Management of multiple myeloma in the newly diagnosed patient

María-Victoria Mateos[1] *and Jesús F. San Miguel*[2]

[1]*Hospital Universitario de Salamanca-Instituto Biosanitario de Salamanca, Salamanca, Spain; and* [2]*Clínica Universidad de Navarra, Centro de Investigación Médica Aplicada, Navarra, Spain*

Multiple myeloma is the second most frequent hematological disease. The introduction of melphalan as high-dose therapy followed by autologous hematopoietic cell transplantation (HDT/ASCT) for young patients and the availability of novel agents for young and elderly patients with multiple myeloma have dramatically changed the perspective of treatment. However, further research is necessary if we want definitively to cure the disease. Treatment goals for transplant-eligible and non–transplant-eligible patients should be to prolong survival by achieving the best possible response while ensuring quality of life. For young patients, HDT-ASCT is a standard of care for treatment, and its efficacy has been enhanced and challenged by the new drugs. For elderly patients, treatment options were once limited to alkylators, but new upfront treatment combinations based on novel agents (proteasome inhibitors and immunomodulatory drugs) combined or not with alkylators have significantly improved outcomes. Extended treatment of young and elderly patients improves the quality and duration of clinical responses; however, the optimal scheme, appropriate doses, and duration of long-term therapy have not yet been fully determined. This review summarizes progress in the treatment of patients with newly diagnosed multiple myeloma, addressing critical questions such as the optimal induction, early vs late ASCT, consolidation and/or maintenance for young patients, and how we can choose the best treatment option for non–transplant-eligible patients.

Learning Objectives

- To consider a systematic approach for the diagnosis and treatment of newly diagnosed myeloma patients
- To take into account all relevant data considering the efficacy, safety, patient condition, and available options in order to make the optimal treatment choice for transplant and non–transplant-eligible patients in real life
- To investigate future treatment options for this population by considering the clinical results of investigational drugs currently in trial

Introduction

Multiple myeloma (MM) is a neoplastic plasma cell disorder characterized by clonal proliferation of malignant plasma cells in the bone marrow and usually monoclonal protein in the blood and/or urine. It is associated with end-organ damage consisting of anemia, renal insufficiency, bone lesions, and/or hypercalcemia, and the International Myeloma Working Group updated the definition to include validated biomarkers present in patients without end-organ damage, but associated with 80% risk of progression to active disease within the first 2 years since diagnosis (i.e., near-inevitable development of end-organ damage, clonal bone marrow plasma cell percentage $\geq$60%, involved/uninvolved serum free light chain ratio $\geq$100, or $>$1 focal lesion on magnetic resonance imaging studies).[1]

MM is the second most frequent hematological neoplastic disease after non-Hodgkin lymphoma and comprises 1% of all cancers and 10% of hematological malignancies. It primarily affects older individuals; the median age at the time of diagnosis is 70 years, and two-thirds of MM patients are $>$65 years when first diagnosed.

The outcome of MM patients has significantly improved in the recent century. Initially, the benefit was mainly accrued by young patients and was based on the introduction of high-dose therapy followed by autologous stem cell transplantation (HDT-ASCT) using upfront and novel agents at the moment of relapse of disease progression. More recently, the use of these novel agents in the upfront setting before HDT-ASCT, especially in elderly patients, has also resulted in a significant benefit with respect to outcome. A better understanding of disease heterogeneity has also contributed to this improvement, so risk assessment is a critical aspect of the diagnostic evaluation, as it informs prognostication and influences treatment decisions.[2]

The optimal treatment approach for both young and elderly newly diagnosed MM patients should provide a good balance of efficacy and safety against costs, and quality of life should also be evaluated, since this is not captured by the response criteria. We can now identify during the initial workup biomarkers that can help identify high-risk MM patients. These high-risk features include patient-specific factors (old age, poor performance status, and comorbidities), clinical features (primary plasma cell leukemia and extramedullary disease), or

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Off-label drug use: Carfilzomib, ixazomib, pomalidomide, and daratumumab are not approved to be used in the upfront setting.

disease-specific biological features (cytogenetics abnormalities such as deletion 17p, translocation (4;14), and high-risk expression profiling signatures) able to identify patients with a survival <3 years. However, it may be too early to develop a treatment algorithm based on risk stratification, as the prospective data are limited.

The novel agent–based combinations are resulting in deeper and longer remissions, and we also need optimized tools to monitor our patients (e.g., minimal residual disease [MRD] assessments and novel imaging techniques) in parallel with the development of new drugs in order to offer personalized and optimized treatment. It is well established that depth of response is one of the most important prognostic factors in MM and that the achievement of deep remissions represents a therapeutic goal for a significant fraction of MM patients.[3] As this topic will be addressed in other chapters of this educational book, we will then focus on the current treatment algorithm for patients, discussing the options for newly diagnosed MM patients.

Therapeutic options for transplant-eligible patients

General management

At the present time, transplant eligibility is guided by biological age, performance status, and comorbidities. The International Myeloma Working Group introduced a frailty score but mainly focused on elderly patients. A German group recently validated a revised Myeloma Comorbidity Index in a large series of patients with MM as a valid prognostic instrument that might be considered as an integral part in the development of individualized risk-adapted therapy.[4]

The general approach for these patients includes induction therapy that is typically administered over a 4- to 6-month period prior to HDT-ASCT or, alternatively, storing stem cells and deferring transplant. Patients who opt against immediate HDT-ASCT can proceed to maintenance therapy until disease progression. Patients who proceed to HDT-ASCT can potentially receive a second consolidation followed by maintenance therapy.

What is the optimal induction regimen? Comparing 2-, 3- and 4-drug combinations

Comparison of the efficacy of different induction regimens is usually done in terms of response rate, because the final outcome is influenced by the consolidations and/or maintenance approaches. Thalidomide, bortezomib, and lenalidomide have all been used in conjunction with dexamethasone in 2-drug combination regimens, producing a higher overall response rate than conventional chemotherapy. However, the complete response (CR) rate was low, and the induction regimens based on 2 drugs are suboptimal. The best results have been obtained with the addition of a third drug to bortezomib and dexamethasone, while other triple combinations (such as thalidomide, Adriamycin, and dexamethasone or cyclophosphamide, thalidomide, and dexamethasone [CTD]) have been less effective.[5]

The bortezomib, thalidomide, and dexamethasone (VTD) regimen has been investigated in 3 randomized phase 3 trials.[6-8] The Italian GIMEMA group,[6] using induction with 3 cycles of VTD, obtained a pretransplant CR rate of 19% compared with the 35% CR obtained from the 6 induction cycles of the Spanish PETHEMA trial.[7] By contrast, in a French trial[8] using 4 cycles of VTD with reduced doses of bortezomib and thalidomide, the pretransplant CR was only 13%, and the same CR rate was reported in another French trial using 4 cycles of VTD with full doses of bortezomib.[9] Thus, dose intensity and exposure to bortezomib-containing regimens seem to be crucial for obtaining high-quality responses. Moreover, in the Spanish study (where 6 cycles of induction with VTD were administered), a significant proportion of the patients who finally achieved CR did so during the final 3 cycles. Obviously, the benefit in terms of response must be weighed against its greater toxicity. The Italian group reported 10% grade 3 peripheral neuropathy (PN) with 3 induction cycles of VTD. The Spanish group (which administered 6 cycles of VTD) reported 14% grade 3-4 PN. The French group reported only 3% grade 3 PN when using 4 cycles of "mini-VTD" and 7% with the 4 cycles of "full VTD." It is of note that the incidence of PN could be reduced by using subcutaneous bortezomib.[10]

The replacement of thalidomide by lenalidomide in the VTD regimen (lenalidomide, bortezomib, and dexamethasone [VRD]) was evaluated in an attempt to increase the efficacy and reduce toxicity. The EVOLUTION trial, which included VRD in 1 arm, achieved a pretransplant CR rate of 24%.[11] Two other phase 2 trials evaluated this combination and recorded CR rates between 23% and 29%.[12,13] The Spanish PETHEMA group is also testing the efficacy of 6 cycles of VRD as an induction pretransplant regimen in a phase 3 trial, and the French IFM2009 trial tested VRD as 3 induction cycles in a series of 700 newly diagnosed MM patients followed by either HDT-ASCT or 5 additional VRD cycles, resulting in a complete plus very good partial response (VGPR) rate of 47%.[14]

Other bortezomib-based combinations, such as bortezomib and dexamethasone plus cyclophosphamide (VCD), have been evaluated. VCD was inferior to VTD as induction prior to HDT-ASCT in terms of overall response rate (83% vs 92%) and VGPR rate or better (56% vs 66%) in the French IFM2013-04 trial, but the main weakness of this trial is that neither progression-free survival (PFS) nor overall survival (OS) was assessed.[9] Cavo et al presented a matched-pair analysis comparing VTD with VCD in which the triplet VTD induction therapy was associated with significantly higher CR (19% vs 7%).[15] Thus, the efficacy of VTD is superior to VCD in terms of response rate, but we do not know how this translates in terms of outcome.

The new proteasome inhibitor (PI) carfilzomib has been tested as a pretransplant induction in some phase 2 trials with preliminary results. Carfilzomib plus thalidomide and dexamethasone resulted in an 18% CR rate after 4 induction cycles, and the maximum tolerated dose of carfilzomib was not reached using up to 56 mg/m^2.[16] The results of the combination of carfilzomib, lenalidomide, and dexamethasone as a pretransplant induction regimen are promising pending confirmation in large trials. This regimen has been evaluated in 2 different trials, and the CR rate was 16% and 11% after 4 cycles in the Zimmerman et al[17] and Roussel et al[18] trials, respectively. In all of these studies, the dose was 36 mg/m^2, and the toxicity profile was acceptable, with cardiovascular events of grade 3-4 present in no more than 10% (with the exception of the study by Roussel et al), but the definition of cardiovascular events was not homogeneous. Ixazomib as an oral PI was tested in a phase 2 trial, also in combination with lenalidomide and dexamethasone (Rd), and 4 cycles of ixazomib, lenalidomide, and dexamethasone resulted in a CR rate of 12% in a series of 42 patients.[19]

Four-drug combinations as an induction regimen have also been investigated. The results of the randomized EVOLUTION trial comparing VRD plus cyclophosphamide, VRD, and VCD, and the

Table 1. Three-drug–based combinations evaluated as induction, incorporating IMiDs or PIs, followed by HDT-ASCT

Reference	Regimen	CR pretransplant	ORR pretransplant	CR posttransplant	ORR posttransplant
6	VTD vs TD (3 cycles)	19 vs 5% ($P < .0001$)	93 vs 79% ($P < .0001$)	38 vs 23% ($P = .0004$)	93 vs 84% ($P = .0025$)
8	VTD vs TD (4 cycles)	13 vs 12 (P = NS)	88 vs 81% (P = NS)	31 vs 33% (P = NS)	89 vs 86% (P = NS)
7	VTD vs TD vs VBMCP/VBAD/B (6 cycles)	35 vs 14 vs 21%*	85 vs 62 vs 75%†	46 vs 24 vs 38%‡	77 vs 57 vs 73%‡
36	PAD vs VAD (3 cycles)	7 vs 2% ($P < .001$)	78 vs 5 ($P < .001$)	21 vs 9% ($P < .001$)	88 vs 75 ($P < .001$)
15§	VTD vs VCD	19 vs 7%	93 vs 89%	NA	NA
9	VTD vs VCD (4 cycles)	66.3 vs 56.2% (VGPR) ($P = .05$)	92.3 vs 83.4% ($P = .01$)	NA	NA
13	VRD (3 cycles)	23%	Not available	42%	NA
14	VRD (3 cycles)	46% (CR + VGPR)	Not available	88% (CR + VGPR)	NA
16	KTD (4 cycles)	18%	94%	31%	NA
17	KRd (4 cycles)	16%	73% (≥VGPR)	27%	90% (≥VGPR)
18	KRd (4 cycles)	11%	47% (≥VGPR)	19%	56% (≥VGPR)
19	IRd (4 cycles)	11.9%	38% (≥VGPR)	18.9%	70% (≥VGPR)

IRd, ixazomib, lenalidomide, and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; KTD, carfilzomib, lenalidomide, and dexamethasone; NA, not available; NS, not significant; ORR, overall response rate; PAD, bortezomib, adriamycin, and dexamethasone; TD, thalidomide and dexamethasone; VBCMP/VBAD, vincristine, BCNU, cyclophosphamide, melphalan, prednisone, adriamycin, dexamethasone.
*VTD vs TD, $P = .0001$; VTD vs VBMCP/VBAD/B, $P = .01$.
†VTD vs TD, $P = .0001$; VTD vs VBMCP/VBAD/B, $P = .06$.
‡VTD vs TD, $P = .0001$; VTD vs VBMCP/VBAD/B, $P = .01$.
§Matched-pair analysis.

nonrandomized CYCLONE trial[20] with cyclophosphamide plus carfilzomib, thalidomide, and dexamethasone, showed no substantial advantage over 3-drug combinations. Likewise, Ludwig et al[21] conducted a phase 2 randomized trial to compare the 3-drug combination of VTD with VTD plus cyclophosphamide and found identical efficacy in the 2 arms but a higher frequency of adverse and serious adverse events for the 4-drug combination. However, with the introduction of monoclonal antibodies, the door to use 4-drug combinations has been opened; the combination VTD plus the CD38 monoclonal antibody daratumumab was shown to be feasible in a cohort of 11 patients, and it is being tested in a phase 3 trial and compared with VTD alone. Elotuzumab has been also added to VRD to evaluate feasibility, and a trial is currently ongoing for patients with high-risk features. Panobinostat was also added to VRD, and the preliminary results suggest that it is safe and effective.

How to choose the induction regimen

After the presentation of the different regimens, the results to date show that most MM patients will respond to triple combinations, with at least one-third achieving CR after 4 to 6 induction cycles (Table 1). Based on the previously reported results, the triplet combination should include a PI and dexamethasone. The election of the third drug must take into account various factors, including prognostic factors; the nature and extent of MM-associated organ impairment; the presence of comorbid conditions such as PN, diabetes, or heart failure; as well as patient preferences and resources and availability in different countries. The triplets combining PI, immunomodulatory drugs (IMiDs), and dexamethasone, VTD, or VRD seem to be the optimal choice, effective in both standard and high-risk patients, with good tolerability; VCD would also be appropriate, especially if IMiDs are not available or comorbid conditions make its use not possible.

Upfront vs delayed HDT-ASCT

Before the introduction of novel agents, HDT-ASCT was considered the standard approach for young patients with newly diagnosed MM, although only 2 of 5 randomised clinical trials comparing conventional chemotherapy and ASCT showed a survival advantage.[2] With the introduction of novel agents and the achievement of a high response rate, the role of HDT-ASCT as a component of front-line therapy was again a matter of debate.

HDT-ASCT after induction with novel agent–based regimens can increase the CR rate by an average of 15% to 20%. After VTD as induction, the posttransplant CRs after single and tandem transplants were 38% and 49%, respectively, in an Italian trial.[6] In Spanish[7] and French[8] trials, the posttransplant CR rates were 46% and 29%, respectively. The higher CR rates translated into a median PFS of ~5 years, which was reproduced in the Italian and Spanish trials. After VRD as induction, in the Roussel et al trial,[13] the CR rate after single HDT-ASCT was 42%; in the IFM2009 trial, the complete plus VGPR rate after transplant was 88%, and MRD was not detected in 79% of patients.[14] The trials that incorporated carfilzomib as part of the induction also showed how the CR rate increased from 11% after induction to 19% in the French trial.[18] Rd as induction resulted in a 12% CR rate, and HDT-ASCT increased this rate to 19%[19] (Table 1).

Although HDT-ASCT after induction with novel agents seems to be a complementary rather than alternative strategy, the question has been prospectively addressed in some large phase 3 trials. The Italian group has reported the results of 2 trials[22,23] (one of them international and in collaboration with other countries) showing better outcome in terms of PFS (42 vs 24 months for combined studies) and 4-year OS (84% vs 70%) with HDT-ASCT compared with nontransplant, both in the setting of IMiD-based induction and consolidation therapy, so the patients were never exposed to PIs, which represents an important limitation. The EMN/HO95 MM trial[24] recently showed that HDT-ASCT resulted in a significantly longer PFS (not reached) than nontransplant (44 months), but in the setting of PI drug–based induction (VCD) and consolidation therapy (bortezomib, melphalan, and prednisone [VMP]) in this trial. Although the comparison of upfront vs delayed transplant has been planned in 2 of the previous studies, in the Gay et al study,[23] only

53 patients (43%) in the nontransplant arm upfront received it at relapse, so it is difficult to reach conclusions; results of the EMN/HOV95 trial are not available yet. At the present time, we have the results of the phase 3 randomized IFM2009 trial[14] that evaluated this approach, and a significant benefit for VRD as induction followed by HDT-ASCT in comparison with VRD as induction and consolidation was reported in terms of PFS (50 vs 36 months). Transplantation was also associated with higher CR rate and a lower rate of MRD detection, but the OS was similar in the 2 treatment groups. Transplant at relapse was done in 79% of the patients who relapsed in the VRD arm, and the results of this trial suggest that delayed transplant is feasible and associated with no decrement in OS. However, it is important to note that the median follow-up was too short to reach conclusions in terms of survival. Some subanalyses have shown that more patients in the transplant arm achieved MRD-negative status, and this status translated into a significant benefit in terms of OS.

In summary, if patients receive an optimal induction regimen like VRD, although HDT-ASCT upfront is superior to consolidation with new agents followed by transplant at relapse in terms PFS, the absence of benefit in OS makes possible to evaluate the transplant upfront, either in the context of the risk of toxic effects associated with transplant (especially for young patients with some comorbidities) or in the context of patient preferences. However, in the future, the MRD status will be incorporated into treatment algorithms in order to tailor treatment and improve outcomes.

Single or double HDT-ASCT

The role of double transplant is not well consolidated. At least 5 randomized trials were conducted in the era of conventional agents, and the general consensus was to perform it for those patients who failed to achieve at least VGPR after the first transplant.[2] This concept has been revisited after the introduction of novel agents and in the recent trial by Gay et al.[23] The second transplant was conducted according to the policy of each center; those patients who received the tandem transplant had a significant benefit in terms of PFS. In the EMN/HO95 trial, patients were also allowed to receive a second transplant, and the patients in whom this procedure was done had a significantly longer PFS than those who underwent single HDT-ASCT (hazard ratio, 0.7; $P = .05$). The benefit was observed for patients with high-risk cytogenetic abnormalities (hazard ratio, 0.45; $P = .04$), and double transplant emerged as an independent prognostic factor predicting PFS.[25] A large meta-analysis of 4 European cooperative groups (IFM, GIMEMA, PETHEMA, and HOVON/GMMG) compared single vs tandem HDT-ASCT, and a benefit in favor of tandem HDT-ASCT was reported with respect to PFS and OS in patients with high-risk cytogenetic abnormalities.[26] These results should be cautiously interpreted because of the short follow-up for the EMN/HO95 trial and because the design of the trial was not powered to answer to this question; the meta-analysis for the European cooperative study should also confirm the results with longer follow-up. A prospective phase 3 trial (BMT CTN 0702)[27] conducted in the United States compared tandem HDT-ASCT plus maintenance therapy with the strategy of single HDT-ASCT plus consolidation and maintenance or single HDT-ASCT plus maintenance therapy. There was no significant difference in terms of either PFS or OS among the 3 arms, with a median PFS of ~55 months and >80% of patients alive at 3 years. These results were confirmed in both groups of patients with standard and high-risk cytogenetic abnormalities. Although the results seem to be contradictory to those previously mentioned, longer follow-up is required, as well as subanalysis of the outcome according to the induction regimen or the response achieved after transplant. Some questions need to be clarified, such why some patients required >12 cycles of induction before proceeding to the first transplant or why 32% and 18% patients did not receive the second HDT-ASCT and consolidation, respectively, as planned.

Posttransplant strategies: consolidation and/or maintenance

Posttransplant strategies (consolidation and maintenance) were developed with the aim of extending the duration of the response and prolonging PFS and, ultimately, OS. While consolidation means administering 2 to 4 cycles after transplant or a second transplant with the objective of improving the quality of the response, maintenance consists of the administration of reduced-intensity treatments on a continuous, long-term basis with the dual purpose of boosting and stabilizing the previously achieved response.

Consolidation posttransplant. Over the past few years, all consolidation trials were phase 2 trials showing that consolidation with the same scheme given at induction resulted in an upgrading of the quality of response by 30%.[2] However, the EMN/HO95 and Stamina trials, 2 phase 3 randomized trials with preliminary results, have just introduced debate about consolidation after induction and HDT-ASCT. Sonneveld et al[28] showed a significant prolongation of the PFS for patients randomized to consolidation with VRD vs no consolidation, while Stadtmauer et al[27] did not report any significant benefit in PFS for consolidation with either second transplant or 3 cycles of VRD. The trials were different in terms of design. Of note, patients in the EMN/HO95 trial had never been exposed to IMiDs, while in the Stamina trial, at least 50% of patients had received VRD as induction. The lack of benefit in OS in both studies was influenced by the follow-up as well as by the maintenance given to all patients in both trials.

The second-generation PIs carfilzomib and ixazomib are being evaluated in phase 2 trials as early and late consolidation after induction and HDT-ASCT with encouraging results, although these strategies need to be evaluated in the context of phase 3 trials.

In summary, the role of consolidation posttransplant with either second transplant or regimens similar to those given during the induction is not well established, and additional subanalysis and longer follow-up are required. One hypothesis might be that patients receiving optimal induction with PIs and IMiDs plus monoclonal antibodies in the future followed by transplant and maintenance do not need any consolidation.

Maintenance. It is generally accepted that the PFS and OS benefits for MM patients mainly arise from first-line therapy. Thus, maintaining the response aims to extend the duration of the response through continued treatment, thereby prolonging PFS and OS. Table 2 summarizes the design and results of maintenance post–HDT-ASCT in the available phase 3 clinical trials, and after its revision, it is appropriate to raise the following questions: (1) Does maintenance therapy meet the objective of prolonging the duration of the response? The answer is probably yes, because it has been shown that maintenance can extend the duration of the response previously achieved after induction followed or not by HDT-ASCT and applies to the different options. (2) What is the optimal drug to use as maintenance? Lenalidomide as continuous therapy is the unique new agent approved in European Union and United States based on the

Table 2. Summary of the efficacy and safety results of maintenance in MM after HDT-ASCT in transplant-eligible patients

Reference	n	Trial and follow-up	Maintenance	Response upgrade	PFS/EFS	Survival	Tolerance and additional data
14	614	IFM 2005/02 45 mo	A: Len, 10-15 mg/d × 21 d until PD*; B: placebo	A: CR 29%; B: CR 27%	First data: A, PFS 41 mo ($P < .001$); B, PFS 23 mo; update (64 mo of follow-up): A, 5-y PFS2 ~60% ($P < .07$); B, 5-y PFS2 ~53%	30 mo: 3-y A 80% vs B 88% ($P = .2$); 45 mo: 4-y A 73% vs 75% ($P = .7$); 67 mo: A 82 mo vs B 80 mo ($P = .8$)	A: discontinuations for DRAEs, 21%; maintenance improved the rate of CR and VGPR ($P = .009$); PFS maintenance benefit in 13 q deletion t(4-14) or 17 p deletion cases; reduced survival after first progression (29 vs 48 mo); 2.4-fold greater risk of SPMs with Len maintenance
29	460	CALGB 00104 34 mo	Post-ASCT ≥ stable disease; A: Len, 5-15 mg/d × 21 d until PD; B: placebo	NA	First data: A, 3-y PFS 66% ($P < .001$); B, 3-y PFS 39%	34 mo: A 3-y 88% vs B 80% ($P = .03$); 48 mo: A NR vs 73 mo. ($P = .008$)	A: discontinuations for DRAEs 12%; OS including placebo patients crossing over within 6 mo of randomization on the Len arm ($P = .003$); threefold greater risk of SPMs with Len maintenance; better prognosis for patients treated with Len in induction
22	402	NCT00551928 51 mo	2 × 2 factorial randomized trial; A: Len (10 mg/d × 21 d until PD); B: observation	A: CR 34%; B: CR 29%	A: median PFS: 42 mo ($P < .001$); B: 2-y PFS: 21.6 mo	36 mo OS A 88% vs B 79% (P = NS)	DRAEs similar in the PredLen and Len arms (infections 3% vs 3%)
34	828	Myeloma XI 27 mo	A: Len (10 mg/d × 21 d until PD); B: observation	NA	A: median PFS 50 mo ($P < .0001$); B: 2-y PFS 28 mo	NA	Outcome of high-risk patients better in the Len arm; no increase in DNA instability at the mutational or structural level
23	223	Italian study 52 mo	A: Len (10 mg/d × 21 d) plus prednisone 50 mg every other day until DP; B: Len (10 mg/d × 21 d until PD)	A: CR 30%; B: CR 30%	A: median PFS 37.5 mo (P = NS); B: median PFS: 28.5 mo	36 mo OS A 83% vs B 88% (P = NS)	The frequency of mild cutaneous and hematological adverse events was slightly inferior in the Len plus prednisone arm
32, 36	827	HOVON-65 67 mo	A: VAD-1/2ASCT- Thal 50 mg/d × 2y; B: PAD-1/ 2ASCT- Bor 1.3 mg/m^2 IV/2 wk	A: Thal CR 11%; B: Bor CR 12%	PAD-ASCT-Bor: HR = 0.76, $P = .001$	PAD-ASCT-Bor: HR = 0.78, $P = .02$	5-y OS for PAD-Btz (vs VAD-Thal plus tandem ASCT was superior ($P = .004$)
7, 35	266	GEM05 <65 35 mo	A: Thal 100 mg/d + Bor (1 cycle/ 3 mo) × 3 y; B: Thal 100 mg/d × 3 y; C: α-interferon × 3 y	A: CR 19%; B: CR 15%; C: CR 17%	A: PFS longer compared with B or C ($P = .0009$)	OS similar in the 3 arms	Thal discontinuations: A 16%, B 30%
Nooka et al[46]	45	RVD high-risk patients 26 mo	RVD: Len 10 mg 21/28, Bor 1.3 mg/m^2 subcutaneous/IV weekly, Dexa 40 mg weekly for up to 3 y	51% sCR	32 mo	93% at 3 y	No grade 3-4 PN
11	65	Ixa after IRd of induction 14 mo	Ixa: 4 mg weekly	37% VGPR	88% at 1 y	94% at 1 y	No grade 3-4 side effects

Bor, bortezomib; Dexa, dexamethasone; DRAEs, drug-related adverse events; EFS, event-free survival; HR, hazard ratio; IRd, ixazomib, lenalidomide, and dexamethasone; Ixa, ixazomib; Len, lenalidomide; NA, not available; NR, not reached; NS, not significant; PAD, bortezomib, adriamycin and dexamethasone; PD, progressive disease; RVD, lenalidomide, bortezomib, and dexamethasone; sCR: stringent complete response; SPMs, secondary primary malignancies; Thal, thalidomide.

*Maintenance stopped after a median of 24 mo.

trials conducted by the CALG-B[29] and IFM[30] groups showing a duplication of the PFS. The meta-analysis, which also included the GIMEMA trial,[31] estimated a 2.5-year increase in median OS, so this approach would be recommended for all patients. However, although the PFS benefit was maintained across the different subgroups of patients, the OS benefit was not clearly evident in those with high-risk cytogenetic abnormalities or an advanced International Staging System stage (III).[31] By contrast, in the Myeloma XI trial, where continuous maintenance with lenalidomide was compared with observation, the benefit in terms of PFS was also sustained for patients with high-risk cytogenetic abnormalities. Therefore, in these particular subgroups of patients, optimal maintenance is not well defined. In the Gay et al[23] trial, lenalidomide plus prednisone was slightly superior to lenalidomide alone in terms of PFS (37.5 vs 28.5 months), although this difference did not reach statistical significance. Bortezomib as maintenance after induction with a bortezomib-based combination and tandem HDT-ASCT was able to overcome the poor prognosis linked to the presence of del(17/17p). Thus, this would be one specific recommendation, and maintenance will be for a fixed duration of 2 or 3 years, according to the HOVON and Spanish trials. The same recommendation would be applicable for patients with t(4;14).[32] (3) What is the optimal duration of maintenance? The optimal duration is currently controversial. With respect to lenalidomide, continuous therapy was a concern because of the incidence of secondary primary malignancies (SPMs), but this had not subsequently increased after long-term follow-up.[33] One additional consideration is the potential emergence of immunomodulatory-resistant clones, although the recent Myeloma XI study conducted by the MRC group showed a significant benefit for the continuous use of lenalidomide after HDT-ASCT in comparison with placebo, and continuous treatment with lenalidomide did not induce an excess of mutations or copy-number variants at relapse.[34] Patients who stopped maintenance for reasons other than progression had a significantly shorter PFS, and the longer the time on treatment, the longer the PFS. The PI bortezomib has been evaluated as treatment of fixed duration in all trials,[35,36] so specific recommendations cannot be made at the present time. Results for ixazomib are not available yet, although the trials also included a fixed duration of treatment of 2 years.

Looking forward, the approval of new drugs continues to change the landscape of myeloma maintenance therapy. Currently, trials are incorporating the use of ixazomib, pomalidomide, carfilzomib, and monoclonal antibodies into ongoing maintenance therapy (www.clinicaltrials.gov). Results of these trials will expand our experience and knowledge base while raising new questions, concerns, and recommendations. Table 3 summarizes the main characteristics of the drugs used as part of maintenance. The second relevant area for developing research is the individualization of maintenance therapy according to the quality of the response and MRD status to confidently make recommendations about the use of maintenance for those patients who can benefit from its administration as well as the optimal duration.

Therapeutic options for transplant-ineligible patients

As previously mentioned, transplant-ineligible patients are no longer myeloma patients >65 or 70 years, and eligibility is now more influenced by frailty status.

Alkylator-containing induction regimens

Melphalan was the first active alkylating agent used to treat MM patients and has been the backbone of PI and IMiD combinations, as well as the comparator arm for the evaluation of novel agents for the treatment of elderly MM patients.

Table 4 shows the results of trials conducted in elderly, newly diagnosed MM patients based on alkylators. Melphalan, prednisone, and thalidomide (MPT) was once the standard of care but has now been replaced by continuous treatment with Rd. Melphalan and prednisone plus lenalidomide as induction was similar to melphalan and prednisone in 1 randomized trial and not superior to MPT in 2 randomized trials,[37,38] so this combination is not considered as a standard of care. VMP continues to be recognized as a standard of care for this patient population, although the original scheme has been optimized to weekly as well as subcutaneous administration of bortezomib to reduce PN and gastrointestinal toxicity but maintain or even improve efficacy in comparison with classical VMP due to the use of maintenance therapy.[39,40] In the Myeloma IX study, CTD was superior to melphalan and prednisone, and in the Myeloma XI study, CRD (lenalidomide instead of thalidomide) was not significantly superior to CTD. However, one-third of patients achieved partial or minor response, and half received a second induction with a PI that was able to increase the response by 38%, which translated into a prolongation of PFS by 1 year (from 8 to 20 months).[41] The results of this trial support exploring combinations with PIs, and the Myeloma XI trial included an additional arm including carfilzomib with CRD. The combination of alkylators with second-generation PIs has been evaluated, but with disappointing results, so carfilzomib or ixazomib in combination with melphalan and prednisone will not be new standards of care (Table 4).

Non–alkylator-containing induction regimens

Continuous treatment with Rd recently emerged as a new standard of care for this patient population based on the FIRST trial, in which continuous Rd was compared with MPT (18 cycles) and Rd for a fixed time (18 cycles [Rd18]). Continuous Rd treatment was superior to MPT and Rd18 in terms of PFS (26 vs 21.9 vs 21 months, respectively). In terms of OS, continuous Rd was superior to MPT, but not to Rd18 (59.1 vs 49.1 vs 62.3 months, respectively).[42] The continuous treatment with Rd should be suggested for all patients, and especially for those achieving CR or VGPR. In these patients, the median PFS increased up to 52.5 months and the median time to next therapy was 69.5 months, while the median PFS for patients receiving Rd18 and achieving CR or VGPR was 39.9 months. Because of the efficacy and safety results obtained with continuous Rd, this combination has become a new standard of care for newly diagnosed MM patients and has so far been approved in the United States and European Union.

However, the future of continuous Rd treatment will be its use as the backbone of combination regimens with PIs and other novel agents. The SWOG-SO777 trial compared in a phase 3 trial continuous Rd with Rd plus bortezomib during the first 8 cycles followed by continuous Rd thereafter.[43] Median PFS was significantly improved in the VRD group (43 months vs 30 months) compared with the Rd group, with translation into a significant prolongation of the OS (75 months vs 64 months for VRD vs Rd). Although this trial was not specifically conducted in non–transplant-eligible patients, an age-adjusted PFS and OS multivariate model was done, and after accounting for the effects of the age, the benefit in terms of PFS and OS remained significant for this group of patients >65 years. VRD therefore represents an attractive option to improve the efficacy of Rd by the addition of bortezomib without increasing toxicity, with the exception of PN, which would improve with subcutaneous and weekly (if appropriate) administration of bortezomib (Table 4).

Table 3. Characteristics of drugs that could be used as maintenance therapy in MM

Drug	Route of administration	Clinical benefit		Adverse events						Cost
		PFS	OS	BM suppression	SPMs	PN	DVT	Kidney toxicity	Others	
IFN-α-2b	SC	NC	+	+	−	−	−	+	Poor tolerability (influenza-like syndrome)	+
Thal	Oral	++	NC	+	−*	++	+†	+	Poor tolerability	+
Len	Oral	++	++	++	+*	−	+†	++	Rash, infections	++
Bor	IV/SC	++	NC	+	−	++/?	−	−	Herpes virus reactivation‡	++

Clinical benefit: +, yes, but limited; ++, yes. Adverse effects: −: rare; +, common; ++, very common; ?, unknown (probably less common with Bor SC). Cost: +, cheapest option; ++, more expensive option.

Bor, bortezomib; DVT, deep vein thrombosis; IFN, interferon; Len, lenalidomide; NC, not clear; SC, subcutaneous; Thal, thalidomide.

*Avoid melphalan-lenalidomide/thalidomide combination in elderly patients.

†Prophylactic anticoagulant treatment is recommended.

‡Acyclovir treatment is recommended.

Novel PIs, such as carfilzomib and ixazomib, and monoclonal antibodies, such as elotuzumab and daratumumab, are also being combined with Rd, and it seems almost certain that they will give rise to new standards of care for elderly patients with MM.

Do we have to abandon the alkylators?

If we look forward, continuous treatment with Rd seems to be the backbone used to generate combinations of 3 or 4 alkylator-free drugs. However, VMP and Rd are 2 of the most efficient regimens used today for elderly MM patients, and the Spanish Myeloma Group decided to combine them in this patient population.[44] Since the combination of 5 drugs, given simultaneously, is associated with poor tolerance in this elderly population, the trial was designed to evaluate the feasibility and efficacy of the addition of Rd to the conventional VMP regimen but in either a sequential or alternating manner and for a fixed period. The results showed that the sequential and alternating approaches are similar in outcome and safety, with a PFS close to 3 years, which was particularly remarkable in patients aged 65 to 75 years and ≤80 years, and an acceptable associated toxicity profile was found in this population. In fact, the benefit of this regimen could be increased through the continuous treatment with lenalidomide beyond 18 cycles. VMP has been combined with daratumumab in a phase 1 trial, and its feasibility prompted a currently ongoing phase 3 trial comparing VMP with or without daratumumab; it is the basis for a new alkylator-based standard of care. In spite of the fact that alkylators will be used less in this population, outside of clinical trials, the availability of novel drugs differs slightly from country to country, and this clearly affects the choice of therapy, so it is attractive to generate new "low cost" combinations based on alkylators such as melphalan and cyclophosphamide plus novel agents or monoclonal antibodies, resulting in combinations that are affordable in countries with limited resources.

Table 4. Induction regimens as primary treatment in elderly patients

Induction regimen	N	Maintenance regimen	CR (%)	ORR (%)	PFS (months)	Median OS (months or %)	Reference
Alkylator (melphalan) based							
MPV; MP	344; 338	None; none	30; 4	71; 35	NA, NA	56; 43 ($P < .001$)	39
VMP	130	Randomized to VT or VP up to 3 y	20	80	37	60% at 5 y	45
VMP	257	None	24	81	27	51% at 5 y	47
VMPT	254	VT up to 2 y	38	89	37	61% at 5 y	47
VMP	167	V (5 cycles) in all arms	32	69	NA	NA	48
KMP; VMP	478; 477	None	25.9; 23.1	84.3; 78.8	22.3; 22.1	>80% at 2 y; >80% at 2 y	49
Non–alkylator based							
Len/Dex (RD); Len/dex (Rd)	214, 208	None; none	5; 4	81; 70	19; 25 (P = NS)	75% at 2 y; 87% at 2 y ($P = .00002$)	50
Len/Dex (continuous Rd); Len/Dex 18 cycles; MPT	535; 541; 547	Len/Dex; none; none	15; 14; 9	75; 73; 62	26; 21; 21.9 ($P < .00001$, Rd vs MPT)	59.1; 62; 49.1 ($P = .023$, Rd vs MPT)	42
VLen/Dex × 8; Len/Dex	264; 261	Len/Dex; Len/Dex	16; 8	82; 72	43; 30 ($P = .0018$)	75; 64 ($P = .025$)	43
KRd	23	Len alone	83	100	100% at 1 y	100% at 1 y	51

D, high-dose dexamethasone; d, low-dose dexamethasone; Dex, dexamethasone; K, carfilzomib; Len, lenalidomide; M, melphalan; NS, not significant; ORR, overall response rate; P, prednisone; T, thalidomide; V, bortezomib.

Is there any role for maintenance in elderly patients?

s mentioned in the section transplant-eligible patients, recent findings indicate that long-term treatment can sustain remission by keeping the tumor under control. In elderly patients, the efficacy of long-term treatment should be weighed against its tolerability and convenience of use. As mentioned previously, a benefit of Rd in the FIRST trial was observed in terms of PFS as continuous therapy, including those >75 years. The benefit of continuous therapy has been especially reported for patients who achieve at least VGPR and tolerate the treatment well.[42] The MRC Myeloma XI trial reported that lenalidomide as maintenance was able to significantly prolong PFS (26 months) vs placebo (12 months, $P < .0001$).[34] A recent analysis of the MRC trials reported that age (>74 years) was the risk factor with the highest incidence of SPMs observed in the non–transplant-eligible population receiving lenalidomide maintenance.[33] However, after long-term follow-up, in both young and elderly populations, the risk was considered low compared with the overall benefit in outcome achieved, but elderly patients will require ongoing monitoring.

The Spanish Myeloma Group compared maintenance therapy with either bortezomib and thalidomide (VT) or bortezomib and prednisone (VP) for up to 3 years after induction with bortezomib-based combinations. Although both arms included maintenance (with either VT or VP), the median PFS was 35 months, with 55% of patients alive at 5 years.[45] An Italian group conducted another trial that compared VT as maintenance with observation after induction with bortezomib, melphalan, prednisone, and thalidomide or VMP. The median PFS was significantly longer with VMPT-VT than with VMP (37 vs 27 months, $P < .0001$), translating into a significant OS benefit (61 vs 51% at 5 years, $P = .01$). As in young patients, there is a trial currently ongoing comparing ixazomib for 2 years with placebo (TOURMALINE-MM4), and the other trials currently ongoing evaluating Rd vs Rd plus a third drug will evaluate the role of 3-drug–based combinations as continuous therapy.

How can we manage elderly patients with newly diagnosed MM?

The first thing to be borne in mind about this elderly population is that they are a heterogeneous group, and many of them, regardless of their biological age, are physically frail, with multiple comorbid conditions (eg, diabetes, renal impairment, and cardiovascular disease) and physical disabilities (eg, arthritis and dementia). Tolerability is also a key issue for them. Therefore, all physicians treating elderly MM patients should do 3 things before prescribing treatment: (1) assess the patient's biological age, comorbidities, frailties and disabilities (it would be desirable to have simple geriatric surveys to evaluate whether a patient is frail); (2) evaluate the degree of functional impairment in order to select the most appropriate drug regimen, adapting the dose if required; and (3) optimize the supportive care treatment with bisphosphonates, antibiotics, antivirals, anticoagulants, growth factors, and pain control.

Outside of clinical trials, the availability of novel drugs differs slightly from country to country based on approvals as well as resources. Bortezomib is widely used around the world to treat elderly patients and many non-US physicians continue to use the VMP combination, while in the United States, cyclophosphamide is preferred to melphalan for combination with bortezomib. Continuous treatment with Rd is being chosen by many physicians in and outside the United States, in combination with bortezomib during the first 8 cycles in countries in which this approach is affordable, and will be a backbone in the near future around the world.

Clinical research in the elderly population will be based on the use of frailty-adapted therapy together with a sensitive response assessment, even including immune profiling, in order to help to deliver the appropriate regimen with the optimal duration and avoid under- or overtreatment.

Summary and future perspectives

The optimal treatment approach for young and elderly newly diagnosed MM patients should provide a good balance of efficacy and safety against costs. Quality of life should also be evaluated, since this is not captured by the response criteria. During the initial workup, we can now identify biomarkers that help identify high-risk MM patients, although it may be too early to develop a treatment algorithm based on risk stratification, because the prospective data are very limited.

The novel agent–based combinations are producing deeper and longer remissions. The use of optimized tools to monitor our patients alongside the development of new drugs will help us offer our patients a personalized and optimized treatment in the future. The impact of second-generation novel agents, monoclonal antibodies, and advances in immunotherapy challenge the current standards of care, calling into question, for example, the use of HDT-ASCT as a strategy for all eligible patients or only for selected subsets of patients.

Correspondence

María-Victoria Mateos, Hospital Universitario de Salamanca, Paseo San Vicente 58-182, 37007 Salamanca, Spain; e-mail: mvmateos@usal.es.

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