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HOW I TREAT FRAGILE MYELOMA PATIENTS

Alessandra Larocca[1] and Antonio Palumbo[1]

[1]Myeloma Unit, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino; Italy.

Corresponding author:

Antonio Palumbo, Myeloma Unit, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino; Italy; tel.: +39 01 1663 5814; fax: +39 01 1696 3737; e-mail: appalumbo@yahoo.com

Introduction

Multiple myeloma (MM) is largely a disease of older adults, with a median age at diagnosis of 70 years. A consistent and continuous increase in life expectancy is recorded worldwide and the global population is rapidly aging. Consequently, the number of patients with MM is expected to considerably increase in the next future. In particular, an increase of nearly 80% of older patients diagnosed with MM each year is expected in the next two decades.[1-3]

Although effective novel agents and supportive care have substantially improved survival, patients ≥75 years have a shorter survival.[4-6] Thus, a deeper knowledge of the factors causing such poor outcomes is needed.

Aging is a complex process characterized by a gradual, progressive decrease in physiological reserve, with changes in body composition and clinically significant reductions in renal, gastric, hepatic and cardiovascular functions.[7,8] It is commonly associated with the concomitant occurrence of multiple diseases (co-morbidity),[9] and an increased risk of developing physical and cognitive decline (disability).[10,11]

In addition, older people are at high risk of developing cancer and frailty. Frailty is a state of increased vulnerability, with cumulative deficits in several physiological systems, which results into a diminished resistance to stressors, such as MM and its treatment. This state has a negative effect on patients' quality of life (QoL), and on treatment efficacy and tolerability, with a consequent increase in healthcare costs.

Approximately one third of MM patients at diagnosis are frail.[1,12] Yet, these patients are poorly characterized, underrepresented or even excluded from clinical trials due to stringent eligibility criteria, comorbidities, .[13] abnormal laboratory test results, and physical disability. Thus, frail patients usually receive regimens tested in fit patients, which may be too toxic for them and lead to early treatment discontinuation, low efficacy and poor QoL. On the contrary, fit elderly patients may receive reduced-dose treatments based solely on their age. An appropriate definition of frailty is fundamental to better assess patients and provide them with effective, tailored treatments.

Case 1. A frail patient who does not tolerate full-dose treatment with bortezomib twice weekly

A 80-year old man presented with anemia (Hb 9 g/dl) and back pain in September 2013. MM diagnosis was based on the presence of an IgA-lambda serum M-protein (2800 mg/dL) and a 70% bone marrow plasma cells invasion. By FISH analysis, deletion 13 was detected. The skeletal survey reported compressive fractures of D9, D10, D12, L1, L2, L4, and several rib fractures. The patient's medical history was significant for hypertension; his ECOG performance status was 2. In October 2013 he started treatment with bortezomib at 1.3 mg/m^2 twice weekly, oral melphalan at 9 mg/m^2 and oral prednisone at 60 mg/m^2 on days 1–4 (VMP). VMP treatment was poorly tolerated. During the second course the patient developed a

grade 2 neuropathy with pain and grade 3 thrombocytopenia requiring the interruption of treatment. ECOG performance status was 3 and the patient's QoL was seriously affected by pain, consequent insomnia, and sedation caused by analgesics. After 2 months neuropathy partially recovered to grade 1, platelet count was normal and reduced-dose VMP was restarted, including weekly bortezomib and 25% melphalan dose reduction. ECOG performance status improved to grade 1 and he was able to continue induction treatment for 9 cycles, achieving a complete response, without further toxicity.

Case 2. A frail patient who does not tolerate full-dose treatment with full-dose lenalidomide.
A 73-year old man presented with anemia (Hb 9.8 g/dl) and mild renal insufficiency (creatinine clearance 55 ml/min) in January 2010. Light chain MM diagnosis was based on the presence of Bence Jones protein (5.15 g/d) and a 40% bone marrow plasma cells invasion. No cytogenetic abnormalities were detected. The skeletal survey was negative, except for osteopenia. The patient's medical history was significant for chronic atrial fibrillation treated with flecainide, bisoprolol and oral anticoagulant therapy; his ECOG performance status was 0. Charlson comorbidity index (CCI) was 2; Activity of Daily Living (ADL) score was 6 and Instrumental Activity of Daily Living (IADL) score was 8.

In February 2010 the patient started treatment with lenalidomide 25 mg/day for 21 days and dexamethasone 40 mg/week (Rd). Full-dose lenalidomide was poorly tolerated and the patient experienced a grade 4 neutropenia (neutrophil 450/mm^3) and grade 3 thrombocytopenia (platelet 43000/mm^3), requiring interruption of treatment and anticoagulation therapy. In addition, supportive therapy with prophylactic antibiotic and G-CSF was needed. In the following days, hematological toxicity slowly recovered, and the patient was able to start the second course of Rd with reduced-dose lenalidomide 15 mg/day. The patient obtained a very good partial response and was able to continue treatment without further toxicities until progression. He relapsed in November 2014 and was then treated with bortezomib-dexamethasone (Vd), that is still ongoing.

These are two cases of frail patients treated with full-dose therapy, who experienced serious adverse events (AEs) leading to drug discontinuation, and worsening of patient's condition and QoL. After appropriate dose adjustments, both patients were able to continue treatment and achieved a good response.

Geriatric assessment
Elderly MM patients are highly heterogeneous; chronological age, performance status or clinician judgment are not sufficient to properly differentiate them. In MM, the term "frail" often refers to a person >75 years, which sometimes leads to an improper under-treatment of patients based only on age.
The geriatric assessment (GA) is a more sensitive predictor of frailty. A comprehensive GA is a systematic procedure to objectively appraise the health status of older people, focusing on somatic, functional and psychosocial domains, which enables the categorization of patients according to frailty.[14] A simplified GA that includes Katz's ADL, Lawton's IADL and CCI should be adopted. The ADL and IADL scores are used to assess self-care activities, tasks of household management and independence status; the CCI is used to estimate the number and severity of comorbidities.[15,16]
Age and GA are fundamental determinants of our approach. The cut-off age that we consider to define frail patients is 80 years.[17] However, irrespective of age, the presence of either a functional decline on ADL and IADL, or the presence of comorbidities, may identify frail patients (Table 1). Frail patients are at high risk of non-hematologic AEs and treatment discontinuation, regardless of other prognostic factors, and should be appropriately evaluated to determine their ability to tolerate treatment.

When to start treatment?

In frail patients, treatment should be delayed in case of non-specific symptoms or early-CRAB (hypercalcemia, renal failure, anemia, bone lesions) criteria, and it should be started based on the presence of confirmed late-CRAB criteria.[18-20]

Particular attention is needed with frail patients and their comorbid conditions. They may present with CRAB-like symptoms that do not lead to actual organ dysfunction and do not require immediate anti-myeloma treatment, but only a close monitoring.[21] For instance, patients may have age-related osteopenia, or mild renal impairment due to hypertension or diabetes, or mild anemia secondary to iron or vitamin deficiency, renal failure, chronic inflammatory diseases or concomitant dyserythropoietic/ myelodysplastic syndrome.

Clear clinical manifestations of serious end organ damage that can be attributed to myeloma should be considered as late-CRAB, such as a progressive worsening of serum creatinine caused by light chain cast nephropathy or a decrease in hemoglobin levels from baseline. Creatinine clearance should be considered with caution. Many of the methods used to estimate glomerular filtration rate have not been well validated at the extremes of age. For example, using the Cockcroft-Gault method, serum creatinine of 1.5 mg/dl in a patient weighing 70 Kg corresponds to an estimated glomerular filtration rate of 38 and 33 mL/min in a 80 year-old man and woman, respectively. In this case, a progressive renal impairment rather than a fixed concentration cut-off should be considered to confirm MM diagnosis.

Recently, the International Myeloma Working Group has provided updated criteria for MM diagnosis.[22] These changes are based on the identification of biomarkers associated with near inevitable development of CRAB features. They include clonal bone marrow plasma cell percentage ≥60%, involved/uninvolved serum free light chain ratio ≥100, >1 focal lesions on magnetic resonance imaging (MRI) studies. Even if no data are present about this special patient population, the assessment of these parameters may avoid organ damage that could inevitably worsen patients' condition. We use skeletal survey and low-dose computed tomography scan as routine investigations to assess bone disease. More complex investigations, such as MRI or positron emission tomography (PET), can be unnecessary on a routine basis in frail patients, and should be considered in selected cases.

Aim of therapy

The goals of care for frail patients facing a serious disease are symptom control, maintenance of independence status, and preservation of cognitive function over prolonged survival.

Although the achievement of a complete response is highly important and has become an attainable aim also in the elderly, toxicity may cancel the benefits derived from such a response.[23] Therefore, the choice of therapy should not focus on the quality of response, but rather on controlling symptoms and preventing disease progression, thus stabilizing the disease. In frail MM patients, the real goal of therapy should be to achieve and maintain the asymptomatic status for as long as possible, while preserving a good QoL. The achievement of a stable disease is an acceptable goal and therapy should not be changed.

Frail patients have a diminished resistance to stressors that may alter their physical and social status. Treatment should not cause excessive toxicities, which may lead to treatment interruption and reduced efficacy. If toxicities occur, it is likely that inappropriate drug doses are used and dose reductions are needed. Therefore, keeping the balance between disease control and toxicity is fundamental.

Therapy at diagnosis

The treatment of elderly MM patients has evolved substantially over the last decade.[12] New effective treatments including thalidomide, bortezomib and lenalidomide, have replaced the former standard MP. Today, MPT and melphalan-prednisone-bortezomib (MPV) are the reference treatments for elderly patients

ineligible for high-dose therapy.[24-31] Recently, Rd continuously was shown to be more effective than MPT at diagnosis.[32]

Of note, currently approved combinations were validated in studies that included highly selected elderly patients, and a geriatric evaluation was not performed. Frail patients are frequently underrepresented or even excluded from these trials, thus limiting the generalization of the study data.[13]

Furthermore, the major advances obtained with new drugs were limited in older patients, primarily due to an increased treatment-related toxicity. Advanced age (≥75 years), the occurrence of severe cardiac, gastrointestinal and infective AEs, and drug discontinuation predicted shorter survival in newly diagnosed MM patients treated with MP, either alone or in combination with thalidomide and/or bortezomib. This was particularly evident with the use of more complex combinations including both bortezomib and thalidomide.[33,34] Moreover, drug discontinuation due to AEs was correlated with an increased risk of death within the first six months of treatment.

These data underline the importance of avoiding treatment interruption and reducing the risk of side effects during the initial phase of therapy, thus low-dose intensity treatments should be preferred for frail patients.

Choice of initial therapy

After the diagnosis of symptomatic MM, an appropriate treatment should be determined on the basis of patient's age and GA (Table2). Frailty is an important factor affecting treatment decision. Based on the results of the GA it is possible to stratify patients into fit patients suitable for full-dose therapy with 3-drug combinations, and frail patients requiring dose-adjusted therapy.

Treatment strategies for frail patients should have minimal cumulative toxicity, which does not exacerbate any pre-existing comorbid conditions. In particular, in this setting 2-drug regimens showed similar efficacy and lower toxicity as compared to multi-drug combinations.

A recent phase 3 trial compared Rd, melphalan-prednisone-lenalidomide (MPR) and cyclophosphamide-prednisone-lenalidomide in newly diagnosed elderly MM.[35] The addition of an alkylating agent to the lenalidomide-steroid combination did not show any significant advantage in patients >75 years. In another trial, the doublet Vd proved to be less toxic and equally effective in comparison with the triplets VMP and bortezomib-thalidomide-dexamethasone in an elderly and frail population.[36]

Dosing, schedule and route of administration can make a substantial difference in the safety profile of therapy. Different trials showed that once-weekly bortezomib significantly reduced the incidence of grade 3-4 AEs (35% versus 51%) and the rate of discontinuation due to toxicity (17% versus 23%) compared with the twice-weekly schedule. In addition, bortezomib administered subcutaneously showed to be as effective as the intravenous administration; [37] this, combined with an improved safety profile, had a very positive effect on the QoL. Similarly, lenalidomide plus low-dose dexamethasone was better tolerated than lenalidomide plus high-dose dexamethasone and proved to be even more effective.[38]

In frail patients, we prefer the oral regimen Rd in case of non-aggressive disease. Bortezomib has the inconvenience of the hospitalization and the subcutaneous injection (Table 3). Lenalidomide has the advantage of the oral administration, and patients do not need to attend frequent hospital visits. In addition, Rd may be the treatment of choice in patients with pre-existing neuropathy.[32,38] We use Vd in case of aggressive disease, which needs a rapid cytoreduction and symptom control.[36,39] Similarly, in case of acute renal dysfunction, bortezomib exerts faster and more potent action, and has a greater chance of reversal of renal failure.

In frail patients we also administer modified drug doses to minimize toxicity. The initial dose of lenalidomide should not exceed 10-15 mg/day, and the dose can be adjusted based on renal function and blood counts to avoid profound and prolonged myelosuppression. In this setting, it is reasonable to use

prophylactic growth factors and antimicrobial, at fixed dose and timing, to avoid myelosuppression and infections, and to permit the patient to stay longer on treatment. A previous history of cardiovascular disease or thromboembolism does not preclude the use of lenalidomide, if an adequate thromboprophylaxis is associated.

Corticosteroids may cause elevation of blood pressure and fluid retention, and thus should be reduced, particularly in cardiopathic frail patients. Other adverse effects include hyperglycemia, gastritis, mood swings, insomnia, and increased risk of opportunistic infections. The dose of dexamethasone should be reduced to as little as 10 mg once a week. Alternatively, prednisone 25 mg every other day is a valid option. Subcutaneous weekly bortezomib can be used without dose reductions, although thrombocytopenia could be a concern.[40,41] This is especially relevant in frail patients, in whom the better tolerability may allow them to continue treatment, with a higher chance of disease control.

Bortezomib can cause peripheral neuropathy, differently from novel proteasome inhibitors.[42,43] In frail patients, the use of weekly carfilzomib and oral ixazomib and oprozomib may be implemented in the future.

A conservative approach should be suggested in frail patients: an initial gentler therapy may be used, and dose escalation may be considered in the subsequent cycles if the treatment is optimally tolerated, in the absence of significant toxicities, or in case of inadequate response.

Finally, in patients with severe impairment of cognitive function or social dependency, palliation is suggested. In these cases, we treat patients with reduced-dose corticosteroids or MP or cyclophosphamide-prednisone, to induce only a relief of disease symptoms.

Continuous treatment

Evidence of clear benefit of maintenance therapy has only recently emerged in elderly MM patients.[12,44] Continuous Rd improved progression-free survival (PFS) compared with fixed duration Rd for 18 cycles (Rd18) and significantly prolonged PFS and overall survival (OS) compared with MPT.[32] The superiority of continuous Rd over Rd18 was achieved at the expense of a modest increase in toxicity, and most toxicities occurred within the first 18 months and decreased over time. In this study, 35% of patients were >75 years, and 9% had severe renal impairment. The superiority of continuous Rd over MPT for both PFS and OS was noted also in patients >75 years. Although toxicities were more common in patients >75 years than in younger patients, there was no marked difference in AEs rates with continuous Rd and Rd18 within this age subgroup.

On the contrary, the more complex combinations melphalan–prednisone–lenalidomide followed by lenalidomide maintenance (MPR-R) compared to MPR or MP followed by placebo, was associated with a reduced rate of progression in patients 65–75 years and not in patients >75 years.[45] This observation can be explained by the increased rate of AEs associated with MPR and the need for more frequent dose modifications in patients >75 years. In that study, the major benefit on PFS was achieved with lenalidomide maintenance therapy. A landmark analysis showed that lenalidomide maintenance reduced the rate of progression by 66% as compared with placebo, regardless of age.

Maintaining an asymptomatic disease status is particularly relevant for frail patients, because advanced age and co-existing morbidities may compromise subsequent salvage therapies at disease relapse. Nevertheless, the benefits associated with continuous therapy should be balanced against the toxicity due to prolonged drug-exposure, particularly in frail patients, who are more susceptible to treatment-related toxicities. We use a continuous therapy provided that it does not cause toxicity or worsening of patient's condition. Frail patients whose disease is responding slowly and who tolerate therapy well, may benefit from maintenance therapy. However, in case of significant adverse effects, dose reductions or treatment interruption should be considered.

Treatment at relapse

In patients with asymptomatic serological relapse, treatment should be delayed. It can be started when clinical relapse, defined by the CRAB criteria, occurs; in frail patients, treatment should be initiated when symptoms and/or organ dysfunctions are imminent, or confirmed late-CRAB features are present. A significant paraprotein relapse with doubling M-component within 2 months is an indirect indicator of increasing disease.[46] In frail patients, a close monitoring of paraprotein levels is required and treatment should be started at the first sign of clinical disease progression.

Similarly to diagnosis, rather than achieving a deep response, the aim of therapy at relapse for frail patients is to maintain the disease asymptomatic and preserve the independency of patients, without an excessive toxicity.

Novel agents are the mainstay of treatment at relapse. Lenalidomide showed to be an effective option, and the addition of steroids even at low doses had a synergistic activity.[47-49] Bortezomib combined with steroids is effective and well tolerated,[50,51] particularly when the subcutaneous weekly administration is adopted.[41,52]

The patient's overall condition and the previous toxicities should be considered to determine the patient's ability to tolerate treatment and consequently to choose the appropriate treatment. Time of relapse and type of previous therapy are also fundamental aspects to take into account.

Bortezomib and lenalidomide re-treatment showed to be a valuable option, with no cumulative toxicity.[46] Re-challenge with an agent previously used may be considered, if treatment produced a substantial benefit and had an acceptable toxicity. In newly diagnosed patients, we consider re-treatment with the previous agents in case of a response lasting at least 12 months. In relapsed patients, we re-challenge with previous drugs in case of a benefit lasting at least 6 months.

In case of short-term response duration (less than 6-12 months, based on the number of previous lines of therapy) or progression while on therapy, we propose an alternative regimen.[46] Sequencing of drugs is preferable: if lenalidomide is used as front-line treatment, a drug-class switch is necessary and bortezomib may be used. In frail patients, a continuous therapy until progression could be recommended, if therapy has an acceptable long-term safety profile. Alkylator-based regimens such as low-dose cyclophosphamide-prednisone or MP or thalidomide may still play a role in frail patients relapsing after lenalidomide and bortezomib. Cyclophosphamide 50 mg every other day or melphalan 2 mg every other day or thalidomide 50 mg every other day may be used.

In case of aggressive relapse or short treatment-free interval, in frail patients with poor condition a more palliative approach is needed. In these cases, palliative care aims to optimize the comfort, function, and social support of patients and their families. To relieve the disabling myeloma-related symptoms, low doses of cyclophosphamide, melphalan, corticosteroids, or thalidomide may be used. Treatment of pain should be always introduced.

Management of toxicities

Frail patients are more susceptible to AEs and treatment interruption. Therefore, appropriate supportive care and an early identification of toxicity are needed.

Proteasome inhibitors necessitate antiviral prophylaxis for Herpes Zoster reactivation; immunomodulatory agents require an appropriate risk-based thromboprophylaxis. Corticosteroids may need gastrointestinal prophylaxis, and a more accurate glycemic control in diabetic patients should be recommended. Antibacterial prophylaxis may be warranted in case of severe myelosuppression. Neutropenia and anemia may necessitate growth factors.

A careful review of the patient's previous medications and attention to potential drug interactions are essential in frail patients.

Prompt action, particularly in frail patients, is needed when AEs occur. When a grade 3-4 toxicity occurs while on treatment, therapy should be stopped. It can be restarted when toxicity decreases to at least grade 1, and appropriate dose reductions should be applied.[12] Lenalidomide dose may be decreased from 15 to 10 mg/day, or from 10 to 5 mg/day or, if required, to 5 mg every other day on days 1-21 every 4 weeks. Bortezomib may be reduced from 1.3 mg/m^2 weekly to 1.0 mg/m^2 once weekly or even 0.7 mg/m^2 once weekly.

Emerging options and future perspectives

New targeted agents have improved the treatment options for MM. Carfilzomib is a novel keto-epoxide tetrapeptide proteasome inhibitor recently approved by the Food and Drug Administration for the treatment of relapsed/refractory MM in patients previously treated with bortezomib and lenalidomide. The most common grade 3-4 AEs reported with this agent were fatigue, anemia, nausea, and thrombocytopenia; peripheral neuropathy was mainly limited to grade 1-2. In a recent phase 3 study, carfilzomib plus lenalidomide-dexamethasone showed to be more effective than lenalidomide-dexamethasone.[53] Carfilzomib showed to be effective also in newly diagnosed patients.[54,55]

Ixazomib (MLN9708) is another novel proteasome inhibitor that showed promising results in both relapsed and newly diagnosed settings. Two phase 2 studies are evaluating oral ixazomib as monotherapy in relapsed/refractory patients previously exposed to proteasome inhibitors, and one trial has adopted a weekly administration of the drug.[56] The most frequent AEs included thrombocytopenia, fatigue, nausea and diarrhea.[57] Positive results were also reported in a phase 1/2 study evaluated weekly ixazomib in combination with lenalidomide-dexamethasone in newly diagnosed myeloma patients followed by maintenance with ixazomib alone.[58]

Oprozomib is a carfilzomib structural analog orally available, it has been tested in a phase 1b/2 trial including also patients with relapsed MM. The most common grade 3-4 toxicities included diarrhea, nausea, neutropenia, hypophosphatemia, thrombocytopenia, vomiting and fatigue.[59]

The monoclonal antibodies elotuzumab and daratumumab are other promising agents. Daratumumab is an anti-CD38 monoclonal antibody. Infusion reactions were the most common toxicity.[60-62] Elotuzumab is an anti-CS1 fully humanized monoclonal antibody. Elotuzumab was not so effective as monotherapy, and treatment-related toxicities were largely limited to grade 1-2 infusion reactions.[63] In two phase 1 studies elotuzumab plus bortezomib or plus lenalidomide and low-dose dexamethasone showed to be effective. Two phase 3 trials are comparing elotuzumab plus lenalidomide-dexamethasone versus lenalidomide-dexamethasone in relapsed and newly diagnosed patients.

Based on the results available, in frail patients, weekly carfilzomib can be a valuable option because of the reduced toxicity. Ixazomib can be suggested because of the low toxicity and the advantage of the oral administration. Elotuzumab and daratumumab are effective options and have a very good tolerability.

Conclusion

The growing number of older adults with myeloma is increasing the need for practical strategies to recognize and appropriately manage frail patients and to avoid undertreatment of fit patients and overtreatment of frail ones. The GA is the most adequate tool and it should be introduced in everyday clinical practice.

Frail patients need effective tailored treatments to better control the disease while minimizing the risk of toxicity and treatment discontinuation. Improving survival may not be the primary goal of therapy in frail patients. The real aim in this setting should be to keep patients asymptomatic as long as possible, preserve their functional status and independence, and improve their QoL.

The selection of therapy should be based on the risk of toxicity and the capacity of patients to tolerate treatment. Lenalidomide and bortezomib have an essential role in the treatment of frail patients. Two-drug regimens including low-dose steroid in combination with lenalidomide or bortezomib are indicated. Second generation proteasome inhibitors or immunomodulatory drugs or even monoclonal antibodies, are potential candidates to improve the care of frail patients with MM in the future.

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Table 1. Geriatric assessment to determine frailty status of elderly patients with MM.

		Score
Age	≤ 75 years	0

Geriatric assessment		
	76-80 years	1
	> 80 years	2
	ADL	
	>4	0
	≤4	1
	IADL	
	>5	0
	≤5	1
	CCI	
	≤1	0
	≥2	1

Additive total score	Patient status
≥2	Frail

ADL, Activity of Daily Living; IADL, Instrumental Activity of Daily Living; CCI, Charlson Comorbidity Index.

Adapted from Palumbo A, et al. *Geriatric assessment predicts survival and toxicities in elderly myeloma: an International Myeloma Working Group report*. Blood 2015.

Table 2

Factors to consider in clinical decision-making in frail patients with MM	
Age Geriatric assessment	To assess frailty

Late-CRAB criteria
  Calcemia
  Renal failure
  Anemia
  Bone lesions
	To start treatment

Cardiovascular history History of diabetes Renal function Neuropathy Psyco-social status	To choose treatment

Table 3. Treatment strategy in frail patients with myeloma

Frontline treatment	Second-line treatment	Following lines of treatment
Lenalidomide-steroid R:* 10-15 mg/d, days 1-21 d: 10 mg/d once weekly *or* P: 25 mg/d every other day	**Bortezomib- steroid** V: 1.3 mg/m^2 once weekly d: 10 mg/d once weekly *or* P: 25 mg/d every other day	**Melphalan-prednisone** M: 2 mg every other day P: 25 mg/d every other day
Bortezomib- steroid V: 1.3 mg/m^2 once weekly d: 10 mg/d once weekly *or* P: 25 mg/d every other day	**Lenalidomide- steroid** R:* 10-15 mg/d, days 1-21 d: 10 mg/d once weekly *or* P: 25 mg/d every other day	**Cyclophosphamide-prednisone** C: 50 mg every other day P: 25 mg/d every other day
	Re-treatment	**Thalidomide-prednisone** T: 50 mg every other day P: 25 mg/d every other day

R, lenalidomide; d, dexamethasone; V, bortezomib; P, prednisone; C, cyclophosphamide; T, Thalidomide;*or according to renal function.