First-line treatment of non-transplant eligible multiple myeloma patients

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SUMMARY

Multiple Myeloma (MM) is mainly a disease of the elderly. In 2018 bortezomib-melphalan-prednisone (VMP) and lenalidomide-dexamethasone (Rd) are the established standard of care first-line regimens. Before starting therapy, an accurate evaluation of the frailty of patients is needed which allows physicians to individualize the approach for the individual patient.

INTRODUCTION

Multiple myeloma (MM) is mainly a disease of the elderly, with a median age at diagnosis of 70 years[1]. In general, elderly MM patients are defined as being transplant ineligible. Although they were generally not included in clinical trials evaluating autologous stem cell transplantation (ASCT), fit elderly patients between 65 and 70 years of age may also benefit from this approach.[2] Since the last decade, the prognosis of elderly patients improved due to the use of new drugs, including immunomodulatory drugs (IMID's) and proteasome inhibitors (PI) but the clinical benefit obtained with these treatment modalities in the elderly setting are less pronounced than what is seen in young patients[3].

FRONTLINE TREATMENT

IMID-BASED TREATMENT REGIMENS

In the FIRST trial, lenalidomide in combination with low-dose dexamethasone (Rd) given till progression or for a total of 18 months was compared to a combination of melphalan-prednisone-thalidomide (MPT). In this trial, the median progression-free survival (PFS) proved to be superior with Rd continuously and the overall survival (OS) was significantly improved in the two Rd treatment arms. Based on these findings, MPT is no longer considered as a standard of care.[4]
The MM-015 trial compared melphalan-prednisone-lenalidomide (MPR) induction followed by lenalidomide maintenance (MPR-R) with MPR or melphalan-prednisone (MP) followed by placebo in patients 65 years of age or older with newly diagnosed MM. This trial revealed that MPR without R maintenance does not improve the PFS and OS compared to MP, indicating the need for R maintenance.[5]
Based on the results of several randomized trials, Rd has become the backbone for several triplet regimens. In the SWOG S0777 trial, bortezomib plus Rd (VRd) proved to be superior to Rd in terms of PFS and OS.[6] Results of studies comparing Rd with daratumumab-Rd (MAIA trial), elotuzumab-Rd (ELOQUENT), ixazomib-Rd (TOURMALINE) and carfilzomib-Rd will be presented in the years to come.
Importantly, Rd represents a very convenient all oral treatment regimen. However, antithrombotic prophylaxis is mandatory, as well as dose adaptation for non-fit patients and in case of renal impairment.[4]

PROTEASOME INHIBITOR (BORTEZOMIB) BASED REGIMENS

The VISTA study compared the use of melphalan and prednisone (MP) with or without bortezomib (VMP) in previously untreated patients with MM who were ineligible for high-dose therapy. In this trial, VMP was associated with a significant benefit compared to MP in terms of time to progression (TTP) and OS.[7]
The main toxicity associated with VMP is sensory peripheral neuropathy. The incidence of this adverse event can safely be reduced with subcutaneous administration, with a once weekly administration of the treatment and with careful monitoring and dose adaptation. With this type of therapy,

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Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

TABLE 1. Common induction regimens for transplant-ineligible MM patients.

Combination	Schedule	≥PR	≥VGPR	Median PFS	3y-OS
VMP [7]	Bortezomib: 1.3 mg/m² sq days 1, 4, 8, 11, 22, 25, 29, 32 for first four 6-week cycles, then days 1, 8, 15, 22 for subsequent five 6-week cycles Melphalan: 9 mg/m² orally days 1-4 Prednisone: 60 mg/m² orally days 1-4	71%	30%(CR)	22 months	41%
Once-weekly VMP [8]	Bortezomib: 1.3 mg/m² sq days 1, 8, 15, 22 for 5-week cycles Melphalan: 9 mg/m² orally days 1-4 Prednisone: 60 mg/m² orally days 1-4	85%	55%	33.1 months	88%
VCD [9]	Bortezomib 1.3 mg/m² IV or sq days 1,8,15,22 Cyclophosphamide 300 mg/m² orally days 1,8,15 Dexamethasone 40 mg orally days 1,8,15,22 28-day cycles	88%	71%	NA	NA
Continuous Rd [4]	Lenalidomide 25mg days 1-21 Dexamethasone 40mg days 1,8,15,22 of each 4-week cycle	75%	44%	25.5 months	70%
VRd [6]	Bortezomib, 1.3 mg/m² sq days 1,8,15 Lenalidomide 25 mg orally days 1-21 Dexamethasone 20mg days 1,2,8,9,15,16 every 3 weeks	81.5%	27.8%	43 months	Median OS: 75 months

C: cyclophosphamide; CR: complete response; d: low-dose dexamethasone; D: high-dose dexamethasone; m: months; M: melphalan; OS: overall survival; P: prednisone; PFS: progression-free survival; PR: partial response; R: lenalidomide; T: thalidomide; V: bortezomib; VGPR: very good partial response

thrombosis prophylaxis is not necessary, unless otherwise justified. VMP is often preferred in case of renal impairment, severe thrombotic history or contra-indication to anticoagulation.[8] In addition to VMP, VCD (bortezomib-cyclophosphamide-dexamethasone) is also being used.[9]

In the recently reported ALCYONE trial, the addition of the anti-CD38 monoclonal antibody daratumumab to VMP reduces the risk of progression of 50% with no major safety signals.[10]

HOW TO CHOOSE THE BEST TREATMENT, TAKING INTO ACCOUNT THE VULNERABILITY OF THE PATIENT?

The ultimate aim of therapy is to achieve the maximum durable response with minimal treatment related toxicities, while preserving the quality of life of patients[11] Unfortunately, very elderly patients benefit of the recent advances in therapy to a lesser extent than younger patients. The main reason for this is that most of them are more vulnerable (comorbidities, disabilities) and this frailty results in more treatment-related adverse events which often leads to reduced treatment efficacy and therapy discontinuation.[3,11]

The International Myeloma Working Group (IMWG) developed a frailty score based on age, ADL, IADL (scores of activity daily living and instrumental ADL) and CCI (comorbidities Charlson index) (*Table 2*).[11,12] Based on this score, one can tailor the intensity of therapy to the individual patient and dose reductions are proposed. Currently, a BHS MM observational trial is ongoing in Belgium, to assess the value of these tools in the real-life setting.[13]

CONCLUSION

The majority of new diagnosed MM patients are elderly patients who are not eligible for an ASCT. The care for these patients is challenging and should take into account the vulnerability of patients in order to maximize the response while minimising toxicity.[11] The current standard of care front-line treatment regimens in this setting are VMP and Rd,

TABLE 2. Frailty score and associated dose modifications for tailored therapy in newly diagnosed MM patients aged 65 years or more. (Adapted from *Palumbo et al.* and *Kint et al.*).[5,11]

International Myeloma Working Group Frailty Score Age < 75 y:0; 75-80y: 1; >80y: 2 CCI-score ≤1: 0; ≥2: 1 ADL > 4: 0; ≤4: 1 IADL > 5: 0; ≤5: 1	Frailty scores		
	Fit (total score = 0)	Intermediate fitness (total score = 1)	Frail (total score ³ 2)
Recommended therapy - Other options	Standard (twice-weekly) VMP, Rd - VTD, VRD, VCD (up to 8 cy) - Stem cell transplantation for selected patients	Once-weekly VMP, Rd, Vd	Rd - MR, CP - Palliative care
Dose modifications			
Dexamethasone (d)	40 mg	20 mg per week	10 mg per week
Melphalan (M)	0.25 mg/kg on day 1-4 q 4-6 wks	0.18 mg/kg on days 1-4 q4-6 wks	0.13 mg/kg on days 1-4 q4-6 wks
Thalidomide (T)	100 mg/day	50 mg/day	50 mg qod
Lenalidomide (R)	25 mg, days 1-21 q4 wks	25 or 15 mg days 1-21 q4 wks	10 mg days 1-21 q4 wks
Bortezomib (V)	1.3 mg/m² twice weekly	1.3 mg/m² once weekly	1.0 mg/m² once weekly
Prednisone (P)	60 mg/m² days 1-4	30 mg/m² days 1-4	15 mg/m² days 1-4
Cyclophosphamide (C)	300 mg/m² days, 1, 8, 15 q4w	150 mg/m²	75 mg/m²

but it is to be expected that combinations of these treatment backbones with novel agents will challenge this standard in the near future.[4,6,7,10] The assessment of patient frailty and an interdisciplinary approach should be used to tailor the treatment to the individual patient and form the keys to optimize the treatment.

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