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How to treat elderly patients with multiple myeloma: combination of therapy or sequencing

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Patients with multiple myeloma aged older than 65 years have traditionally received an oral regimen combining melphalan and prednisone (MP). The introduction of novel agents, such as immunomodulatory drugs and proteasome inhibitors, has substantially changed the treatment paradigm of this disease. Five randomized phase III studies, comparing MP plus thalidomide (MPT) versus MP, have shown that MPT increased time to progression (TTP); however, only two of these five studies showed improvement in overall survival (OS). One randomized study has shown that MP plus bortezomib (MPV) increases both TTP and OS compared with MP. Both MPT and MPV are now regarded as the new standards of care for elderly patients. Other promising results have been reported with MP plus lenalidomide or lenalidomide plus dexamethasone, or the combination of cyclophosphamide, thalidomide, and dexamethasone. Reduced-intensity transplantation can be an option for some patients, especially when novel agents are incorporated into pre-transplant induction and post-transplant consolidation. For patients aged older than 75 years a gentler approach should be used, and doses of standard MPT or MPV should be reduced. An accurate management of treatment-related adverse events with prompt dose-reduction can greatly reduce the rate of early discontinuation and significantly improve treatment efficacy. The choice of treatment should be tailored according to the patient's biologic age and co-morbidities, and the expected toxicity profile of the regimen.

Epidemiology

Multiple myeloma (MM) is an incurable plasma cell disorder that comprises 1% of all cancer and 10% of hematologic neoplasms. MM was estimated to account for 19,920 new cancer cases in the USA in 2008, including 11,190 cases in men, 8,730 cases in women, and 10,690 deaths overall.[1] Incidence increases greatly with age: the median age at diagnosis is 70 years, with 35% of patients younger than 65 years, 28% aged 65 to 74 years, and 37% older than 75 years.[2,3] The number of geriatric patients is expected to rise over time because of the increased life-expectancy of the normal population.

Diagnosis and Treatment Strategy

Recognition of organ damage and its correlation with MM is the first step to correctly identify either a) symptomatic MM or b) evolution of monoclonal gammopathy of undetermined significance (MGUS) or smoldering MM to symptomatic MM. Appropriate therapy should then be started (**Table 1**). Early intervention has shown no benefit in the treatment of asymptomatic MM.[4] Patients with symptomatic MM should be treated immediately. Multiple myeloma is defined by serum and/or urine monoclonal (M) protein (in patients with no detectable M-protein, an abnormal serum free light-chain [FLC] ratio) and bone-marrow plasma cells greater than 10%.

Symptomatic MM is defined by the evidence of end-organ damage attributable to plasma cell proliferation according to the CRAB criteria: *C*: hypercalcemia (> 11.5 mg/dL); *R*: renal failure (serum creatinine > 1.73 mmol/L); *A*: anemia (hemoglobin < 10 g/dL or > 2 g/dL below the lower limit of normal); and *B*: bone disease (lytic lesions, severe osteopenia or pathologic fractures).[5]

The criteria for retreatment at relapse are the same as those used at diagnosis, except that retreatment should be done in patients without organ damage if the M-protein has doubled in less than 2 months.

Treatment choice should be based on scientific evidence (randomized phase III studies) and patient's characteristics (age and presence of comorbidities). Patients older than 65 years of age are generally not considered candidates for transplantation, although an age cut off for autologous

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Table 1. Plasma cell–related disorder diagnostic criteria.

	Diagnostic criteria: all three required
Symptomatic multiple myeloma (MM)	1) Monoclonal plasma cells in the bone marrow ≥ 10% and/or presence of a biopsy-proven plasmacytoma 2) Monoclonal protein present in the serum and/or urine* 3) Myeloma-related organ dysfunction (≥ 1)† [C] Calcium elevation in the blood (serum calcium >10.5 mg/L or upper limit of normal) [R] Renal insufficiency (serum creatinine >2 mg/dL) [A] Anemia (hemoglobin <10 g/dL or 2 g <normal) [B] Lytic bone lesions or osteoporosis‡
Monoclonal gammopathy of undetermined significance (MGUS)	1) Serum monoclonal IgG <3.0 g/dL, or serum IgA <2.0 g/dL, or urine monoclonal kappa or lambda <1.0 g/24 hours 2) Monoclonal bone marrow plasma cells <10% 3) Normal serum calcium, hemoglobin concentration, and serum creatinine No bone lesions on full skeletal radiograph survey and/or other imaging if done No clinical or laboratory features of amyloidosis or light-chain deposition disease
Smouldering or indolent myeloma	1) Monoclonal protein present in the serum and/or urine 2) Monoclonal plasma cells present in the bone marrow and/or a tissue biopsy 3) Not meeting criteria for MGUS, MM, or solitary plasmacytoma of bone or soft tissue
Solitary plasmacytoma of bone	1) Biopsy-proven plasmacytoma of bone in one site only. Radiographs and MRI and/or FDG PET imaging (if done) must be negative outside the primary site. The primary lesion may be associated with a low§ serum and/or urine M-component 2) The bone marrow contains <10% monoclonal plasma cells 3) No other myeloma-related organ dysfunction

*If no monoclonal protein is detected (non-secretory disease), then ≥ 30% monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytoma required.
†A variety of other types of end-organ dysfunctions can occasionally occur and lead to a need for therapy. Such dysfunction is sufficient to support classifications myeloma if proven to be myeloma related.
‡If a solitary (biopsy-proven) plasmacytoma or osteoporosis alone (without fractures) is the sole defining criteria, then ≥ 30% plasma cells are required in the bone marrow.
§Low is defined as serum IgG < 3.0 g/dL, serum IgA < 2.0 g/dL, and urine monoclonal kappa or lambda <1.0 g/24 hours
MRI indicates magnetic resonance imaging; FDG: fludeoxyglucose; PET: positron emission tomography.

transplantation at 65 years does not reflect standard practice throughout the world. Since biologic age can differ from chronologic age, biologic age should be taken into account when determining whether a patient is suitable for transplantation. Furthermore, selected patients in good clinical conditions can be considered for reduced-dose intensity transplantation (melphalan 100 mg/m^2, Mel100). For patients aged 65 to 75 years, full-dose conventional therapy is recommended, whereas a gentler approach should be used for patients older than 75 years or those who are younger but with significant comorbidities (serious heart, lung, renal, or liver dysfunction), with appropriate dose reductions. Adverse events should always be graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC).[6] Treatment should be promptly interrupted when serious adverse events arise (grade 4 or higher hematologic toxicities or grade 3 or higher non-hematologic toxicities). When serious adverse events resolve completely or at least to grade 1, treatment should be restarted with an appropriate reduction in dose (see section on "Management of adverse events" for details). Physicians should always consider the expected treatment-related side-effects in choosing the appropriate treatment, especially in elderly patients with multiple comorbidities.

The role of prognostic factors in the choice of therapy is still controversial. Patients with symptomatic myeloma are categorized according to disease stage, on the basis of the International Staging System (ISS) that defines three risk groups: stage I with median survival of 62 months (serum β2-microglobulin < 3.5 mg/L and serum albumin ≥ 35 g/L), stage II with median survival of 44 months (serum β2-microglobulin > 3.5 mg/L and serum albumin < 35 g/L or serum β2-microglobulin 3.5-5.5 mg/L), and stage III with median survival of 29 months (serum β2-microglobulin ≥ 5.5 mg/L).[7] Serum FLC ratio incorporated into the ISS can improve the risk stratification.[8,9] Cytogenetics and fluorescent in-situ hybridization (FISH) can be used to detect chromosomal abnormalities. Of FISH-based abnormalities, patients with isolated deletion 13 (del13) do not have a worse outcome, although del13 associated with 17p deletion (del17) or t(4;14) are associated with poorer outcomes. With use of FISH, del17 or t(4;14) or t(14;16) are associated with poorer outcome, t(11;14) does not have negative outcome, and

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hyperdiploid is associated with good outcome.[10,11] Preliminary evidence shows that targeted therapy with bortezomib, and possibly lenalidomide, can be used to overcome the effects of cytogenetic abnormal changes; however, since this evidence is from a small cohort of patients, no specific therapy should be routinely recommended on the basis of chromosomal abnormal changes at present.

Therapeutic Options

Novel Agent-based Therapy

For many years, conventional treatment for elderly patients (older than 65 years) or young patients who are ineligible for high-dose therapy has been the combination of oral melphalan and prednisone (MP). In a randomized trial, MP has been compared with melphalan plus dexamethasone (MD), or high-dose dexamethasone or high-dose dexamethasone plus interferon-α. Improvement in progression-free survival (PFS) was reported in patients receiving melphalan as part of the induction treatment (both MP and MD) but not in those receiving high-dose dexamethasone only.[12] These findings suggest the need to incorporate an alkylating agent in combination regimens including new drugs. A randomized study comparing MP with thalidomide plus dexamethasone (TD) in patients with a median age of 72 years found that TD resulted in a higher proportion of at least very good partial response (VGPR) (26% vs 13%; P = .006) and partial response (PR) (68% vs 50%; P = .002) than did MP. Time to progression (TTP) (21.2 vs 29.1 months; P = .2) and PFS were similar (16.7 vs 20.7 months; P = .1), but overall survival (OS) was significantly shorter in the TD group than in the MP group (41.5 vs 49.4 months; P = .024). Toxicity was higher with TD, especially in patients older than 75 years with poor performance status. During the first 12 months of therapy, the number of patients who died from non-myeloma–related causes was twice as high in the TD group compared with those given MP.[13] In another study undertaken in younger patients (median age 64 years), TD showed clear benefit in terms of both PR rate (63% vs 46%, P < .001) and TTP (22.6 vs 6.5 months, P < .001) compared with high-dose dexamethasone alone. Grade 3-4 adverse events were most frequent with TD (79.5% vs 74.2%, P < .001).[14] Thalidomide improves the clinical efficacy of dexamethasone, but high-dose dexamethasone is too toxic in elderly patients. Although TD was better than was high-dose dexamethasone alone, the lack of benefit when compared with MP (in terms of PFS and OS) suggests that this combination is not the best approach for patients with newly diagnosed MM who are ineligible for high-dose therapy and autologous transplantation (ASCT).

Lenalidomide plus high-dose dexamethasone (RD) resulted in a higher complete response (CR) rate (22.1% vs 3.8%) and 1-year PFS (77% vs 55%, P = .002) than did high-dose dexamethasone alone;[15,16] the combination of lenalidomide plus low-dose dexamethasone (Rd) showed further benefit in terms of OS at 2 years (87% vs 75%, P < .001) and adverse events were reduced compared with RD.[17] Since these differences were even more pronounced in patients older than 65 years, Rd can be regarded as a reasonable option, although a formal comparison with MP has still not been done.

In elderly patients with newly diagnosed MM, five randomized studies have compared the combination of MP plus thalidomide (MPT) with MP. In all studies MPT resulted in higher PR (42%-76% vs 28%-48%), higher at least VGPR or near-CR (nCR) rate (15%-47% vs 6%-8%), and longer PFS (14-27.5 vs 10-19 months) than did MP.[18-23] However, only two studies reported improved OS with MPT (45.3-51.6 vs 27.7-32.2 months).[21,22] These data lend support to the use of MPT as the standard of care. Thalidomide therapy was generally well tolerated, even in patients aged 75 years and older,[22] although the MPT regimen was associated with a significantly higher incidence of grade 3–4 non-hematologic adverse events, including neurologic adverse events, infections, cardiac toxicity, and deep-venous thrombosis (DVT). After the introduction of prophylactic enoxaparin, the incidence of DVT was substantially lowered from 20% to 3%.[19] Antithrombotic prophylaxis is recommended when MPT is used, although which is the best thromboprophylaxis to use in these patients is debated. To address this issue, the Italian Myeloma Network GIMEMA designed a phase III study to prospectively investigate the efficacy and safety of low-molecular-weight heparin (LMWH), low-fixed-dose warfarin (1.25 mg per day), or low-dose aspirin as prophylaxis for venous thromboembolism (VTE) in newly diagnosed patients with MM, who were randomly assigned to receive primary induction therapy with thalidomide-containing regimens. Patients at risk of VTE were excluded from the study. The risk of VTE was 3.9% with low-fixed-dose warfarin, 4.5% with LMWH, and 5.5% with aspirin. No significant relation was recorded between the frequency of VTE and thromboprophylaxis, induction treatments, or age of patients. In patients at standard risk of VTE, LMWH, warfarin, and aspirin are likely to be an effective thromboprophylaxis.[24] The duration of MP treatment should be limited to 6 to 9 cycles; prolonged exposure to melphalan induces thrombocytopenia that hinders the delivery of subsequent effective salvage regimens.

A randomized trial comparing the combination of bortezomib plus MP (VMP) with standard MP reported a significant improvement in PR (71% vs 35%), CR rate (30% vs 4%; P < .001), TTP (24 months vs 16.6 months, P < .001), and OS at 3 years (72% vs 59%, P = .0032) with the

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VMP regimen**.** This superiority was also recorded in patients older than 75 years. The incidence of peripheral neuropathy (13% vs 0%), gastrointestinal complications (20% vs 5%), and fatigue (8% vs <1%) was higher with VMP than with MP. The number of patients with herpes zoster infection was also higher in patients given VMP than in those given MP (14% vs 4%), but the frequency dropped to 3% in those who received acyclovir prophylaxis.[25, 26]

In a study comparing VMP with the regimen of bortezomib, thalidomide, and prednisone (VTP), PR, TTP, and OS did not differ significantly, but VTP had more grade 3-4 non-hematologic adverse events than did VMP, including cardiac toxicity (8.5% vs 0%, $P < .001$), thromboembolic events (4% vs <1%, P = not significant [NS]), and peripheral neuropathy (9% vs 5%, P = NS), resulting in a higher rate of treatment discontinuation (17% vs 8%, $P = .03$). Patients given VMP had a higher rate of neutropenia (37% vs 21%, $P = .003$), thrombocytopenia (22% vs 12%, $P = .03$), and infections (7% vs <1%, $P = .01$) than did those given VTP.[27] Although equally effective, VMP was better tolerated than was VTP.

The first randomized study comparing a four-drug combination including MP plus bortezomib and thalidomide (VMPT) with VMP reported higher rates of VGPR (55% vs 45%, $P < .001$) and CR (39% vs 21%, $P < .001$) with VMPT; however, longer follow-up is needed to assess the effects of both regimens on PFS and OS. The incidence of the most common adverse events (neutropenia, thrombocytopenia, peripheral neuropathy, and infections) was similar in both groups. When the standard twice-weekly infusion of bortezomib (1.3 mg/m^2 on days 1, 4, 8, and 11) was reduced to a weekly schedule (1.3 mg/m^2 on days 1, 8, 15, 22), the incidence of grade 3-4 peripheral neuropathy was significantly reduced from 24% to 6% in the VMPT group and from 14% to 2% in the VMP group; the incidence of CR was reduced from 27% to 20% in the VMP group but not in the VMPT group (36% vs 39%).[28] If longer follow-up proves no decrease in survival despite dose reduction, the once-weekly infusion may be considered an option for patients older than 75 years and in younger patients who have grade 1 or higher peripheral neuropathy.

Cyclophosphamide, another alkylating agent, has been assessed in combination with thalidomide. In the Medical Research Council (MRC) Myeloma IX trial, the combination of cyclophosphamide (500 mg on day 1, 8, and 15 every 3 weeks) plus TD (CTD) was compared with standard MP in 900 patients. Patients given CTD showed higher rates of PR (82% vs 49%) and CR (23% vs 6%) than did those given MP. Unfortunately, data for PFS duration are not yet available because of the short follow-up of the trial. If PFS is better with CTD than with MP, CTD should be regarded as an alternative standard of care for elderly patients.[29]

The combination of melphalan, prednisone, and lenalidomide (MPR) has been investigated in a phase I/II study. Patients given the maximum tolerated dose (MTD: 0.18 mg/kg melphalan, 2 mg/kg prednisone, and 10 mg lenalidomide) achieved a PR rate of 81%, including 47.6% at least VGPR and 24% CR; median TTP and PFS were 28.5 months, and 2-year OS was 90.5%.[30,31] Grade 3 or 4 neutropenia was reported in 52.4% of patients, and 42.3% of patients required administration of granulocyte-colony stimulating factor (G-CSF). Grade 3 and 4 non-hematologic adverse effects were mild and included febrile neutropenia (9.5%), skin rash (9.5%), and thromboembolism (4.8%). This combination is being assessed in an international randomized trial comparing MPR with MP. If this study reports improvement in PFS, another standard of care will be available for elderly patients.

Table 2 summarizes the efficacy of the main treatment regimens, and **Table 3** summarizes the most frequent adverse events.

Reduced-intensity Transplantation in Elderly Patients

Elderly patients or patients with significant comorbidities are generally not eligible for standard melphalan 200 mg/m^2 followed by ASCT. Two randomized studies compared intermediate Mel100 plus reduced-intensity ASCT with MP. In one study including patients aged 65 to 70 years, ASCT was better than was MP in terms of both event-free survival (EFS) and OS.[32] In another study, including patients aged 65 to 75 years, reduced-intensity ASCT induced a response rate better than MP and fairly similar to MPT, with no difference for PFS and OS. MPT was associated with a significant improvement in survival and a significantly lower extra-hematologic toxicity than was ASCT.[21] These data suggest that patients aged 65 to 70 years can successfully be treated with Mel100, but this regimen is too toxic for those aged 70 to 75 years and MPT would be more effective.

The efficacy of bortezomib, pegylated liposomal doxorubicin, and dexamethasone (PAD) induction therapy before reduced-intensity ASCT, followed by consolidation with lenalidomide and prednisone (LP), and maintenance with lenalidomide alone (L) was assessed in patients aged 65 to 75 years. The CR rate was 13% after PAD, 43% after Mel100, and 73% after LP-L consolidation-maintenance therapy. These data suggest that this approach, incorporating bortezomib as induction and lenalidomide as consolidation-maintenance treatment, improves response rate by

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Table 2. Efficacy of regimens used as front-line treatment in elderly patients with multiple myeloma.

Regimen		N	CR, %	≥ PR, %	PFS/EFS/ TTP, %	OS, %	Study
MPT	Mel: 4 mg/m^2 days 1–7 Pdn: 40 mg/m^2 days 1–7 for six 4-week cycles Thal: 100 mg/day until PD	129	16	76	50 at 22 mo	50 at 45 mo	Palumbo et al[19,20]
MPT	Mel: 0.25 mg/kg days 1–4 Pdn: 2 mg/kg days 1–4 Thal: 400 mg/day for 12 6-week cycles	125	13	76	50 at 28 mo	50 at 52 mo	Facon et al[21]
MPT	Mel: 0.25 mg/kg days 1–4 Pdn: 2 mg/kg days 1–4 Thal: 100 mg/day for 12 6-week cycles	113	7	62	50 at 24 mo	50 at 45 mo	Hulin et al[22]
MPT	Mel: 0.25 mg/kg days 1–4 Pdn: 100 mg days 1–4 Thal: 200-400 mg/day in a 6-week cycle until plateau Thal: 200 mg/day until disease progression	182	6	42	50 at 20 mo	50 at 29 mo	Gulbrandsen et al[18]†
MPT	Mel: 0.25 mg/kg Pdn: 1 mg/kg days 1–5 Thal: 200 mg/day for eight 4-week cycles, followed by Thal: 50 mg/day until disease progression	165	2	66	50 at 14 mo	50 at 37 mo	Wijermans et al[23]†
VMP	Mel: 9 mg/m^2 days 1–4 Pdn: 60 mg/m^2 days 1–4 Bor: 1.3 mg/m^2 days 1,4,8,11,22,25,29,32 for the first four 6-week cycles; days 1,8,15, 22 for the subsequent five 6-week cycles	344	30	71	50 at 24 mo	72 at 36 mo	S Miguel et al[25,26]†
VMP	Mel: 9 mg/m^2 days 1–4 Pdn: 60 mg/m^2 days 1–4 Bor: 1.3 mg/m^2 days 1,8,15,22 Thal: 50 mg days 1–42 for nine 5-week cycles	177	20	82	70 at 36 mo	87 at 36 mo	Palumbo et al[28]†
VMP	Mel: 9 mg/m^2 days 1-4 Pdn: 60 mg/m^2 days 1-4 Bor: 1.3 mg/m^2 twice weekly (days 1, 4, 8, 11; 22, 25, 29 and 32) for one 6-week cycle, followed by once weekly (days 1, 8, 15 and 22) for five 5-week cycles	130	22	81	72 at 24 mo	88 at 24 mo	Mateos et al[27]†
VTP	Thal: 100 mg/day Pdn: 60 mg/m^2 days 1–4 Bor: 1.3 mg/m2 twice weekly (days 1, 4, 8, 11; 22, 25, 29, and 32) for one 6-week cycle, followed by once weekly (days 1, 8, 15, and 22) for five 5-week cycles	130	27	81	65 at 24 mo	93 at 24 mo	Mateos et al[27]†
CTD	Ctx: 500 mg days 1,8,15 Thal: 100-200 mg/day Dex: 40 mg days 1–4, 12–15 in a 3-week cycles	450	23	82	ND	ND	Morgan et al[29]

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Table 2. Continued from previous page.

Regimen		N	CR, %	≥ PR, %	PFS/EFS/ TTP, %	OS, %	Study
VMPT	Mel: 9 mg/m^2 days 1–4 Pdn: 60 mg/m^2 days 1–4 Bor: 1.3 mg/m^2 days 1,8,15,22 Thal: 50 mg days 1–42 for nine 5-week cycles followed by Bor: 1.3 mg/m^2 every 15 days and Thal: 50 mg/day as maintenance	152	39	87	74 at 36 mo	88 at 36 mo	Palumbo et al[28]†
MPR	Mel: 0.18-0.25 mg/kg days 1–4 Pdn: 2 mg/kg days 1–4 for nine 4-week cycles Len: 5-10 mg days 1–21 until relapse or progressive disease	54	24	81	80 at 24 mo	91 at 24 mo	Palumbo et al[30,31]†
Rd	Len: 25 mg days 1–21 Dex: 40 mg days 1, 8, 15, 22 in a 4-week cycles	220	ND	70	ND	87 at 24 mp	Rajkumar et al[17]

†Updated information was presented at the meetings of the American Society of Clinical Oncology, European Haematology Association and American Society of Hematology congress.
N indicates number of patients; CR, complete response; PR, partial response; PFS, progression-free survival; EFS, event-free survival; TTP, time to progression; OS, overall survival; Mel, melphalan; Pdn, prednisone; Thal, thalidomide; Bor, bortezomib; Len, lenalidomide; Ctx, cyclophosphamide; MPT, melphalan-prednisone-thalidomide; VMP, bortezomib-melphalan-prednisone; VTP, bortezomib-thalidomide-prednisone; VMPT, bortezomib-melphalan-prednisone-thalidomide; CTD, cyclophosphamide-thalidomide-dexamethasone; MPR, melphalan-prednisone-lenalidomide; Rd, lenalidomide- low-dose dexamethasone; ND, not determined.

Table 3. Safety (grade 3-4 adverse events) of regimens used as front-line treatment in elderly patients with multiple myeloma.

Regimen	N	Neutropenia, %	Thrombo-cytopenia, %	Infection, %	Peripheral neuropathy, %	VTE, %	Study
MPT	129	16	3	10	8	9	Palumbo et al[19,20]
MPT	125	48	14	13	6	12	Facon et al[21]
MPT	113	23*	ND	ND	20*	6	Hulin et al[22]
MPT	165	ND	ND	14	9	3	Wijermans et al[23†]
VMP	344	40	38	11	13	1	S Miguel et al[25,26†]
VMP	177	28	17	9	2	2	Palumbo et al[28†]
VMP	130	37	22	7	5	<1	Mateos et al[27†]
VTP	130	21	12	<1	9	4	Mateos et al[27†]
VMPT	152	32	21	13	6	3	Palumbo et al[28†]
CTD	450	ND	ND	ND	ND	ND	Morgan et al[29]
MPR	54	52	23	10	0	5	Palumbo et al[30,31†]

*Grade 2-4.
†Updated information was presented at the meeting (American Society of Clinical Oncology, European Haematology Association and American Society of Hematology congress).
N indicates number of patients; MPT, melphalan-prednisone-thalidomide; VMP, bortezomib-melphalan-prednisone; VTP, bortezomib-thalidomide-prednisone: VMPT, bortezomib-melphalan-prednisone-thalidomide; CTD, cyclophosphamide-thalidomide-dexamethasone; MPR, melphalan-prednisone-lenalidomide; ND, not determined.

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taking advantage of a sequential exposure to different drugs. Infections were the most frequent non-hematologic adverse event, occurring mainly during PAD induction (16.6%) and Mel100 transplantation (27.1%). Lenalidomide consolidation and maintenance was well tolerated, and the absence of cumulative or persistent neutropenia and/or cumulative thrombocytopenia together with the absence of peripheral neuropathy, further lends support to its use as maintenance agent.[33]

Maintenance

Maintenance therapy has the potential to provide new treatment options for patients with MM. Four different randomized studies explored the role of thalidomide maintenance after ASCT and all showed improvement in PFS in patients who received thalidomide; OS advantage was reported in three of the four studies.[34-37] The main reason for thalidomide discontinuation was the occurrence of peripheral neuropathy that restricted the long-term use of this drug. Thus thalidomide is regarded as a more suitable agent for consolidation treatment rather than maintenance therapy. Because of its lack of neuropathy, lenalidomide seems the ideal candidate for an effective maintenance approach. No studies have investigated the efficacy of maintenance therapy in elderly patients, and the use of maintenance therapy after induction with MP or another regimen is unknown. Ongoing randomized trials will define the role of maintenance therapy with novel agents.

Treatment Strategy

Different treatment options are now available for elderly patients, and physicians have the opportunity to choose treatment regimens according to patient characteristics. The efficacy of these new regimens should be balanced against their higher toxicity. For example, for patients with a high risk of thromboembolism, MPV should be the preferred option; in those with pre-existing peripheral neuropathy, MPR should be considered; whereas in those with renal failure, MPV or MPT are safer and well tolerated, although lenalidomide can be used with appropriate dose reduction. In a fragile population of very elderly patients (≥ 75 years) or younger patients with significant comorbidities, such as lung, heart, liver, or kidney disfunction, all these regimens can be used but lower doses of thalidomide (100 mg or even 50 mg every other day), bortezomib (weekly schedule), and lenalidomide (15-10 mg or even 5 mg) would be recommended on the basis of clinical experience of respected authorities[38] (**Table 4**). MPT should be considered when costs are a concern. Furthermore, compliance is an important factor to consider, especially for elderly patients, and the advantages of oral treatment should be balanced against those of intravenous treatment. Oral treatment can be more convenient and easy, but the patient must be able to carefully follow the prescription; intravenous treatment is more invasive and often requires several admissions to hospital.

Although no randomized clinical trials have shown the advantage of a tailored treatment approach that considers genetic risk when treatment is decided, clinically applicable tests need to be developed to identify patients with more aggressive disease. The Mayo Clinic Group proposed a cytogenetic-based risk classification system: patients with del17p, t(14;16), t(4;14), del13, hypodiploidy by karyotype, or a high plasma cell labeling index (> 3%) are regarded as at high risk; and those with t(11;14), t(6;14), or hyperdiploid karyotype are regarded as at standard risk. On the basis of this algorithm, a regimen such as MPT should be considered in patients who are not eligible for transplantation but who have low-risk disease, whereas MPV should be considered for those at high risk.[39] Since these regimens have not yet been directly compared, randomized trials are needed to lend support to these recommendations before these can be applied to standard clinical practice.

Management of Side Effects

Hematologic Toxicity

A common symptom of MM is myelosuppression, especially anemia, whereas thrombocytopenia tends to appear in end-stage disease. Neutropenia is a common side effect of lenalidomide and alkylating agents, as well as thrombocytopenia, which is also fairly common in patients treated with bortezomib. Supportive care and dose modifications are needed to manage myelosuppression.

Table 4. Age-adjusted dose reduction.

	65–75 years	>75 years	Further dose reduction
Dexamethasone weekly	40 mg	20 mg	10 mg
Melphalan days 1–4	0.25 mg/kg	0.18 mg/kg	0.13 mg/kg
Thalidomide per day	200 mg	100 mg	50 mg
Lenalidomide (in combination with dexamethasone) days 1–21	25 mg	15 mg	10 mg
Lenalidomide (in combination with melphalan plus prednisone) days 1–21	10 mg	5 mg	5 mg every other day
Bortezomib	1.3 mg/m^2 twice-weekly	1.3 mg/m^2 weekly	1.0 mg/m^2 weekly

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Neutropenia

The greatest concern with neutropenia is the occurrence of infections. The use of G-CSF is a safe and effective method to decrease or prevent the occurrence or severity of neutropenia. Treatment should be withheld in case of grade 4 neutropenia (neutrophilic count < 500/mm^3) despite G-CSF administration. When the adverse event resolves to grade 2 (neutrophilic count ≥ 1000/mm^3), treatment can be reintroduced with dose reduction at the start of the next cycle. Prophylaxis with G-CSF is also recommended for the prevention of febrile neutropenia in patients at high risk on the basis of their age, medical history, and disease characteristics, and the myelotoxicity of the chemotherapy regimen.

Anemia

Myeloma-related anemia generally improves with disease response to therapy. Erythropoiesis-stimulating agents (ESAs; epoetin and darbepoetin) can be used to treat chemotherapy-associated anemia, and iron supplements can improve the effectiveness of treatment. ESA treatment is generally recommended when the hemoglobin concentration is less than 9 g/dL; however, treatment can begin earlier (hemoglobin 10 to 12 g/dL) for patients with heart disease or those who have difficulties undertaking regular daily activities. The ESA dose should be adjusted to maintain a hemoglobin concentration of 11 to 12 g/dL to avoid blood transfusion and anemia-related symptoms. Hemoglobin concentration greater than 12 g/dL in patients with cancer can create serious health problems, with an increased risk of thrombosis. For patients at high risk for developing blood clots, the risks of these drugs need to be weighed against the benefits.

Thrombocytopenia

Treatment should be withheld in case of grade 4 thrombocytopenia (platelet count < 25,000/mm^3). When the adverse event resolves to at least grade 2 (platelet count ≥ 50,000/mm^3) treatment can be reintroduced, but dose of the myelotoxic drug needs to be appropriately reduced.

Renal Failure

Renal impairment is common in patients with MM. Factors involved in the pathogenesis of renal failure include the capacity of the light-chain component of the immunoglobulin to cause proximal tubular damage, dehydration, hypercalcemia, hyperuricemia, infections, and use of nephrotoxic drugs. Doses of agents such as thalidomide and bortezomib need no modification in the context of renal dysfunction. Lenalidomide can be used, but hematologic function should be monitored closely, especially in the early cycles. Dose reductions are mandatory on the basis of creatinine clearance (CLcr): if CLcr is between 30 and 60 mL/min, the recommended dose is 10 mg per day; if CLcr is less than 30 mL/min but the patient does not require dialysis, the recommended dose is 15 mg every other day; and if CLcr is less than 30 mL/min and the patient requires dialysis, the dose is 5 mg per day administered after dialysis only on dialysis days.

Peripheral Neuropathy

Peripheral neuropathy is a common adverse event with bortezomib and thalidomide therapy. Since no pharmacologic drugs are available at present to effectively relieve neuropathic symptoms, prompt dose reductions and modifications to the treatment schedule are the most effective means to treat peripheral neuropathy. For bortezomib, a dose reduction to 1.0 mg/m^2 is recommended for grade 1 with pain or grade 2 peripheral neuropathy; dose interruption until peripheral neuropathy resolves with restart at 0.7 mg/m^2 is recommended for grade 2 with pain or grade 3 peripheral neuropathy; and treatment discontinuation is recommended for grade 4 peripheral neuropathy.[40] For thalidomide, patients should be taught to recognize peripheral neuropathy and to immediately decrease the dose or to discontinue the drug when sensory paresthesia is complicated by pain, motor deficiency, or an interference with daily function. A practical rule is to maintain the assigned dose if neuropathy is grade 1, to decrease by 50% if neuropathy is grade 2, to discontinue if neuropathy is grade 3, and to eventually resume thalidomide at a decreased dose if neuropathy improves to grade 1.[41]

DVT

The choice of thromboprophylaxis in patients treated with immunomodulatory agents depends on the risk of VTE associated with a specific regimen. The following risk factors should be considered when determining the form of thromboprophylaxis: individual risk factors (age, obesity, history of VTE, central-venous catheter, comorbidities such as cardiac disease, chronic renal disease, diabetes, infections, immobilization, surgical procedures, and inherited thrombophilia), myeloma-related risk factors (diagnosis and hyperviscosity), and therapy-related risk factors (high-dose dexamethasone, doxorubicin, or multiagent chemotherapies). Aspirin is recommended for patients with no risk factors or those with one individual or myeloma-related risk factor. LMWH or full-dose warfarin are recommended for patients with at least two individual or myeloma-related risk factors and should be considered in all patients receiving high-dose dexamethasone or doxorubicin or multiagent chemotherapy, independently from the presence of additional risk factors.[42] **Table 5** summarizes recommendations for the most frequent adverse events related to the use of novel agents.

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Table 5. Management of adverse events in patients with multiple myeloma treated with novel agents.

	Suspected antimyeloma agent	Management	Dose modification
Hematologic toxicity			
Neutropenia	Lenalidomide and combinations	G-CSF until neutrophil recovery in case of uncomplicated grade 4 toxicity or grade 2-3 adverse events complicated by infection	25%-50% reduction
Thrombocytopenia	Bortezomib, lenalidomide, and combinations	Platelet transfusion if grade 4 adverse events	25%-50% reduction in case of grade 3-4 adverse event
Anemia	Bortezomib, lenalidomide, and combinations	Erythropoietin or darbepoietin in case of hemoglobin concentration ≤ 10 g/dL	25%-50% reduction in case of grade 3-4 adverse event
Extra-hematologic toxicity			
Infection	All the agents	Trimetoprin-cotrimoxazole for *Pneumocystis carinii* prophylaxis during high-dose dexamethasone. Acyclovir or valacyclovir for HVZ prophylaxis during bortezomib-based therapy	25%-50% reduction in case of grade 3-4 adverse event
Neurotoxicity	Bortezomib, thalidomide, and combinations	Neurological assessment before and during treatment. Consider symptomatic treatment with gabapentin, pregabalin, vitamin B complex compounds, amitryptilin or L-carnitina (uncontrolled trials)	Bortezomib: 25%-50% reduction for grade 1 with pain or grade 2 peripheral neuropathy; dose interruption until peripheral neuropathy resolves to grade 1 or better with restart at 50% dose reduction for grade 2 with pain or grade 3 peripheral neuropathy; treatment discontinuation for grade 4 peripheral neuropathy. Thalidomide: 50% reduction for grade 2 neuropathy; discontinuation for grade 3; resume Thalidomide at a decreased dose if neuropathy improves to grade 1
Cutaneous toxicity	Thalidomide, lenalidomide and combinations	Steroids and antihistamines	Interruption in case of grade 3-4 adverse events. 50% reduction in case of grade 2 adverse events.
Gastrointestinal toxicity	Thalidomide, bortezomib, and combinations	Appropriate diet, laxatives, exercise, hydration, antidiarrheic drugs	Interruption in case of grade 3-4 adverse events. 50% reduction in case of grade 2 adverse events.
Thrombosis	Thalidomide, lenalidomide, and combinations	Aspirin 100-325 mg if no or one individual/myeloma thrombotic risk factor is present. LMWH or full-dose warfarin if two or more individual/myeloma risk factors are present and in all patients who receive high-dose dexamethasone or doxorubicin or multiagent chemotherapy	Drug temporary interruption and full anticoagulation, then resume treatment.
Renal toxicity	Lenalidomide	Correct precipitant factors (dehydration, hypercalcemia, hyperuricemia, urinary infections, and concomitant use of nephrotoxic drugs)	Reduce dose according to creatinine clearance: if 30-60 mL/min: 10 mg/day, if < 30 mL/min without dialysis needing: 15 mg every other day; if < 30 mL/min and dialysis: 5 mg/day after dialysis on dialysis day

G-CSF indicates granulocyte colony-stimulating factor; HVZ, herpes-varicella-zooster; LMWH, low-molecular-weight heparin.

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Conclusions

The combination of conventional chemotherapy or low-dose dexamethasone with new drugs has substantially changed the treatment paradigm of patients with MM. Randomized studies have shown that MPT and MPV are both better than MP and can now be regarded as the standard of care for elderly patients. Preliminary results suggest that Rd, CTD, or MPR could be valid alternative options. The choice of the best treatment strategy for each patient should be based on scientific randomized studies and tailored to account for the patient's biologic age, comorbidities, and the expected toxicity profile of different regimens.

Disclosures

Conflict-of-interest disclosure: AP received honoraria from Celgene and Janssen-Cilag. FG declares no competing financial interests.

Off-label drug use: Thalidomide, lenalidomide, bortezomib.

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