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Evaluating the Role of Maintenance Therapy in the Management of Multiple Myeloma

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Introduction

Multiple myeloma (MM) is a molecularly heterogeneous disease with a high degree of genomic instability in which specific genetic changes can be linked to clinical presentation and prognosis. Despite recent improvement of event-free survival and overall survival with the use of high-dose chemotherapy and stem cell support, and the development of novel agents such as thalidomide, lenalidomide, and bortezomib, MM remains an incurable disease for the majority of patients.¹⁻⁷ Until a cure is found that can eliminate the malignant clone, the goal of maintenance therapy in MM is to achieve and maintain a durable remission.⁸

Maintenance therapy in MM has been studied for more than 30 years⁹; however, its role remains controversial.^{1,3,10} There is no consensus on the optimal regimen or duration, and many authorities question the advantages of the continuation of therapeutic agents as maintenance therapy, with all their side effects, over observation followed by treatment reimplementations at the time of relapse.^{1,5,9,12} Indeed, alternatives to prolonged treatment with alkylating agents, which increases the likelihood of acute myeloid leukemia, were already being assessed with interferon alfa, corticosteroids (with or without interferon alfa), and recently, novel agents after conventional chemotherapy or autologous stem cell transplantation (ASCT).⁹

At present, NCCN guidelines recommend the following agents as maintenance therapy in MM: interferon alfa (category 2B); corticosteroids (category 2B); thalidomide (category 1) with or without prednisone (category 2B); and lenalidomide (category 2A).³ In addition, bortezomib is currently under investigation in the maintenance setting, but the NCCN panel has deemed current data inadequate to make a recommendation.³

Interferon Alfa as Maintenance Therapy

Interferon alfa as maintenance therapy in MM has been investigated in several clinical trials, but the findings have been inconsistent.^{9,13}

Data from two meta-analyses showed that interferon alfa produced a statistically significant (albeit small) survival advantage when used after conventional therapy.⁹ In one meta-analysis, based on 1615 patients with MM in 13 trials, interferon alfa maintenance therapy, compared with no treatment, prolonged relapse-free and overall survival by 4.4 and 7.0 months, respectively ($P < .01$).¹³ In the second meta-analysis, based on 1543 patients with MM in 12 trials, response duration was better with interferon alfa maintenance therapy (27% vs 19%, respectively, at 3 years; log rank $P < .00001$); furthermore, interferon alfa prolonged median time to progression by approximately 6 months.¹⁴

A clinical trial in 101 patients with MM who had responded to conventional induction chemotherapy showed that maintenance therapy with interferon alfa, compared with no treatment, significantly improved duration of response (26 vs 14 months, respectively; $P = .0002$)¹⁵; median overall survival in the two groups was 52 vs 39 months, respectively ($P = .0526$).¹⁵ In a prospective randomized trial conducted by the Spanish Society of Hematology in 92 patients with MM who had responded to

VCMP/VBAP (vincristine, cyclophosphamide, melphalan, prednisone/vincristine, carmustine, doxorubicin, prednisone) chemotherapy, median duration of response from time of randomization until relapse was 13 months in the interferon alfa group and 7.7 months in the no-treatment group ($P=.042$)¹⁶; median survival from time of randomization was 38.8 and 32.7 months, respectively ($P=.12$).¹⁶

A study conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) in 176 patients with MM who had responded to melphalan and prednisone found that interferon alfa maintenance therapy was associated with a statistically significant improvement in duration of response and overall survival, compared with no treatment¹²; however, maintenance therapy with interferon alfa also led to considerable toxicity that resulted in a dose reduction in 58% of patients and treatment discontinuation in 14% of patients.¹² In two small studies—US Intergroup Trial S9321 ($n=242$) and SWOG 8624 ($n=193$)—no difference in progression-free survival (PFS) or overall survival was noted with interferon alfa maintenance therapy versus observation only in patients with MM who had attained a **reduction in tumor burden of $\geq 75\%$ after initial treatment.**^{10,17}

In general, interferon alfa has been associated with modest improvement in remission duration, and in a few studies, overall survival; however, this therapy has been associated with high toxicity and poor tolerability and, therefore, interferon maintenance is rarely used today.^{10,18,19}

Corticosteroids as Maintenance Therapy

Several clinical trials have investigated the use of corticosteroids as maintenance therapy, but definitive conclusions cannot be drawn from the findings.⁹ SWOG 9210 was the first study to investigate the role of glucocorticoids used alone as maintenance therapy in MM.⁵ In the study, which compared two doses of alternate-day prednisone (10 mg vs 50 mg) as remission maintenance therapy in 126 patients with MM who had responded to induction therapy (either vincristine, doxorubicin, dexamethasone with prednisone [VAD-P] or VAD-P with quinine [VAD-P/Q]),⁵ median PFS was significantly longer with high-dose than low-dose prednisone (14 vs 5 months, respectively; $P=.003$), as was median overall survival (37 vs 26 months, respectively; $P=.05$).⁵ Adverse events were similar in the two treatment arms (**ie, 13 patients experienced toxicity of ≥ 3 grade in each arm**).⁵

In a randomized trial comparing dexamethasone versus interferon alfa as maintenance therapy in 84 patients who had responded to primary therapy with oral melphalan and intermittent high-dose dexamethasone, median remission was 10 months with both regimens, and side effects were rare and mild.¹⁸ median survival from initiation of maintenance therapy was 52 and 58 months with interferon alfa and dexamethasone, respectively.¹⁸ In the NCIC CTG MY.7 study comparing dexamethasone versus observation as maintenance therapy in 292 patients with MM who had responded to induction therapy with melphalan plus dexamethasone or melphalan plus prednisone, median PFS was 2.8 versus 2.1 years, respectively (hazard ratio [HR] = 0.61; 95% confidence interval [CI], 0.47-0.79; $P=.0002$); however, no difference was observed in median overall survival (4.1 vs. 3.8 years, respectively; HR, 0.88; 95% CI, 0.65-1.18; $P=.4$).²⁰

Combination maintenance therapy consisting of a glucocorticoid plus interferon alfa has been shown to improve both progression-free and overall survival in patients with MM compared with interferon alfa alone.⁵ In SWOG 9028—a study in 89 patients with MM who had attained complete or partial remission after VAD induction—PFS with prednisone plus interferon alfa versus interferon alfa alone was 19 and 9 months, respectively ($P=.008$); median survival was 57 and 46 months, respectively ($P=.36$).¹⁹ In general, **maintenance therapy was well tolerated, and toxicity of ≤ 3 grade, which included malaise and leukopenia, was usually correlated with interferon alfa administration.**¹⁹

Again, tolerability and toxicity have prevented widespread use of steroids as maintenance therapy. This, and the recent recognition of the negative impact steroids have in the newly diagnosed setting, especially in combination with novel agents, limits the use of steroids in myeloma therapy in general.^{10,18,19}

Thalidomide as Maintenance Therapy

Thalidomide was the first novel agent to be studied in the maintenance setting.⁹ In a recent meta-analysis of three randomized controlled trials, the use of thalidomide maintenance therapy following ASCT in patients with previously untreated MM was associated with a significant overall survival

advantage (HR, 0.49; 95% CI, 0.32-0.74),²¹ but also an increased relative risk (RR) of venous thromboembolism (RR, 1.95; 95% CI, 1.15-3.30).²¹

Most studies investigating thalidomide maintenance therapy have focused on younger patients who have completed ASCT, a setting in which such therapy has led to improvement in PFS and mixed results with regard to overall survival (see [Table 1](#)).

In the Intergroupe Francophone du Myélome (IFM) 99-02 trial in 708 patients with MM (aged 65 years or younger) who were nonprogressing after high-dose therapy followed by double ASCT, maintenance therapy with pamidronate plus thalidomide led to a complete or very good partial response in 67% of patients, compared with rates of 55% and 57% in patients receiving no maintenance and pamidronate alone, respectively.¹ Of interest, the benefit of thalidomide in terms of event-free survival was substantial in patients who did not have a deletion of chromosome 13; in contrast, thalidomide was not effective in patients who had a deletion of chromosome 13.¹ The main adverse events associated with thalidomide included neuropathy (68%), fatigue (34%), and constipation (20%); adverse events led to discontinuation of thalidomide in 39% of patients.¹

Trial/Author (Year)	Design	Endpoints	Outcome	Safety/Tolerability
IFM 99-02 trial, Attal et al. (2006)	Randomization after second ASCT to: • Arm A (n=200): no maintenance • Arm B (n=196): pamidronate • Arm C (n=201): thalidomide/pamidronate	• CR/VGPR • EFS • OS	Arm A vs B vs C: • CR/VGPR: 55%, 57%, 67% • EFS at 3 years: 36%, 37%, 52% • 4-year post-diagnosis probability of OS: 77%, 74%, 87%	Grade 3/4 AEs more common in Arm C than A or B: • Peripheral neuropathy • Fatigue • Constipation • Neutropenia • Cardiac events
TT2 trial, Barlogie et al. (2006)	Randomization to: • Thalidomide (n=323) • No thalidomide (n=345)	• EFS • CR • OS	Thalidomide vs no thalidomide: • 5-year EFS: 56% vs 44% • CR: 62% vs 43% • 5-year OS: about 65% in both groups • Median survival after relapse: 1.1 vs 2.7 years	AEs >grade 2, thalidomide vs no thalidomide: • Neutropenia, 94% vs 91% • Thrombosis/embolism, 30% vs 17% • Peripheral neuropathy, 27% vs 17% • Bowel obstruction, 14% vs 8% • Tremor, 13% vs 6% • Syncope, 12% vs 4%
Spencer et al. (2009)	Randomization after ASCT to: • Thalidomide arm (n=114): prednisolone/thalidomide • Control arm (n=129): prednisolone	• PFS • OS • Tolerability	Thalidomide vs control: • 3-year PFS: 42% vs 23% • OS: 86% vs 75%	Grade 3/4 AEs, thalidomide vs control: • Peripheral neuropathy, 10% vs 0% • Infection, 11% vs 8% • Constipation, 4% vs 0% • Thrombosis, 4% vs 2%
NCIC CTG MY.10 trial, Stewart et al. (2010 ASH abstract)	Randomization after ASCT to: • Observation only • T/P Patients enrolled: n=332	• OS • PFS • QoL • Toxicity • VTE incidence	Observation vs T/P: • Median OS: 5 years vs not yet reached • 4-year OS: 60% vs 68% • Median PFS: 17 vs 28 months	Grade 3 nonhematologic toxicities, observation vs T/P: 49% vs 92% Grade 4 nonhematologic toxicities, observation vs T/P: 7% vs 16%
Brinker et al. (2006)	Therapy after ASCT: • Thalidomide (n=36) • No thalidomide (n=76)	• OS	Thalidomide vs no thalidomide: • Median OS: 65 vs 46 months	Most common toxicities associated with thalidomide: • Neuropathy, 28% • Fatigue, 19% • Constipation, 11%

AEs, adverse events; ASCT, autologous stem cell transplant; ASH, American Society of Hematology; CR, complete response; EFS, event-free survival; IFM, Intergroupe Francophone du Myélome; NCIC CTG, National Cancer Institute of Canada Clinical Trials Group; OS, overall survival; PFS, progression-free survival; QoL, quality of life; T/P, thalidomide/prednisone; TT2, Total Therapy 2; VTE, venous thromboembolic event; VGPR, very good partial response

In another study—243 patients (median age, 57 years) who had achieved stable disease or better with induction chemotherapy, high-dose melphalan therapy, and ASCT—were assigned to either maintenance prednisolone only or maintenance prednisolone plus consolidation thalidomide.²² At median follow-up of 3 years, estimated PFS was 42% versus 23% in the thalidomide and control arms, respectively ($P=.001$),²² and estimated overall survival was 86% and 75%, respectively ($P=.004$).²²

In the NCIC CTG MY.10 study, a randomized trial comparing daily thalidomide plus alternate-day prednisone (T/P) as maintenance therapy versus observation only following ASCT in 332 patients with MM (median age, 58 years), T/P did not significantly prolong overall survival (HR, 0.77; 95% CI, 0.53-1.13; $P=.18$); the 4-year overall survival rate was 68% and 60%, respectively.²³ Although median PFS was significantly improved in the T/P versus observation-only arm (28 and 17 months, respectively; HR, 0.56; 95% CI, 0.43-0.73; $P<.0001$), grade 3/4 nonhematologic toxicity and common toxicities of all grades were higher with treatment; the 4-year PFS rate was 32% versus 14%, respectively.²³

Another study investigated the efficacy of thalidomide as maintenance or salvage therapy versus no

treatment in 112 patients with MM (median age, 53 years) who had undergone ASCT.²⁴ Patients receiving thalidomide post-transplantation had improved median survival, compared with those in the no-treatment group (65.5 vs. 44.5 months, respectively; $P=.09$); additionally, overall survival was longer in patients who received thalidomide as maintenance therapy than as salvage therapy (65 vs. 54 months, respectively; $P=.05$).²⁴

In contrast to the above randomized trials, where thalidomide was given after ASCT, the Total Therapy 2 (TT2) trial randomized newly diagnosed MM ($n=668$) to thalidomide upfront and through various stages of induction, tandem transplants, consolidation and maintenance; about 80% of the patients were younger than 65 years. At median follow-up of 42 months, complete response was 62% in patients receiving thalidomide and 43% in those not receiving thalidomide ($P<.001$); however, 5-year overall survival was about 65% in both study arms ($P=.90$). The incidence of severe peripheral neuropathy and deep vein thrombosis was higher in the thalidomide group than in the control group. Also of note, an update to the TT2 trial showed that thalidomide improved survival and duration of complete remission in patients with high-risk cytogenetics. At 7 years from onset of complete remission, 45% of patients with cytogenetic abnormalities who received thalidomide versus 20% of patients in the control arm remained relapse free ($P=.05$).²⁵

The role of thalidomide as maintenance therapy in older patients who are ineligible for ASCT remains to be clearly elucidated.¹¹ One recent study assessed the effect of thalidomide plus interferon alfa versus interferon alfa alone as maintenance therapy in 128 elderly patients with MM who had stable disease or better after induction therapy with either thalidomide plus dexamethasone or melphalan plus prednisolone.¹¹ PFS was significantly longer in patients receiving thalidomide plus interferon alfa than interferon alfa alone (27.7 vs. 13.2 months; $P=.0068$)¹¹; however, overall survival was similar in the two groups (52.6 vs. 51.4 months; $P=.81$) and did not differ between older and younger patients ($P=.39$).¹¹

In a study in 103 elderly patients with MM who had achieved at least a minor response after conventional induction therapy with thalidomide, dexamethasone, and pegylated liposomal doxorubicin, PFS and overall survival were significantly better with thalidomide plus dexamethasone (TD) than interferon alfa plus dexamethasone (ID) maintenance therapy.⁶ Two-year PFS was 63% in patients in the TD arm versus 32% in the ID arm ($P=.024$); overall survival was 84% versus 68%, respectively ($P=.030$).⁶ Main adverse events were peripheral neuropathy and constipation in the TD arm and fatigue, anorexia, and hematological toxicity in the ID arm.⁶

Investigators have also studied the effectiveness and tolerability of different doses of thalidomide used as maintenance therapy. In a phase 2 study in 100 patients with nonprogressive MM investigating thalidomide maintenance therapy in five dose-escalating cohorts (ie, 50, 100, 200, 250, and 300 mg) after high-dose melphalan-based ASCT, dosage did not affect disease outcome, but had a substantial effect on toxicity.²⁶ At median follow-up of 32.3 months, 77 patients had discontinued thalidomide because of side effects ($n=53$), disease progression ($n=23$), or financial reasons ($n=1$).²⁶ The main toxicity, peripheral neuropathy, led to discontinuation of maintenance therapy in nearly one-third of patients.²⁶ At 3 years, PFS and overall survival were 41% and 76%.²⁶ Thalidomide maintenance doses >200 mg were mostly unattainable.²⁶

A study in 31 patients with MM who were nonprogressing after ASCT examined the tolerability and efficacy of maintenance therapy with thalidomide, starting with 50 mg/day and escalating in 50-mg increments, as tolerated, to a maximum dose of 200 mg/day.²⁷ At 1 and 2 years, complete or very good partial response was reported in 65% and 42% of patients, respectively²⁷; median PFS was 20.8 months, and median overall survival was longer than 5 years.²⁷ The median tolerated dose of thalidomide was 100 mg/day²⁷; only 17 patients attained dosing at 200 mg/day.²⁷ The main reason for intolerance to thalidomide was sensory neuropathy.²⁷

A major limitation of thalidomide maintenance is the toxicity profile of the drug, as mentioned above, and its association with poor compliance. Lower doses of thalidomide are better tolerated and can be given for prolonged periods of time; however, data for differences between dose/duration and outcome are lacking.²⁷ More importantly, with the recent data for lenalidomide in the maintenance setting, thalidomide is falling out of favor as a therapy for MM patients, as lenalidomide has demonstrated an acceptable tolerability and ease of long-term use.²⁸

Lenalidomide as Maintenance Therapy

Lenalidomide as maintenance therapy has been investigated in 3 key randomized phase 3 studies, 2 of which were for transplant-eligible patients (CALGB 100104 and IFM 2005-02) and produced results that led to a category 2A recommendation by the NCCN panel (see [Table 2](#)).³ The third trial, MM-015, included ASCT-ineligible patients.³

The first trial, CALGB 100104, compared maintenance lenalidomide (10 mg daily escalated to 15 after 3 months) versus placebo after ASCT in 460 patients (age, 70 years or younger) with stable disease or better and showed a median time to progression of 42.3 in lenalidomide-treated patients and 21.8 months in the placebo arms^{29,30}; that resulted in unblinding of the results by the Data Safety Monitoring Committee (DSMC) and crossover for those receiving placebo.^{29,30} A recent update showed that lenalidomide was associated with a 61% reduction in risk of disease progression or death (estimated HR, 0.39; 95% CI, 0.27-0.56; $P < .0001$) at median post-ASCT follow-up of 17.5 months.²⁹ Pooled grade 3 and higher adverse events attributed to lenalidomide included: thrombocytopenia (11% vs. 3%, respectively; $P = .01$), neutropenia (44% vs. 8%, respectively; $P < .0001$), anemia (5% vs. 1%, respectively; $P = .0082$), and all infections (16% vs. 3%, respectively, $P < .0001$).²⁹

Table 2. Major Trials Investigating Lenalidomide as Maintenance Therapy in Patients With Multiple Myeloma

Trial/Author (Year)	Design	Endpoints	Outcome	Safety/Tolerability
CALGB 100104 trial, McCarthy et al. (2010 ASH and ASCO abstracts)	Randomization after single ASCT to: • Lenalidomide (n=231) • Placebo (n=229)	• TTP	Lenalidomide vs placebo: • Preliminary estimated median TTP: 42.3 vs 21.8 years	Pooled grade 3-5 AEs, lenalidomide vs placebo: • Thrombocytopenia, 11% vs 3% • Neutropenia, 44% vs 8% • Anemia, 5% vs 1% • All infections, 16% vs 3%
MM-015 trial, Palumbo et al. (2009 and 2010 ASH abstracts)	Regimens: • Fixed duration MP (n=154) • Fixed duration MPR (n=153) • Continuous MPR-R (n=152)	• PFS • OS • TTP • Response rate • Time to response • Response duration • Time to next anti-myeloma therapy • Safety • QoL • Cytogenetic abnormalities	MPR-R vs MP: • 2-year PFS, 55% vs 16%	Grade 3/4 AEs, MPR-R vs MP: • Neutropenia, 71% vs 30% • Thrombocytopenia: 38% vs 14% • Anemia, 24% vs 17%
IFM 2005-02 trial, Attal et al. (2010 ASH and ASCO abstracts)	Randomization after ASCT to: • Lenalidomide (n=307) • Placebo (n=307)	• PFS	Lenalidomide vs placebo: • Median PFS from randomization, 42 vs 24 months • Median PFS from diagnosis,	Definitive interruption rate for SAEs, lenalidomide vs placebo: 8% vs 5%

AEs, adverse events; ASCO, American Society of Clinical Oncology; ASCT, autologous stem cell transplant; ASH, American Society of Hematology; CALGB, Cancer and Leukemia Group B; IFM, Intergroupe Francophone du Myélome; MP, melphalan/prednisone; MPR, melphalan/prednisone/lenalidomide; MPR-R, melphalan/prednisone/lenalidomide followed by lenalidomide maintenance therapy; PFS, progression-free survival; QoL, quality of life; SAEs, serious adverse events; TTP, time to progression

In the IFM 2005-02 trial, 614 patients with MM (age, younger than 65 years) who had nonprogressive disease after ASCT received consolidation therapy with lenalidomide (25 mg daily) for 2 months, followed by maintenance therapy with either lenalidomide (10-15 mg daily) or placebo.^{31,32} Median PFS from time of randomization and diagnosis was 24 and 34 months, respectively, in patients receiving placebo, compared with 42 and 52 months, respectively, in patients receiving lenalidomide maintenance therapy (HR = 0.5; $P < .10$ -8).³² The study was stopped by the DSMC, but with no crossover for placebo patients.³²

The third trial, MM-015, from Italy, randomized 459 ASCT-ineligible patients with newly diagnosed MM (aged 65 years or older) to receive one of three regimens: (1) melphalan, prednisone, and lenalidomide (MPR) induction therapy followed by continuous lenalidomide maintenance therapy; (2) fixed duration MPR; or (3) fixed duration MP.^{33,34} Two-year PFS was 55% and 16% with MPR-R versus MP, respectively.³⁴ Overall response rates with MPR followed by continuous lenalidomide maintenance therapy versus fixed duration MP were 77% and 50%, respectively ($P < .001$); complete response rates were 16% versus 4%, respectively ($P < .001$).³⁴ In addition, overall risk of disease progression was reduced by 58% with MPR followed by continuous lenalidomide maintenance therapy versus fixed duration MP (HR, 0.423; $P < .001$), and 2-year PFS was 55% versus 16%, respectively.³⁴ Grade 3/4 neutropenia, thrombocytopenia, and anemia were reported in 71%, 38%, and 24% of patients, respectively, receiving MPR followed by continuous lenalidomide maintenance therapy versus 30%,

14%, and 17% of patients, respectively, receiving fixed duration MP.³⁴ All 3 trials were not matured enough to establish survival benefits for patients. Additionally, in all 3 trials, there was an increased risk of second cancers (Table 3) including breast, prostate, colon, as well as leukemia and Hodgkin and non-Hodgkin lymphomas in patients receiving lenalidomide compared with those on placebo.²⁹⁻³⁴

Table 3. Second Cancers in Patients Receiving Lenalidomide as Maintenance Therapy

Trial/Author (Year)	Study Regimens	Incidence of Second Cancer
CALGB 100104 trial, McCarthy et al. (2010 ASH abstract)	Lenalidomide Placebo	Lenalidomide: 15/231 (6.5%) Placebo: 6/229 (2.6%)
MM-015 trial, Palumbo et al. (2010 ASH abstract)	MP followed by placebo MPR followed by placebo MPR followed by lenalidomide	MP followed by placebo: 2/154 (1.3%) MPR followed by placebo: 8/153 (5.2%) MPR followed by lenalidomide: 5/152 (3.3%)
IFM 2005-02 trial, Attal et al. (2010 ASH abstract)	Lenalidomide Placebo	Lenalidomide: 16/307 (5.2%) Placebo: 3/307 (1%)

ASH, American Society of Hematology; CALGB, Cancer and Leukemia Group B; IFM, Intergroupe Francophone du Myélome; MP, melphalan/prednisone; MPR, melphalan/prednisone/lenalidomide

Bortezomib as Maintenance Therapy

The use of the proteasome inhibitor bortezomib^{35,36} as maintenance therapy is currently under investigation in several clinical trials (see Table 4).³

In the US community-based, randomized, open-label, multicenter, phase 3b UPFRONT study, 300 elderly patients who were ineligible for high-dose therapy and ASCT were randomized to one of three bortezomib-based induction therapies (bortezomib-dexamethasone, bortezomib-thalidomide-dexamethasone, or bortezomib-melphalan-prednisone) followed by 5 cycles of bortezomib maintenance (bortezomib 1.6 mg/m² days 1, 8, 15, and 22 of a 35-day cycle).³⁷ After eight cycles of induction therapy, overall response in the bortezomib-dexamethasone, bortezomib-thalidomide-dexamethasone, and bortezomib-melphalan-prednisone groups was 68%, 78%, and 71%, respectively; after five cycles of bortezomib maintenance therapy, overall response increased to 71%, 79%, and 73%, respectively, with no increase in the frequency of peripheral neuropathy.³⁷

Table 4. Trials Investigating Bortezomib as Maintenance Therapy in Patients With Multiple Myeloma

Trial/Author (Year)	Design	Endpoints	Outcomes	Safety/Tolerability
UPFRONT trial, Niesvizky et al. (2010 ASH abstract)	Regimens: • Induction with VD (n=100), VTD (n=100), or VMP (n=100), followed by maintenance Zortezomib in all	• PFS • ORR • CR/nCR • VGPR • Safety/ tolerability • Response duration	After 8 cycles of induction (VD, VTD, and VMP groups): • ORR, 68%, 78%, 71% After 5 cycles of maintenance (VD, VTD, and VMP groups): • ORR, 71%, 79%, 73%	Most common grade ≥3 AEs (VD, VTD, and VMP groups): • Peripheral neuropathy, 18%, 28%, 21% • Fatigue, 10%, 15%, 8% • Diarrhea, 11%, 5%, 10% • Neutropenia, 1%, 2%, 21% • Pneumonia, 11%, 0%, 0%
HOVON-65/GMMG-HD4 trial, Sonneveld et al. (2010 ASH abstract)	Regimens: • Arm A (n=305): VAD and ASCT followed by thalidomide • Arm B (n=308): Bortezomib/doxorubicin dexamethasone and ASCT followed by bortezomib	• PFS • CR (EBMT) • Immunofixation-positive CR (nCR) • VGPR • OS	Arm A vs B: PFS at 36 months: 42% vs 46%	WHO grade 3/4 polyneuropathy, arm A and B: 7% vs 16%
Benevolo et al. (2010)	Regimen: • Bortezomib plus dexamethasone (n=49)	• PR • Toxicity • PFS • OS	At median follow-up of 25 months (n=49): • CR, 8% • VGPR, 6% PFS at 1 year: 61%	Most common non-dose-limiting grade 1/2 AEs: • Fatigue • Gastrointestinal symptoms • Herpes zoster reactivation • Pneumonia No grade 3/4 neuropathies or hematologic toxicities observed
Palumbo et al. (2010)	Regimens: • VMPT-VT (n=254) • VMP (n=257)	• PFS • Response rate • Time to first evidence of response • OS • Grade ≥3 AEs	VMPT-VT vs VMP: • 3-year estimated PFS, 56% vs 41% • CR, 38% vs 24% • 3-year OS: 89% vs 87%	Grade 3/4 AEs, VMPT-VT, and VMP: • Neutropenia, 38% vs 28% • Cardiac events, 10% vs 5% • Thromboembolic events, 5% vs 2%
Mateos et al. (2009 ASH abstract)	Regimens: • Induction VMP (n=125) followed by VT as maintenance therapy • Induction VTP (n=128) followed by VP as maintenance therapy	• Effect of reduced intensity induction therapy and addition of maintenance therapy on efficacy and toxicity	VMP and VTP: • CR, 22% vs 27% VT and VP: • CR, 46% vs 38%	Toxicity, VMP, and VTP: • Grade ≥3 neutropenia, 37% vs 21% • Grade ≥3 peripheral neuropathy, 5% vs 9% Most relevant grade ≥3 AEs, VT, and VP: • Cardiac events, n=2 vs n=1 • Gastrointestinal events, n=4 vs n=1

AEs, adverse events; ASH, American Society of Hematology; C/nCR, complete response/near complete response; EBMT, European Group for Blood and Marrow Transplantation; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; VAD, vincristin/doxorubicin/dexamethasone; VD, bortezomib/dexamethasone; VGPR, very good partial response; VMF, bortezomib/melphalan/prednisone; VMPT-VT, bortezomib/melphalan/prednisone/thalidomide induction therapy followed by bortezomib/thalidomide maintenance therapy; VP, bortezomib/prednisone; VT, bortezomib/thalidomide; VTD, bortezomib/thalidomide/dexamethasone; VTP, bortezomib/thalidomide/prednisone; WHO, World Health Organization

The randomized phase 3 HOVON-65/GMMG-HD4 trial compared the efficacy of induction therapy with

standard VAD followed by high-dose melphalan with ASCT and maintenance therapy with 50 mg daily of thalidomide for 2 years (arm A) versus induction therapy with bortezomib, doxorubicin, and dexamethasone followed by high-dose melphalan with ASCT and maintenance therapy with 1.3 mg/m² of bortezomib twice weekly for 2 years (arm B) in 613 evaluable patients with newly diagnosed MM.³⁸ Maintenance therapy was started by 67% of patients in arm A versus 57% of patients in arm B; protocol deviations occurred in 64% and 47% of patients, respectively, because of toxicity, progression, or other reasons.³⁸ At 36 months, PFS was 42% in arm A and 46% in arm B.³⁸

A randomized phase 3 study in 511 patients with MM (aged 65 years or older) who were ineligible for high-dose therapy plus ASCT found that treatment with bortezomib-melphalan-prednisone-thalidomide (VMPT) followed by maintenance therapy with bortezomib-thalidomide (VT) was superior to VMP without maintenance therapy.³⁹ At 3 years, overall survival was 89% and 87% with VMPT followed by maintenance therapy with VT versus VMP without maintenance therapy (HR, 0.92; 95% CI, 0.53-1.60; *P*=.77)³⁹; estimated 3-year PFS was 56% and 41%, respectively (HR, 0.67; CI, 0.50-0.90; *P*=.008).³⁹ Grade 3 to 4 neutropenia occurred in 38% and 28% of patients receiving VMPT followed by maintenance VT versus VMP, respectively (*P*=.02).³⁹

A prospective, multicenter, randomized trial recently investigated induction therapy with VMP versus VTP followed by maintenance therapy with VT versus VP in elderly patients (older than 65 years of age) with MM.⁴⁰ In 143 evaluable patients after maintenance therapy, complete response in the VT and VP arms was 46% and 38%, respectively.⁴⁰ The trend in terms of time to progression at median duration of maintenance therapy (13 months) favored the VT arm over the VP arm (84% vs. 71%, respectively; *P*=.05); 1-year overall survival was 92% versus 89%, respectively.⁴⁰

In a study in 49 patients with advanced MM (median age, 71 years) who were responsive to salvage bortezomib-containing regimens and had measurable disease, the use of bortezomib plus dexamethasone as maintenance therapy was shown to be effective and well tolerated. Median time to progression was 17 months; at 1 year, PFS and overall survival were 61% and 79%, respectively.³⁶ Three patients experienced grade 2 neuropathy, which led to bortezomib dose reduction; no grade 3 or 4 neuropathy or hematologic adverse events were reported.³⁶

The Use of Novel Agents as Consolidation Therapy

Consolidation therapy is maintenance given after induction therapy, but the doses are higher and are usually given for a defined period that varies from 4 cycles in one year to 2 intensive cycles over 2 months.

In a randomized phase 3 study in 474 newly diagnosed patients with MM, investigators compared VTD with TD as induction (three 21-day cycles) and consolidation therapy (two 35-day cycles) before and after double ASCT to analyze response after all phases of treatment and survival.^{1,3,41} The centrally reassessed complete response/near complete response rate was significantly higher in patients receiving VTD than TD after induction therapy (30% vs. 10%; *P*<.0001), double ASCT (54% vs. 42%, respectively; *P*=.008), and consolidation therapy (60% vs. 44%, respectively; *P*=.001).⁴² A per-protocol analysis in 323 patients showed that overall upgraded response with VTD and TD as consolidation therapy was observed in 55% versus 37% of patients, respectively (odds ratio, 1.15-3.77; *P*=.01).⁴² At median follow-up of 31 months, median PFS was 42 months in patients receiving TD and was not yet reached in those receiving VTD.⁴² Furthermore, a molecular substudy using qualitative and quantitative polymerase chain reaction analysis in 67 and 45 evaluable patients, respectively, showed that two 35-day cycles of VTD consolidation after double ASCT versus TD consolidation was associated with a significant increase in the rate of molecular remission and a significant reduction in the burden of residual myeloma cells.⁴³

In another study—in 46 evaluable patients younger than age 65 years with de novo MM—early consolidation with VTD after thalidomide and/or bortezomib induction therapy improved response in nearly 40% of patients.⁴⁴ Overall, consolidation therapy with two cycles of VTD, started within 3 months of ASCT, led to complete response in 36% of patients, complete response/near complete response in 68% of patients, and very good partial response in 91% of patients.⁴⁴

Data from the open-label, phase 2 IFM 2008 study in 31 evaluable patients younger than age 65 years with newly diagnosed MM showed that induction therapy with

bortezomib/lenalidomide/dexamethasone (VRD) followed by ASCT and VRD consolidation therapy yielded responses of high quality.⁴⁵ After consolidation, stringent complete response was achieved in 5 patients, and complete response was achieved in 5 patients.⁴⁵ The overall response rate after consolidation was 94%.⁴⁵

A recent study assessing the prognostic implications of cumulative dosing and premature discontinuation of the components of VTD from the outset of protocol therapy into maintenance therapy supports the upfront usage of all active agents in a dose-dense and dose-intense manner, as in the Total Therapy 3 (TT3) protocol.⁴⁶ In TT3, the addition of bortezomib, plus the shortening of induction and consolidation therapies to 2 cycles (from 4 cycles in TT2),⁴⁷ led to superior outcomes.⁴⁸

Summary

The role of maintenance therapy after conventional chemotherapy or high-dose therapy followed by ASCT in patients with MM is evolving.^{1,5,9,10} At present, clinical trials established improvement of PFS and, in many studies, OS with the use of thalidomide; the data for lenalidomide is immature to show OS difference, but established an impressive improvement of EFS.⁹ The addition of bortezomib in consolidation/limited maintenance therapy has shown improvement in the depth of response, including in many cases of molecular remission, which may establish a role for such intervention in eliminating minimal residual disease, a goal that is rarely obtained in MM patients.⁴⁴

Additional studies are needed to determine optimal dose and duration of any maintenance therapy and to identify patients who would most benefit from such treatment. Additionally, more research is needed to determine the impact of such therapy on the pattern of relapse and the response to salvage therapy.⁹

The current NCCN recommendations for maintenance therapy in MM include interferon alfa (category 2B); corticosteroids (category 2B); thalidomide (category 1) with or without prednisone (category 2B); and lenalidomide (category 2A). All are rarely used today because of side effects, as they are replaced mostly by lenalidomide (category 2A).³ Use of the proteasome inhibitor bortezomib as maintenance therapy lacks a formal NCCN recommendation.³

References

1. Attal M, Harousseau JL, Leyvraz S, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood*. 2006;108:3289-3294.
2. Magarotto V, Palumbo A. Evolving role of novel agents for maintenance therapy in myeloma. *Cancer J*. 2009;15:494-501.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Multiple myeloma. Version 1.2011. July 27, 2010. Available at: <http://www.nccn.org>. Accessed February 10, 2011.
4. Ghobrial IM, Stewart AK. ASH evidence-based guidelines: what is the role of maintenance therapy in the treatment of multiple myeloma? *Hematology*. 2009;587-589.
5. Berenson JR, Crowley JJ, Grogan TM, et al. Maintenance therapy with alternate-day prednisone improves survival in multiple myeloma patients. *Blood*. 2002;99:3163-3168.
6. Offidani M, Corvatta L, Polloni C, et al. Thalidomide-dexamethasone versus interferon-alpha-dexamethasone as maintenance treatment after ThAD induction for multiple myeloma: a prospective, multicentre, randomized study. *Br J Haematol*. 2008;144:653-659.
7. Dimopoulos MA, Terpos E. Multiple myeloma. *Ann Oncol*. 2010;21(suppl 7):vii143-vii150.
8. Anderson KC, Kyle RA, Rajkumar SV, et al. Clinically relevant end points and new drug approvals for myeloma. *Leukemia*. 2008;22:231-239.
9. Badros AZ. The role of maintenance therapy in the treatment of multiple myeloma. *J Natl Comp Cancer Netw*. 2010;8(suppl 1):S21-S27.
10. Salmon SE, Crowley JJ, Grogan TM, Finley P, Pugh RP, Barlogie B. Combination chemotherapy, glucocorticoids, and interferon alfa in the treatment of multiple myeloma: a Southwest Oncology Group study. *J Clin Oncol*. 1994;12:2405-2414.
11. Ludwig H, Adam Z, Tóthová E, et al. Thalidomide maintenance treatment increases progression-

- free but not overall survival in elderly patients with myeloma. *Haematologica*. 2010;95:1548-1554.
12. Browman GP, Bergsagel D, Sicheri D, et al. Randomized trial of interferon maintenance in multiple myeloma: a study of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 1995;13:2354-2360.
 13. Fritz E, Ludwig H. Interferon-alpha treatment in multiple myeloma: meta-analysis of 30 randomised trials among 3948 patients. *Ann Oncol*. 2000;11:1427-1436.
 14. Myeloma Trialists' Collaborative Group. Interferon as therapy for multiple myeloma: an individual patient data overview of 24 randomized trials and 4012 patients. *Br J Haematol*. 2001;113:1020-1034.
 15. Mandelli F, Avisati G, Amadori S, et al. Maintenance treatment with recombinant interferon alfa-2b in patients with multiple myeloma responding to conventional induction chemotherapy. *N Engl J Med*. 1990;322:1430-1434.
 16. **Bladé J, San Miguel JF, Escudero ML, et al. Maintenance treatment with interferon alfa-2b in multiple myeloma: a prospective randomized study from PETHEMA (Program for the Study and Treatment of Hematological Malignancies, Spanish Society of Hematology).** *Leukemia*. 1998;12:1144-1148.
 17. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. *J Clin Oncol*. 2006;24:929-936.
 18. Alexanian R, Weber D, Dimopoulos M, et al. Randomized trial of alpha-interferon or dexamethasone as maintenance treatment of multiple myeloma. *Am J Hematol*. 2000;65:204-209.
 19. Salmon SE, Crowley JJ, Balcerzak SP, et al. Interferon versus interferon plus prednisone remission maintenance therapy for multiple myeloma: a Southwest Oncology Group study. *J Clin Oncol*. 1998;16:890-896.
 20. Shustik C, Belch A, Robinson S, et al. A randomized comparison of melphalan with prednisone or dexamethasone as induction therapy and dexamethasone or observation as maintenance therapy in multiple myeloma: NCIC CTG MY.7. *Br J Haematol*. 2006;136:203-211.
 21. Hicks LK, Haynes AE, Reece DE, et al. A meta-analysis and systematic review of thalidomide for patients with previously untreated multiple myeloma. *Cancer Treat Rev*. 2008;34:442-452.
 22. Spencer A, Prince HM, Roberts AW, et al. Consolidation therapy with low-dose thalidomide and prednisone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. *J Clin Oncol*. 2009;27:1788-1793.
 23. Stewart AK, Trudel S, Bahlis N, et al. A randomized phase III trial of thalidomide and prednisone as maintenance therapy following autologous stem cell transplantation (ASCT) in patients with multiple myeloma (MM): the NCIC CTG MY.10 trial. Abstract presented at: 2010 American Society of Hematology Annual Meeting; Orlando, FL; December 4-7, 2010. Abstract 39.
 24. Brinker BT, Waller EK, Leong T, et al. Maintenance therapy with thalidomide improves overall survival after autologous hematopoietic progenitor cell transplantation for multiple myeloma. *Cancer*. 2006;106:2171-2180.
 25. Barlogie B, Pineda-Roman M, van Rhee F, et al. Thalidomide arm of Total Therapy 2 improves complete remission duration and survival in myeloma patients with metaphase cytogenetic abnormalities. *Blood*. 2008;112:3155-3121.
 26. Feyler S, Rawstrom A, Jackson G, et al. Thalidomide maintenance following high-dose therapy in multiple myeloma: a UK myeloma forum phase 2 study. *Br J Haematol*. 2007;139:429-433.
 27. Chang JE, Juckett MB, Callander NS, et al. Thalidomide maintenance following high-dose melphalan with autologous stem cell support in myeloma. *Clin Lymphoma Myeloma*. 2008;8:153-158.
 28. Zeldis JB, Knight RD, Jacques C, Tozer A, Bizzari JP. Lenalidomide in multiple myeloma: current role and future directions. *Expert Opin Pharmacother*. 2010;11:829-842.
 29. McCarthy PL, Owzar K, Anderson KC, et al. Phase III Intergroup study of lenalidomide versus placebo maintenance therapy following single autologous hematopoietic stem cell transplantation (AH SCT) for multiple myeloma: CALGB 100104. Abstract presented at: 2010 American Society of Hematology Annual Meeting; December 4-7, 2010; Orlando, FL. Abstract 37.
 30. McCarthy PL, Owzar K, Anderson KC, et al. Phase III Intergroup study of lenalidomide versus placebo maintenance therapy following single autologous stem cell transplant (ASCT) for multiple myeloma (MM): CALGB 100104. Abstract presented at: 2010 American Society of Clinical

31. Attal M, Cristini C, Marit G, et al. Lenalidomide maintenance after transplantation for myeloma. Abstract presented at: 2010 American Society of Clinical Oncology Annual Meeting; June 4-8, 2010; Chicago, IL. Abstract 8018.
32. Attal M, Lauwers VC, Marit G, et al. Maintenance treatment with lenalidomide after transplantation for myeloma: final analysis of the IFM 2005-02. Abstract presented at: 2010 American Society of Hematology Annual Meeting; Orlando, FL; December 4-7, 2010. Abstract 310.
33. Palumbo A, Dimopoulos MA, Delforge M, et al. A phase III study to determine the efficacy and safety of lenalidomide in combination with melphalan and prednisone (MPR) in elderly patients with newly diagnosed multiple myeloma. Abstract presented at: 2009 American Society of Hematology Annual Meeting; December 5-8, 2009; New Orleans, LA. Abstract 613.
34. Palumbo A, Delforge M, Catalano J, et al. A phase 3 study evaluating the efficacy and safety of lenalidomide combined with melphalan and prednisone in patients ≥ 65 years with newly diagnosed multiple myeloma (NDMM): continuous use of lenalidomide vs fixed-duration regimens. Abstract presented at: 2010 American Society of Hematology Annual Meeting; Orlando, FL; December 4-7, 2010. Abstract 622.
35. Morgan GJ, Davies FE, Cavenagh JD, Jackson GH. Position statement on the use of bortezomib in multiple myeloma. *Int J Lab Hematol*. 2008;30:1-10.
36. Benevolo G, Larocca A, Gentile M, et al. The efficacy and safety of bortezomib and dexamethasone as a maintenance therapy in patients with advanced multiple myeloma who are responsive to salvage bortezomib-containing regimens. *Cancer*. 2010 Nov 18 [Epub ahead of print].
37. Niesvizky R, Flinn IW, Rifkin RM, et al. Phase 3b UPFRONT study: safety and efficacy of weekly bortezomib maintenance therapy after bortezomib-based induction regimens in elderly, newly diagnosed multiple myeloma patients. Abstract presented at: 2010 American Society of Hematology Annual Meeting; Orlando, FL; December 4-7, 2010. Abstract 619.
38. Sonneveld P, Schmidt-Wolf I, van der Holt B, et al. HOVON-65/GMMG-HD4 randomized phase III trial comparing bortezomib, doxorubicin, dexamethasone (PAD) vs VAD followed by high-dose melphalan (HDM) and maintenance with bortezomib or thalidomide in patients with newly diagnosed multiple myeloma (MM). Abstract presented at: 2010 American Society of Hematology Annual Meeting; Orlando, FL; December 4-7, 2010. Abstract 40.
39. Palumbo A, Bringhen S, Rossi D, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. *J Clin Oncol*. 2010;28:5101-5109.
40. Mateos M-V, Oriol A, Martinez J, et al. A prospective, multicenter, randomized trial of bortezomib/melphalan/prednisone (VMP) versus bortezomib/thalidomide/prednisone (VTP) as induction therapy followed by maintenance treatment with bortezomib/thalidomide (VT) versus bortezomib/prednisone (VP) in elderly untreated patients with multiple myeloma older than 65 years. Abstract presented at: 2009 American Society of Hematology Annual Meeting; December 5-8, 2009; New Orleans, LA. Abstract 3.
41. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomized phase 3 study. *Lancet*. 2010;376:2075-2085.
42. Cavo M, Perrone G, Buttignol S, et al. Bortezomib-thalidomide-dexamethasone compared with thalidomide-dexamethasone as induction and consolidation therapy before and after double autologous transplantation in newly diagnosed multiple myeloma: results from a randomized phase 3 study. Abstract presented at: 2010 American Society of Hematology Annual Meeting; Orlando, FL; December 4-7, 2010. Abstract 42.
43. Terragna C, Zamagni E, Petrucci MT, et al. Molecular remission after bortezomib-thalidomide-dexamethasone compared with thalidomide-dexamethasone as consolidation therapy following double autologous transplantation for multiple myeloma: results of a qualitative and quantitative analysis. Abstract presented at: 2010 American Society of Hematology Annual Meeting; Orlando, FL; December 4-7, 2010. Abstract 861.
44. Roussel M, Dörr G, Vaillant W, Huynh A, Attal M. Consolidation with bortezomib, thalidomide and dexamethasone after high dose therapy is feasible, safe and effective in de novo multiple

myeloma patients who already received new drugs containing-induction regimen. Abstract presented at: 2010 American Society of Hematology Annual Meeting; Orlando, FL; December 4-7, 2010. Abstract 3041.

45. Roussel M, Avet-Loiseau H, Moreau P, et al. Frontline therapy with bortezomib, lenalidomide, and dexamethasone (VRD) induction followed by autologous stem cell transplantation, VRD consolidation and lenalidomide maintenance in newly diagnosed multiple myeloma patients: primary results of the IFM 2008 phase II study. Abstract presented at: 2010 American Society of Hematology Annual Meeting; Orlando, FL; December 4-7, 2010. Abstract 624.
46. van Rhee F, Szymonifka J, Anaissie E, et al. Total Therapy 3 for multiple myeloma: prognostic implications of cumulative dosing and premature discontinuation of VTD maintenance components, bortezomib, thalidomide, and dexamethasone, relevant to all phases of therapy. *Blood*. 2010;116:1220-1227.
47. Barlogie B, Tricot G, Anaissie E, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *N Engl J Med*. 2006;354:1021-1030.
48. Barlogie B, Haessler J, Pineda-Roman M, et al. Completion of pre-maintenance phases in Total Therapies 2 and 3 improves clinical outcomes in multiple myeloma: an important variable to be considered in clinical trial designs. *Cancer*. 2008;112:2720-2725.

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