e.g. non-transplant eligible patients 6-9 cycles of CTD or VCD are performed) is important.

(TD) as induction for newly diagnosed, transplant-eligible patients, the same triplet or doublet regimens were planned as two 35-day cycles of consolidation after double-ASCT. In comparison with TD, the rate of CR (47% *vs.* 61%; *P*=0.012) and CR/nCR (61% *vs.* 73%; *P*=0.020) was significantly higher after VTD consolidation. Overall, VTD offered a 30.5% probability of up-grading the response from less than CR before consolidation to CR after consolidation. With a median follow up of 30.4 months from start of consolidation, PFS at three years was significantly longer for the VTD compared to TD (60% *vs.* 48%; *P*=0.042). Patients who did not achieve CR (HR 0.59; *P*=0.037) and CR/nCR (HR 0.49; *P*=0.018) after double-ASCT most benefited from VTD consolidation.[29] Combination maintenance with bortezomib plus thalidomide (VT) or bortezomib plus prednisone (VP) in elderly patients has demonstrated a better PFS for VT (39 months) than VP (32 months) and OS was longer with VT (5-year OS 69% *vs.* 50%), although these differences did not reach significance.[60] Nevertheless, these results suggest that VP is the preferred maintenance approach for elderly patients because of the lesser side effects. These results of maintenance or consolidation trials should be discussed with the patient, especially in those with suboptimal response to ASCT or HR disease, and a bortezomib-based maintenance or clinical trial might be recommended.[28,59,60]

Recommendation: thalidomide (1B) or lenalidomide (1A) maintenance post ASCT increases PFS and possibly OS (2A). Bortezomib-based regimens are a valuable treatment option, especially for patients who failed VGPR or CR/nCR after ASCT (2A).

Options for initial treatment in patients not eligible for transplant

For patients not eligible for transplant, randomized controlled trials have demonstrated that the addition of a novel agent to melphalan and prednisone (MP) results in improved outcomes. The meta analysis of 6 MPT *versus* MP trials demonstrated improved PFS and OS in some, but also increased toxicity with MPT. Similarly, VMP *versus* MP has resulted in a PR or better in 71% *versus* 35%, respectively, with a hazard ratio for OS clearly favoring bortezomib (0.61; *P*=0.008). Therefore, patients with newly diagnosed MM who are not candidates for ASCT due to age, comorbidities, impaired fitness or preference, may receive MPT or VMP (Table 3). MP may still have a role in elderly patients in whom therapy with MPT or VMP is not considered safe or feasible. MPR (without lenalidomide maintenance) does not improve PFS or OS compared with MP alone,[55] but is currently being compared to MPT in an ECOG randomized trial (E1A06), the results of which are eagerly awaited.

Interestingly, age, formerly used as the discriminator for choosing treatment, is considered of lesser importance today as compared to a careful geriatric assessment (GA) to define fit *versus* unfit patients and consequently select and/or dose-reduce therapy.[61,62] Important comorbidity factors seem to be the Karnofsky Performance Status (KPS) and organ impairment (specifically lung and renal). Comorbidity scores, such as the Freiburg Comorbidity Index (FCI) or others (HCT-CI, Charlson Comorbidity Index; Kaplan Feinstein) are currently assessed, as well as the significance of locomotion (timed 'up and go' test) and impaired IADL (instrumental activities of daily living).[61,62] A therapeutic algorithm for newly diagnosed MM patients based on fitness and a defined GA testing may be better than age alone to identify patients who can be considered for reduced intensity ASCT, novel agent combination or only two-drug combinations (Figure 2).[61-63] Unfortunately, the various options in elderly patients have not been compared in adequately powered clinical trials with relevant

end points to determine best treatment strategies, although useful dose-adjustment recommendations have been published, alongside guidelines as to how to treat elderly MM patients.[63-65]

Recommendations: VMP or MPT are the standards of care for transplant-ineligible patients (1A). Due to its excellent tolerability, lesser induction of polyneuropathy (PNP) and longer therapy endurance, weekly bortezomib schedules are preferred, especially in elderly, unfit or frail patients (2B). MPR+R increases PFS, but OS data are needed. Rd is also an effective option for these patients (2B).

Optimal management of myeloma-related bone disease

High potency intravenous bisphosphonates are a critical component of supportive care and have been shown to reduce skeletal-related events (SRE). Both pamidronate (PAM) and zoledronic acid (ZOL) are effective at reducing SRE in MM patients.[66,67] ZOL has an increased risk of adverse renal toxicity. The UK MRC IX trial randomized patients to ZOL or clodronate (CLO) regardless of the presence of radiographically detected bone disease and reported a 5.5 month increase in median OS.[68] This survival improvement was independent of SRE, suggesting that bisphosphonates have anti-myeloma properties. In the follow-up report of patients treated for more than two years, ZOL improved OS compared to CLO (P=0.02) and disease progression (P=0.03), suggesting that ZOL can be given over prolonged treatment periods and anti-myeloma properties are induced.[69] At present, intravenous bisphosphonates are recommended for all MM patients requiring therapy, which should be continued with active disease and reassumed after disease relapse (1A).[70] It is important to note that denosumab, a monoclonal antibody to RANK-ligand approved for use in breast and prostate cancer metastatic to bone, is currently being tested in a large randomized trial against ZOL, because the smaller randomized trial in fewer than 200 MM patients of denosumab *versus* ZOL showed an inferior survival in the subset of MM patients treated with denosumab.[71] The currently available data, therefore, do not yet support the use of denosumab for the treatment of myeloma-related bone disease.

Management and treatment of toxicity

Both IMiDs and proteasome inhibitors are associated with unique toxicities that require specific management. IMiDs, when combined with steroids or anthracyclines result in a marked increase in venous thromboembolic events. The rate of VTE in these regimens ranges from 20-40% without prophylaxis. A randomized trial of aspirin (100 mg/day), mini-dose warfarin (1.25 mg/day) and enoxaparin (40 mg s.c. daily) in patients receiving thalidomide-based regimens demonstrated equivalence between aspirin and mini-dose warfarin, whereas enoxaparin was more efficacious in preventing thrombotic events and should be used for patients at high-risk of thrombosis (1A).[72]

Patients with MM are also at increased risk of infections as a consequence of disease-related immunodeficiency as well as anti-myeloma therapies.[15] Traditional high-dose dexamethasone-based regimens increased infectious risks compared to low-dose dexamethasone.[33] Antibacterial prophylaxis is commonly included in dexamethasone-containing and multi-agent regimens.[64] Bortezomib-based regimens are associated with varicella zoster reactivation rates that are nearly eliminated with acyclovir prophylaxis.[15,73] For patients with recurrent, severe bacterial infections, intravenous immune globulin can be effective.[65]

Peripheral neuropathy (PNP) is an important toxicity of both thalidomide and bortezomib occurring in approximately 50% of patients.[74] PNP from thalidomide is cumulative, dose dependent and usually permanent. Bortezomib neuropathy is related to dose, schedule and mode of administration and is mostly reversible. Careful attention to the development of PNP is essential while patients are on therapy, and prompt dose reductions are required with development of neuropathy of any grade with thalidomide. A randomized trial of subcutaneous administration compared to intravenous administration of bortezomib showed a dramatic decrease in PNP of all grades (38% *vs.* 53%) and grade 3 or 4 (6% *vs.*16%), leading to its universal use and substantially improved tolerance and therapy endurance of bortezomib (2A).[75,76]

SPMs have attracted attention after recent randomized trials consistently demonstrated more hematologic malignancies in patients treated with lenalidomide (or thalidomide) than placebo maintenance. Most prior studies that have attempted to clarify the phenomenon of SPMs have, however, been restricted by small numbers of patients, inadequate follow up and limitations of ascertainment of SPMs. The aim of subsequent studies is to assess genetic risks, underlying MM/disease-, patient- and therapy-related risks, and to characterize the biological mechanisms in order to minimize SPMs,[77-80] bearing in mind that SPMs may emerge as an important long-term sequela of continuous improvements in MM care, of more intensively performed treatment, and also because of the longevity with this disease.

Unsolved and future issues

The debate surrounding ASCT, including allo-SCT for HR, young, still chemo-responsive MM patients, also involves important advances in the understanding of the biology of the disease, including the complexity and dynamics of genomics.[81] The concept of risk-adapted strategies relies on prognostic factors, such as ISS stage, chromosomal and genetic abnormalities or gene expression profiling, the combination of ISS and FISH or ISS and FCI, or other biological parameters (Table 2). Currently, the Arkansas and Mayo groups are applying risk-adapted therapies with TT5 aimed at sustaining the duration of CR[10] or using the mSMART algorithm to define standard, intermediate- or HR-disease and recommend treatment options according to these risk categories.[25] Although neither of these approaches is based on results of phase III trials, nor is the mSMART algorithm evidence-based, these risk-adapted approaches need to be further tested.

In addition to treatment response (where achievement of VGPR and CR has been shown to strongly correlate with improved outcomes), MRD status, gene expression profiling and refined bone evaluations are currently included in clinical trials as important prognostic parameters which need to be validated by clinical end points. Moreover, since several groups have demonstrated substantial genetic heterogeneity between MM patients,[82-85] subclones, linear disease evolution, genetic instability and dynamics of clonal evolution, as well as profound changes in the BM microenvironment, are currently being evaluated by several groups.[86-89] Intratumor genetic heterogeneity occurs in addition to intertumor heterogeneity and contributes to the emergence of drug resistance in HR MM. Given this, in conjunction with the MM cellular hierarchy and the BM

microenvironment being altered during tumor progression, this makes targeting of both an attractive approach, and fuels the ongoing pursuit of *in vitro* assays and murine models as crucial steps forward.[89-92] That clinical drug resistance is linked to interconvertible phenotypic and functional states of tumor-propagating cells has been described for MM subpopulations, where post-germinal pre-PCs are more quiescent, enriched in epigenetic regulators and 300-fold more drug-resistant than mature PCs, suggesting that these might be responsible for MRD, drug-resistant relapse and require development of alternative therapeutic strategies.[93] Understanding genetic events in MM also involves clarification of the genetic predisposition of MGUS and MM.[94,95] As the treatment armentarium has greatly increased in MM, the aim is to achieve higher response rates with lower toxicity, define most appropriate therapies for specific patient groups, and allow the pendulum to gradually shift from control to cure.[96]

Conclusions

The treatment paradigm for MM has evolved over the past 20 years resulting in substantial improvements in survival. This trend is expected to continue with agents approved for relapsed disease moving earlier into the disease course. In addition, new classes of drugs to combine with existing regimens are under development, notably monoclonal antibodies.

Emerging therapies include next generation proteasome inhibitors, IMiDs, signal transduction modulators (perifosine), HDAC-inhibitors and targeted therapies (inhibitors of NF-kB, MAPK, HSP90, AKT).[97-99] The majority of MM patients diagnosed today can expect to have disease control over long periods of time, with access to all available therapies. In the attempt to define the best therapeutic strategies, future trials should not only investigate prognostic parameters at diagnosis, but also evaluate disease response within the BM and extramedullary (EM) sites and assess the dynamics of clonal expansion of the disease. A major challenge remains that of developing effective therapies for HR MM, for elderly and frail patients, for those outside clinical trials, and for patients with extensively pre-treated, refractory or EM disease and plasma cell leukemia.[21,100]

Acknowledgments

Thanks to Johannes Waldschmidt, University of Freiburg, for critical reading of the manuscript and valuable suggestions, as well as to all participants and discussants of the 6th Trialist Forum, European Myeloma Network, Baveno 15-16 September, 2013.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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