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**REVIEW**

# Advances in treatment for newly diagnosed multiple myeloma patients ineligible for autologous stem cell transplantation

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The majority of newly diagnosed multiple myeloma patients are over 65 years and/or physically unfit, and, therefore, are not eligible for standard treatment with high-dose chemotherapy and stem cell transplantation. The treatment goals in these patients should be to ensure improvement in disease management and to prolong survival while ensuring quality of life. Until recently, treatment options for such patients were limited, but new treatment combinations based on the novel agents thalidomide, bortezomib and lenalidomide have improved outcomes and survival. Moreover, phase III data indicate that maintenance treatment with novel agents may contribute to extended progression-free survival; however, the optimal duration of long-term therapy has not yet been defined. The potential for novel treatment regimens to improve the adverse prognosis associated with high-risk cytogenetic profiles, such as deletion 17p, also requires further research. Elderly patients, particularly those over 75 years and the clinically vulnerable, require close monitoring and individualized, dose-modified regimens to improve tolerability and treatment efficacy, while maintaining quality of life.

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**Keywords:** elderly; newly diagnosed multiple myeloma; lenalidomide

## INTRODUCTION

Multiple myeloma (MM) is a disease that primarily affects older individuals. The median age at MM diagnosis is 69 years, and two-thirds of patients with MM are over 65 years of age when they are first diagnosed.[1,2] Recent analyses of survival among MM patients have indicated that overall median survival times have increased by 50% in patients diagnosed between 1996 and 2006 from 29.9 months to 44.8 months.[3] This is mainly because of the use of high-dose chemotherapy (HDT) plus autologous stem cell transplantation (ASCT) and the introduction of treatment with the novel anti-myeloma agents. Improvements in survival among newly diagnosed MM (NDMM) patients have largely been confined to younger patients aged $<65$ years at diagnosis,[3] whereas the prognosis for estimated 5- and 10-year survival times for older patients have remained rather poor, especially for those aged $>75$ years.[1,4]

Improved outcomes in younger patients can be attributed in part to the use of HDT–ASCT.[3] Although advanced age is not necessarily a contraindication for HDT–ASCT,[5,6] many patients aged $>65$ years are ineligible for HDT–ASCT because they have multiple comorbidities or poor physical condition that would prevent them from withstanding the toxicity of conditioning regimens. Until recently, treatment options for NDMM patients unable to undergo HDT–ASCT have been limited to combination treatment with melphalan plus prednisone (MP), or high-dose dexamethasone alone. Although the MP regimen is well tolerated in elderly patients and associated with survival outcomes equivalent to more complex chemotherapy combinations,[7] the availability of new frontline treatment regimens based on the novel agents thalidomide, bortezomib and lenalidomide have extended the options for transplantation-ineligible MM patients, and longer survival has been reported in some clinical trials.[8-11]

This paper reviews the novel thalidomide-, bortezomib- and lenalidomide-based treatment regimens emerging as the standard of care in patients with NDMM, who are ineligible for ASCT (summarized in Table 1).[8,9,12–24] The emerging role of maintenance/continuous treatment is also discussed as part of the strategy for optimal disease control, and areas for further research are highlighted.

## OPTIONS OF TREATMENT AS INDUCTION THERAPY

### Thalidomide-based regimens

The alkylating agent melphalan, in combination with prednisone, is an effective frontline regimen for NDMM patients ineligible for ASCT, and it was the standard of care for more than 40 years until the introduction of novel drugs.[7] The addition of thalidomide to MP (MPT) has been associated with superior response rates and improved survival outcomes (Table 1), and current guidelines from the International Myeloma Working Group recommend MPT as the standard of care for elderly NDMM patients.[5] In a study from the GIMEMA (Italian Multiple Myeloma Network) group, MPT was associated with improved response rates and progression-free survival (PFS) in patients aged 65–75 years, but no overall survival (OS) benefit was seen compared with MP.[12,13] However, two studies from the Intergroupe Francophone du Myélome (IFM), which were designed to assess OS, demonstrated significant improvements in OS (and PFS) with MPT compared with MP.[8,9] In the IFM99-06 study of 447 NDMM patients aged 65–75 years, MPT was associated with a median OS of 51.6 months compared with 33.2 months with MP (hazard ratio (HR) $= 0.59$, $P = 0.0006$).[8] In the IFM01-01 study, conducted in 232 very elderly patients (aged $>75$ years), median OS was significantly longer in patients treated with MPT compared with MP alone (44.0 versus 29.1 months; HR $= 0.68$; $P = 0.028$).[9] A borderline significant improvement in OS for MPT versus MP was also reported by the Dutch-Belgium Hemato-Oncology Cooperative Group in the HOVON-49 study (40 versus 31 months; $P = 0.05$).[14] However, three other studies (conducted

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**Table 1.** Efficacy and safety of regimens used as frontline treatment for newly diagnosed, transplantation-ineligible patients with multiple myeloma: phase III studies

| *Study/reference* | *Induction regimen* | *n* | *Maintenance regimen* | *CR, %* | *VGPR, %* | *ORR, %* | *PFS, months* | *Median OS, %* |
|---|---|---|---|---|---|---|---|---|
| GIMEMA/Palumbo *et al.*[12,13] | MPT | 129 | T until progression | 15.5 | 29.3 | 76.0 | 21.8* | 45.0 |
| | MP | 126 | None | 2.4 | 11.0 | 47.6 | 14.5 | 47.6 |
| IFM099-06/Facon *et al.*[8] | MPT | 125 | None | 13 | 47 | 76 | 27.5* | 51.6* |
| | MP | 196 | None | 2 | 7 | 35 | 17.8 | 33.2 |
| IFM01-01/Hulin *et al.*[9] | MPT | 113 | None | 7 | 21 | 62 | 24.1* | 44.0* |
| | MP | 116 | None | 1 | 7 | 31 | 18.5 | 29.1 |
| HOVON-49/Wijermans *et al.*[14] | MPT | 164 | T until relapse | 23 (CR+VGPR) | | 66 | EFS: 13* | 40* |
| | MP | 167 | | 8 (CR+VGPR) | | 45 | EFS: 9 | 31 |
| Beksac *et al.*[15] | MPT | 60 | None | — | 59.2 | — | — | — |
| | MP | 62 | None | — | 3.8 | — | — | — |
| NMSG 12/Waage *et al.*[10] | MPT | 182 | T until progression | 13 | 10 | 57 | 15 | 29 |
| | MP | 175 | None | 4 | 3 | 40 | 14 | 32 |
| Ludwig *et al.*[16] | TD | NS | Patients randomized to IFN or IFN-T | 2 | 24 | 68 | 16.7 | 41.5* |
| | MP | NS | | 2 | 11 | 50 | 20.7 | 49.4 |
| Morgan *et al.*[17] | CTDa | 426 | T or no maintenance until progression | 13.1 | 16.9 | 63.8 | 13.0* | 33.2 |
| | MP | 423 | | 2.4 | 1.7 | 32.6 | 12.4 | 30.6 |
| VISTA/San Miguel *et al.*[18] | MPV | 344 | None | 33 | 8 | 71 | — | Not reached* |
| 3-year follow-up data/Mateos *et al.*[19] | | | | | | | | |
| | MP | 338 | None | 4 | 4 | 35 | — | 43.1 after 3-years |
| PETHEMA/GEM/Mateos *et al.*[20] | VMP | 130 | Randomized to VT or VP | 20 | 12 | 80 | — | — |
| | VTP | 130 | | 28 | 8 | 81 | — | — |
| GIMEMA MM-03-05/Palumbo *et al.*[21] | VMPT | 254 | VT | 38 | — | — | 3-year: 55%* | — |
| | VMP | 257 | None | 24 | — | — | 3-year: 38% | — |
| SWOG S0232/Zonder *et al.*[22] | RD | 97 | None | — | 63 | 78 | 1-year: 78%* | 1-year: 94% |
| | Dexamethasone | 95 | None | — | 16 | 48 | 1-year: 48% | 1-year: 88% |
| E4A03/Rajkumar *et al.*[23] | RD | 223 | None | 5 | 33 | 81 | 19.1* | Not reached |
| | Rd | 222 | None | 4 | 26 | 70 | 25.3 | Not reached |
| MM-015/Palumbo *et al.*[24] | MPR–R | 152 | R until progression | 10 | 23 | 77 | 31* | Not reached |
| | MPR | 153 | Placebo until progression | 3 | 29 | 68 | 14 | Not reached |
| | MP | 154 | Placebo until progression | 3 | 9 | 50 | 13 | Not reached |

Abbreviations: CR, complete response; CTDa, cyclophosphamide, thalidomide and attenuated dexamethasone; EFS, event-free survival; IFN, interferon; MP, melphalan plus prednisone; MPR, MP and lenalidomide; MPR–R, MPR plus melphalan maintenance; MPT, MP plus thalidomide; MPV, MP plus bortezomib; NS, not specified; ORR, overall response rate (at least partial response); OS, overall survival; PFS, progression-free survival; PN, peripheral neuropathy; Rd, lenalidomide plus low-dose dexamethasone; RD, lenalidomide plus standard-dose dexamethasone; T, thalidomide; TD, thalidomide plus dexamethasone; VGPR, very good partial response; VMP, bortezomib plus MP; VMPT, VMP plus thalidomide; VTP, bortezomib, thalidomide and prednisone.
*$P \leqslant 0.05$ vs control arm.

by the Nordic Myeloma Study Group,[10] GIMEMA[12] and the Turkish Myeloma Study Group[15]) failed to show a persistent survival advantage with MPT. A meta-analysis of the six randomized trials of MPT versus MP (three of which included thalidomide maintenance therapy) has identified that the addition of thalidomide to MP as a frontline regimen in elderly NDMM patients significantly prolongs both PFS and OS by around 6 months compared with MP.[25] Recently, safety profile has also been evaluated in a meta-analysis of the six trials with the observation that the addition of thalidomide to the MP combination could be associated with increased toxicities. The cumulative incidence of hematologic toxicity was higher with MPT compared with MP (28% versus 22%, HR = 1.32, 95% confidence interval: 1.05–1.66), and the differences were even more evident for the cumulative incidence of non-hematologic toxicity (39% versus 17%, HR = 2.78, 95% confidence interval: 2.21–3.50). The most common grade 3–4 non-hematologic toxicity was infection (13% for MPT and 9% for MP); other adverse events (AEs) more common among MPT than MP were peripheral neuropathy (PN; 15% versus 3%), deep vein thrombosis (6% versus 2%) and dermatologic toxicity (3% versus 1%).[26]

Two other thalidomide-based combinations have been evaluated in phase III trials as frontline treatment for patients who are ineligible for ASCT: the combination of thalidomide and dexamethasone (TD)[16] and an attenuated regimen of cyclophosphamide and TD (CTDa).[17] The TD regimen was compared with MP in 289 elderly NDMM patients. Response rates were higher with TD compared with MP (68% versus 50%; $P = 0.0023$), but median OS was significantly shorter with TD (41.5 versus 49.4 months; HR = 1.55, $P = 0.024$). The Myeloma IX study group recently compared the efficacy and safety of the CTDa regimen with that of MP in elderly patients unable to undergo ASCT.[17] CTDa significantly improved overall response rates (ORRs) by twofold (64% with CTDa versus 33% with MP; $P < 0.0001$), owing to increases in the rate of complete responses (CRs; 13% versus 2%) and very good partial responses (17% versus 2%), with the quality of response correlating with survival outcomes. Median PFS was marginally better with CTDa than with MP (13 versus 12.4 months; HR = 0.82; $P = 0.01$), and there was no significant difference in median OS (33.2 versus 30.6 months; HR = 0.89; $P = 0.24$). In comparison with MP, CTDa was associated with higher rates of thromboembolic complications (any grade, 16% versus 5%; $P < 0.0001$), sensor neuropathy (grade 3–4, 3% versus < 1%; $P = 0.021$), motor neuropathy (grade 3–4, 4% versus 1%; $P = 0.039$), infection (grade 3–4, 13% versus 7%; $P = 0.0086$) and constipation (grade 3–4, 4% versus 1%; $P = 0.039$), indicating that adequate management of AEs is required to allow patients to continue the regimen and eventually benefit from treatment.

### Bortezomib-based regimens

In the randomized phase III VISTA trial (Velcade as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone), the addition of bortezomib to MP (VMP) was compared with MP as the frontline treatment for elderly MM patients.[18] Median time to progression, which was the primary endpoint of the study, was significantly longer with VMP than with MP (24 versus 16.6 months; HR = 0.48, $P < 0.001$). Median PFS was

21.7 months with VMP and 15.2 months with MP (HR = 0.56; $P < 0.001$). The VMP regimen was also associated with a higher ORR (71% versus 35%; $P < 0.001$), including CR rates of 30% and 4%, respectively ($P < 0.001$). A subanalysis indicated that the quality of treatment response improved during continued VMP treatment, with 28% of CRs achieved during cycles 5–9, and the durability of the CR was similar regardless of when the CR was attained.[27] Furthermore, CR was associated with significantly longer time to progression, time to next therapy and treatment-free interval versus partial response, but there was no difference in the OS.[27] Updated results from the VISTA study after a median of 36.7 months follow-up showed that VMP significantly reduced the risk of death by ~35% compared with MP (HR = 0.65, $P < 0.001$); 3-year OS rates for the two regimens were 68.5% and 54.0%, respectively.[19] The final OS analysis, conducted after a median follow-up of 60.1 months, demonstrated a persistent OS benefit of VMP over MP, with a 13.3-month increase in median OS (56.4 versus 43.1 months; HR = 0.695; $P = 0.0004$).[11] This study also showed that the use of VMP upfront is significantly superior to the potential paradigm of using MP upfront followed by bortezomib at the time of disease relapse.[11] The addition of bortezomib to the MP regimen increased the rate of grade 3–4 AEs associated with treatment (81% versus 71%), particularly PN (13% versus 0%) and hematologic AEs.[18,19] PN was manageable and reversible in two-thirds of the patients, and antiviral prophylaxis reduced the rate of herpes infection to levels similar to that seen in MP treatment (3–4%). On the basis of these data, VMP has been also recognized as a new standard of care.[28]

To maintain efficacy and improve the safety profile of the VMP regimen, the phase III PETHEMA/GEM study investigated a novel combination regimen of reduced-intensity bortezomib (weekly) with either thalidomide and prednisone (VTP) or VMP, in 260 elderly NDMM patients.[20] The study also included a maintenance phase, in which patients were randomized to receive bortezomib plus either thalidomide (VT) or prednisone (VP). As induction therapy, VTP and VMP achieved similar ORR (81% and 80%, respectively) and CR rates (28% and 20%, respectively). However, VTP was associated with more serious AEs than VMP (31% versus 15%; $P = 0.01$) and a higher level of treatment discontinuations (17% versus 12%; $P = 0.03$).[20] The incidence of grade 3–4 PN with VMP using the weekly dose was only 7% compared with 13% as reported in the VISTA trial. Considering the efficacy and safety profile, the weekly schedule of bortezomib appears to be a preferable option in the VMP scheme. Interestingly, with maintenance therapy the CR rate increased to 42% with a global PFS of 31 months and 3-year OS of 70%.[29]

The four-drug combination VMP and thalidomide (VMPT) followed by VT maintenance (VMPT–VT) was compared with VMP in the phase III GIMEMA MM-03-05 study of 511 NDMM ineligible for HDT–ASCT.[21] The median PFS was significantly longer with VMPT–VT compared with VMP (35.5 versus 24.8 months; HR = 0.58; $P < 0.0001$). The VMPT–VT regimen was also associated with improved CR rate (38% versus 24%; $P < 0.001$). The 5-year OS rates were also significantly longer for the four-drug combination as induction followed by maintenance compared with VMP without maintenance (61% versus 51%; HR = 0.70; $P = 0.01$). A higher incidence of AEs was seen in the VMPT–VT group, in particular neutropenia, cardiovascular events and venous thromboembolism (VTE). During the study, the frequency of bortezomib dosing was changed from twice- to once-weekly; this reduced the incidence of PN from 16% to 3% and reduced the discontinuation rate.[21]

### Lenalidomide-based regimens

The combination of MP and lenalidomide (MPR) followed by maintenance with lenalidomide (MPR–R) has been compared with fixed-duration regimens of MPR and MP in a randomized placebo-controlled phase III trial (MM-015) in 459 elderly patients with NDMM.[24] With a median follow-up of 30 months, the primary endpoint, PFS, was significantly longer with MPR–R (median 31 months) than with MPR (14 months; HR = 0.49; $P < 0.001$) or MP (13 months; HR = 0.40; $P < 0.001$). The ORR (partial response or better) was significantly greater with lenalidomide-based therapy than with MP (77% for MPR–R ($P < 0.001$), 68% for MPR ($P = 0.002$) and 50% for MP). Time to response was more rapid with lenalidomide-based therapy (2 versus 3 months for MP; $P < 0.001$), and the median duration of response was significantly longer with MPR–R (29 months) than with MPR (13 months; $P < 0.001$) or with MP (13 months; $P < 0.001$). Median OS had not been reached, and the 3-year OS rate was similar for the three arms (70% with MPR–R, 62% with MPR and 66% with MP). The most relevant AEs observed with the MPR regimen were neutropenia (36% at grade 4), thrombocytopenia (13% at grade 3) and infections (15% at grade 4).

Lenalidomide is effective and generally well tolerated in combination with dexamethasone as the initial therapy for MM.[22,23] Lenalidomide plus dexamethasone (RD) demonstrated superiority over dexamethasone plus placebo in a randomized Southwest Oncology Group S0232 trial in 196 NDMM patients, including those aged >65 years, although the number of patients in each treatment group was small because of stopping the trial early.[22] The 1-year PFS rate was significantly higher with RD than with dexamethasone plus placebo (78% versus 52%; $P = 0.002$), as was ORR (78% versus 48%; $P < 0.0001$), but 1-year OS rates were similar in both treatment groups (87% versus 88%; $P = 0.28$), probably because of the crossover design of this study. A randomized, open-label Eastern Cooperative Oncology Group study compared lenalidomide plus high-dose dexamethasone (RD) with lenalidomide plus low-dose dexamethasone (Rd) in NDMM patients.[23] Patients in this trial included elderly transplantation-ineligible patients as well as younger patients able to choose whether or not to proceed to ASCT after four treatment cycles. This trial was also stopped early because of a significant improvement in survival favoring the Rd group that was observed during a planned interim analysis. Later analyses indicated that the RD regimen was associated with a higher ORR than Rd (81% versus 70%; $P = 0.008$), but a shorter 1-year OS, time to progression and PFS. In patients aged >65 years, a more clear survival benefit with Rd was observed; in this age group, the 1-year survival rates were 83% for RD and 94% for Rd. Furthermore, lower-dose dexamethasone also improved tolerability and was associated with less grade 4 toxicity, halving the incidence of grade 3–4 VTE events from 26% in the RD group to 12% in the Rd group.[23] On the basis of these data, the combination of lenalidomide and low-dose dexamethasone may be considered an attractive option for elderly patients with NDMM.[30] A case–control study suggests that lenalidomide plus dexamethasone can have comparable efficacy with MPR, but prospective studies are needed to validate this.[30]

Other new lenalidomide treatment combinations that have shown clinical potential in phase I/II trials in NDMM patients include the following: lenalidomide, bortezomib and dexamethasone;[31] lenalidomide, bortezomib, pegylated liposomal doxorubicin and dexamethasone;[32] and clarithromycin, lenalidomide and dexamethasone.[33] Larger studies are warranted to evaluate these promising lenalidomide combination regimens.

## IS THERE A ROLE FOR MAINTENANCE THERAPY?

Despite the improvement in treatment responses and survival associated with the introduction of novel anti-myeloma treatments, all patients with MM eventually relapse because of the persistence of residual disease.[34,35] Recent data indicate that long-term treatment either as maintenance or prolonged therapy can be an approach to sustain the remission by keeping the tumor

under control. However, the efficacy of long-term treatment should be balanced with tolerability and the risk of inducing more resistant relapses. The following sections will discuss the role of novel agents in this setting.

### Thalidomide maintenance

In three of the randomized studies comparing MPT with MP, patients assigned to MPT received thalidomide maintenance therapy (50–200 mg/day) until progression (MPT–T).[10,13,14] In the GIMEMA trial (thalidomide maintenance 100 mg/day), PFS (primary endpoint) was significantly longer with MPT–T than with MP (21.8 versus 14.5 months; HR = 0.63; $P = 0.004$), but OS (secondary endpoint) was similar in both treatment groups (45.0 versus 47.6 months; HR = 1.04; $P = 0.79$).[13] In the Nordic Myeloma Study Group trial (thalidomide maintenance 200 mg/day), there was no significant difference in OS (primary endpoint) between MPT–T and MP (29 versus 32 months; $P = 0.16$).[10] Only the Dutch-Belgian HOVON-49 trial (thalidomide maintenance 50 mg/day) demonstrated an improvement in event-free survival (primary endpoint; 13 versus 9 months; $P < 0.001$) as well as OS (secondary endpoint; 40 versus 31 months; $P = 0.05$).[14] However, the incidence of PN of grade $\geqslant 2$ during maintenance was 54%.

The Myeloma IX factorial-design study of CTDa versus MP in transplant-ineligible NDMM patients also contained a thalidomide maintenance randomization. Patients were randomized to receive either thalidomide maintenance (50–100 mg/day) or no maintenance.[36] Thalidomide maintenance therapy was associated with a significant improvement in PFS (11 versus 9 months; HR = 1.35; $P < 0.001$), but OS was not significantly prolonged (38 versus 39 months; HR = 1.00; $P = 0.995$). Thalidomide maintenance was not well tolerated, and patients remained on treatment for a median of only 6 months (range, 0–46 months). Altogether, these studies suggest that thalidomide maintenance probably does not represent a treatment of choice because of its poor tolerability.

### Bortezomib maintenance

Two phase III studies have included bortezomib maintenance treatment. The GIMEMA MM-03-05 study compared VMPT–VT with VMP alone in elderly NDMM patients.[21] The 1-year landmark analysis revealed a median PFS of 31.5 months in the VMPT–VT group compared with 17.8 months for the VMP group alone, showing that maintenance therapy was associated with a highly significant 42% reduced risk of disease progression ($P < 0.05$). However, the PFS advantage was less evident in patients aged $>75$ years with advanced stage of the disease and in those with adverse cytogenetics, and no significant improvement in OS has been reported so far in these groups. Maintenance with VT was well tolerated; grade 3–4 hematologic AEs were reported by 5% of patients, grade 3–4 PN was reported in 7% of patients and the treatment discontinuation rate due to AEs was 12%.[21] The Spanish PETHEMA/GEM study[20] compared VMP and VTP as induction therapy followed by maintenance therapy with either VT or VP for up to 3 years. After median follow-up of 38 months on maintenance therapy, PFS was 39 months in the VT group compared with 32 months in the VP arm ($P = 0.1$); no difference in OS was observed. Both regimens were well tolerated with no serious hematologic toxicities, although VT maintenance was associated with a higher incidence of PN (7% versus 2%). These results indicate that although no significant differences were observed between VT and VP, efficacy is in favor of VT and safety in that of VP.

### Lenalidomide maintenance

The oral administration of lenalidomide together with its manageable safety profile[23] makes it a promising candidate for long-term maintenance treatment. The efficacy and safety of continuous treatment with lenalidomide in elderly transplantation-ineligible patients was evaluated in the phase III MM-015 study.[24] Following induction with MPR or MP, patients received maintenance therapy either with lenalidomide or placebo until disease progression. To determine the contribution of maintenance therapy to PFS, a landmark analysis was conducted that included all patients who remained on treatment beyond cycle 9 (that is, the start of the maintenance therapy phase). This analysis revealed an unprecedented 66% reduction in the risk of disease progression with MPR followed by lenalidomide maintenance (MPR–R) compared with fixed duration MPR plus placebo ($P < 0.001$). PFS was significantly improved in the MPR–R group compared with MPR (31 versus 13 months; $P < 0.001$), and the PFS benefit was seen with lenalidomide maintenance regardless of the quality of induction response (at least very good partial response or partial response). The PFS benefit associated with the continuous treatment with lenalidomide was consistent across all subgroups of patients, except those older than 75 years. Although so far there are no differences in OS, a longer follow-up duration of this study is required to identify any significant differences in OS between the treatment groups.

## ARE THESE NOVEL TREATMENT OPTIONS ABLE TO IMPROVE/OVERCOME THE POOR PROGNOSIS OF PATIENTS WITH HIGH-RISK CYTOGENETIC ABNORMALITIES?

Approximately 25% of patients with NDMM have cytogenetic abnormalities that are associated with a high risk of disease progression and very poor prognosis. The specific abnormalities considered as poor risk are the cytogenetically detected 13q, t(4;14) and del(17p), and the detection of t(4;14), t(14;16) and del(17p) by fluorescence *in situ* hybridization.[37] The ability of novel agents to improve survival times in elderly patients with such cytogenetic abnormalities is unclear, particularly for patients with the del(17p) mutation.

Early data from the IFM099-06 trial indicated that the addition of thalidomide to MP was able to overcome the negative effect of del(13q) in elderly NDMM patients,[8] but this has not been explored in other trials. In the Myeloma IX trial of CTD/CTDa in NDMM patients, PFS was not improved after thalidomide maintenance in patients with high-risk cytogenetics, and OS was shorter in these patients compared with those who had a favorable fluorescence *in situ* hybridization profile ($P = 0.009$).[36]

In the VISTA trial of VMP versus MP, patients with high-risk cytogenetic profiles, including the presence of a t(4;14), t(14;16) and/or del(17p), had the same CR rate, and similar time to progression and OS times to patients with standard-risk cytogenetics, suggesting that the addition of bortezomib to MP was able to overcome the poor prognosis of these patients.[18] However, because of few patient numbers in this subanalysis (26 patients), caution is advised in interpreting these results. Updated results from VISTA after a median of 3 years follow-up have shown that there is a trend to poorer OS in patients with high-risk cytogenetics compared with the standard-risk population (3-year OS: 56.1% versus 71.6%, respectively; $P = 0.399$).[19] In the final OS analysis conducted after a median follow-up of 5 years, no significant difference was observed in the small subgroup with documented high-risk cytogenetics ($n = 46$).[11]

In the GIMEMA study, the PFS benefit in response to VMPT plus VT maintenance were seen in patients at increased risk of disease progression due to adverse cytogenetics (t(4;14) or t(14;16), or del(17p)) as well as in standard-risk patients.[21] In contrast, the most recent Spanish PETHEMA-GEM-2005 trial has reported that although induction with VMP or VTP followed by maintenance treatment with VP or VT was associated with similar response rates and CR rates in patients with adverse cytogenetics, these bortezomib-based maintenance regimens were unable to overcome the negative impact of high-risk cytogenetics on PFS and OS for elderly patients, in particular those with t(4;14) or del(17p).[20] Furthermore, in this study hypodiploid patients had shorter

**Table 2.** Recommended reductions in starting doses for elderly patients newly diagnosed with multiple myeloma[5]

| | *Dose level 0* | *Dose level −1* | *Dose level −2* |
|---|---|---|---|
| Dexamethasone | 40 mg weekly | 20 mg weekly | 10 mg further reduction if needed |
| Prednisone | | 30 mg on alternate days | |
| Melphalan (days 1–4) | 0.25 mg/kg | 0.18 mg/kg | 0.13 mg/kg |
| Cyclophosphamide | | 50 mg/day | Reduction to alternating day dosing |
| Thalidomide | 200 mg/day | 100 mg/day | 50 mg/day |
| Lenalidomide (days 1–21 in combination with dexamethasone) | 25 mg/day | 15 mg/day | 10 mg/day |
| Lenalidomide (days 1–21 in combination with melphalan and prednisone) | 10 mg/day | 5 mg/day | 5 mg on alternate days |
| Bortezomib | 1.3 mg/m$^2$ twice weekly | 1.3 mg/m$^2$ weekly | 1.0 mg/m$^2$ weekly |

Table adapted and expanded from Table 4, Palumbo and Gay, 2009. Republished with permission of *American Society of Hematology* (ASH) from 'How to treat elderly patients with multiple myeloma: combination of therapy or sequencing,' Palumbo A, Gay F, *Hematology Am Soc Hematol Educ Program* 2009:566–577; permission conveyed through Copyright Clearance Center, Inc.

survival outcomes than hyperdiploid patients, in particular those who had VTP induction treatment.[20]

Regarding lenalidomide, the pilot phase I/II study of MPR in NDMM patients has reported that MPR was able to overcome the adverse prognostic impact of del(13q) and t(4;14),[38] but these data have not yet been confirmed in the larger phase III trial. In the trial in which RD was compared with Rd, patients with high-risk cytogenetic abnormalities were less likely to attain very good partial response (46% versus 30% for standard- versus high-risk patients, respectively), although ORR was similar. Moreover, high-risk patients showed lower 2-year OS (91% for standard-risk and 76% for high-risk patients). In a study of 100 NDMM patients who received initial treatment with lenalidomide plus dexamethasone, less durable treatment responses and shorter PFS times (18.5 versus 36.5 months; $P<0.001$) were observed in 16 high-risk patients with hypodiploidy, del(13q), del(17p), t(4;14) or t(14;16). However, the high-risk patients had similar ORRs and OS to standard-risk patients.[39] More recently, a smaller phase II study of combination cyclophosphamide, lenalidomide and dexamethasone induction treatment in 53 NDMM patients has reported similar 2-year PFS and OS outcomes in standard- and high-risk patients defined by del(13q), del(17p), t(4;14) or t(14;16).[40]

In conclusion, there is not enough evidence yet to make specific recommendations regarding the impact of novel treatment regimens on the prognosis of patients with high-risk cytogenetic profiles. Both high-risk and standard-risk patients should be included in future clinical trials; in addition, enrolled patients should undergo a comprehensive genetic analysis upfront to identify those most likely to benefit from certain treatments.

## SPECIAL TREATMENT CONSIDERATIONS FOR PATIENTS WITH NDMM

The current availability of different novel treatment combinations offers physicians the possibility of tailoring treatment approaches based on the individual patient profile and patient preference. For example, in patients who have a history of VTE, VMP may be a preferred treatment choice as it is less thrombogenic. However, appropriate anticoagulant prophylaxis has been shown to reduce VTE complications to $<10\%$ in studies of patients treated with lenalidomide-containing regimens and to reduce VTE in a majority of the studies in patients treated with thalidomide-containing regimens.[41] In patients with pre-existing neuropathy, MPR or lenalidomide plus dexamethasone would be a good choice for an initial regimen as lenalidomide is not associated with neurotoxicity, unlike thalidomide and bortezomib.[42] In renally impaired patients, thalidomide and bortezomib can be administered at the full approved dose; lenalidomide is mainly excreted by the kidneys and, hence, adjustments of the starting dose based on the creatinine clearance have been recommended.[43]

Many patients with NDMM are aged $>75$ years and are physically frail, with multiple comorbid conditions (for example, diabetes, renal impairment and cardiovascular disease) and physical disabilities (for example, arthritis and dementia). Vulnerable elderly patients are more likely to have a poor tolerance to combination treatment regimens, and AE rates can be high in this patient population.[5] Therefore, these patients may benefit from less intensive treatment regimens or may require dose modifications to improve the tolerability of the regimen and sustain quality of life. Recommended reductions in the starting dose for each treatment have been suggested by Palumbo and Gay[5] and are summarized in Table 2. In addition to dose reductions, cyclophosphamide should be considered as an alternative to melphalan, and prednisone may be better tolerated than dexamethasone in frail elderly patients.

Therefore, when treating NDMM patients who are very elderly or have a poor performance status, the improved efficacy of novel treatment regimens needs to be balanced against the increased toxicity, to maintain quality of life. Patients require an individualized treatment tailored to their physical condition, clinical profile and preference, and the proactive management of AEs is required to minimize early discontinuation rates and optimize outcomes.

## CONCLUSIONS

The availability of new combination regimens including the novel agents thalidomide, bortezomib and lenalidomide have improved treatment options for NDMM patients ineligible for HDT–ASCT. The regimens MPT, VMP, MPR and Rd represent new treatment options for these patients. Other combinations, such as bortezomib, lenalidomide, and dexamethasone and MP plus the novel proteasome inhibitors carfilzomib or MLN9708, are also in clinical development. Maintenance treatment with novel agents is emerging as a new strategy to sustain disease control and delay disease progression. Promising data are emerging for bortezomib and lenalidomide as maintenance therapy; however, regimen, scheme and treatment duration have not been determined yet. Numerous studies are ongoing to address these questions and can contribute to defining the benefit of these therapy approaches.

## CONFLICT OF INTEREST

M-VM has served on the speakers' bureau for Onyx Pharmaceuticals, Centocor Ortho-Biotech (Janssen), Millennium and Celgene Corporation, and has received honoraria from Janssen-Cilag, Celgene Corporation and Novartis. JFS-M has received compensation as a scientific advisory board member of Millennium, Celgene Corporation, Janssen-Cilag, Novartis and Bristol-Myers Squibb. JFS-M has also received consulting fees from Janssen-Cilag, Millennium.

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