

Modern Induction Therapy for Transplant-ineligible Multiple Myeloma Patients: Literature of Review

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Abstract

Multiple myeloma (MM) is a clonal plasma cell malignancy, characterized by the proliferation of neoplastic plasma cells the first case was documented in the literature in the year 1844. The current therapeutic strategy for multiple myeloma has witnessed a dramatic improvement when compared with the rhubarb pill and infusion of orange peel that were used in 1844. It is still an incurable disease but the introduction of novel therapies has altered the natural course of the disease, transforming it into a chronic disease from a terminal illness.

Keywords: myeloma, survival, remission

INTRODUCTION

Newly diagnosed myeloma patients, ineligible for transplant constitute a sizeable proportion of patients, as nearly almost two-third of individuals with multiple myeloma are older than 65 years at the time of diagnosis.[1] The immediate goal of therapy with these regimens in such patients, as with younger patients, include rapid control of disease and disease-related complications. However, the choice of therapy should also take into account comorbidities and performance status of the patient.[2]

For decades, melphalan in combination with prednisone (MP), which improved the median overall survival, has been the mainstay of therapy for patients ineligible for transplant. Single-agent dexamethasone has been used in some selected patients.[3] Combinations of vincristine with doxorubicin and dexamethasone, as well as other combinations of alkylation agents have also been evaluated, but with no survival advantage over MP and, often with added toxicity and inconvenience.[4]

Emerging therapeutic options under evaluation for first-line therapy for transplant-ineligible patients include thalidomide, lenalidomide, and the proteasome inhibitor bortezomib alone, and in combination with other agents. Several clinical trials continue to evaluate combinations of these novel agents with MP, and compare them to with what was once the standard approach of melphalan and prednisone. These combinations offer overall and

complete response rates and in some trials survival benefits leading to significant advancement in the treatment of multiple myeloma for transplant-ineligible patients. Recently, trials comparing non-melphalan regimens to melphalan-based combinations have also been initiated.[3,4]

Melphalan, Prednisone, and Thalidomide (MPT)

After the activity of thalidomide against relapsed/refractory myeloma was noted in the late 1990s, the drug was rapidly moved to the front-line, in combination with melphalan.[5] Randomized trials have demonstrated superior progression-free survival (PFS) and some have also shown a significant survival benefit with melphalan, prednisone, thalidomide (MPT) over melphalan/ prednisone (MP) (Table - 1).

The French Intergroupe Francophone du Myélome (IFM) group studied the role of MPT in 447 myeloma patients aged 65-75 years (IFM 99-06).[6] The patients were randomized to one of the three arms: the first was a standard MP arm; the second was the MPT arm; and third, a tandem autologous transplant using vincristine, doxorubicin and dexamethasone (VAD) induction and intermediate-dose melphalan (100 mg/m²). After a median follow-up of 51.5 months, median overall survival (OS) times for MP, MPT, and transplant arms were 33.2 months, 51.6 months, and 38.3 months, respectively; p = 0.0006. The MPT arm was associated with a significantly better overall survival than was the MP arm or the transplant arm. There was no difference in median PFS between the MP and transplant arms. The use of lower dose of melphalan (100 mg/m²) in the transplant arm than a conventional conditioning regimen of melphalan 200 mg/m², however, has limited the analysis of this trial.

The IPM 01/01 trial evaluated MPT and MP in newly diagnosed myeloma patients aged more than 75 years.[7] Patients were randomly assigned to treatment with MP plus placebo or MPT. After a median follow-up of 47.5 months, OS was significantly longer in patients who received MPT (median 44 months) compared with those who received MP plus placebo (median 29.1 months; p =

0.028). Progression-free survival (PPS) was significantly prolonged in the MPT group (median, 24.1 vs 18.5 months; $p = 0.001$). Palumbo et al., reported a complete or near complete response rates (CR/nCR) of 27.9% with MPT regimen compared to 7.2% for MP regimen in newly diagnosed myeloma patients.⁸ After a median follow-up of 38.1 months, the median PPS was 21.8 months for MPT and 14.5 months for MP ($p = 0.004$). However, there was no survival advantage; the median OS was 45 months for MPT and 47.6 months for MP ($p = 0.79$).

In contrast, the Nordic Myeloma Study Group (NMSG)^[9] failed to demonstrate a significant difference in PFS or OS between MPT and MP plus placebo. In the Nordic Myeloma group trial PPS was 16 and 14 months, and OS was 29 and 39 months in the MP and MPT arms, respectively. Likewise, the HOVON Myeloma group^[10] was also unable to find a significant difference between MPT and MP in a randomized trial in either PPS (13 vs 10 months; $p < 0.001$) or OS (37 vs 30 months). It is possible that the dose of thalidomide (Nordic trial) and that of melphalan (HOVON trial) was too high, resulting in excess toxicity and did not permit adequate dosing. Also, the trials that failed to show a survival advantage for MPT used maintenance thalidomide in the MPT arm.

Other Thalidomide-Based Regimens

The therapeutic potential and toxicity of thalidomide and dexamethasone combination (TD) was compared with MP as first-line treatment of elderly patients with multiple myeloma not eligible for high-dose therapy.^[11] Although TD group showed a significantly higher rate of very good responses [CR and very good partial remission (VGPR)] and significantly shorter time to response, there was no difference in time to progression (TTP) and in PFS. Surprisingly, OS, was found to be significantly shorter with TD. This may be explained by the higher incidence of toxicity particularly in patients > 75 years old with a poor performance status, and as a result of the high dose pulses of dexamethasone used in the TD arm.

Preliminary results of a large trial conducted by the MRC myeloma group compared the combination of cyclophosphamide, thalidomide, and dexamethasone (CTD) to the MR regimen.^[12] Patients received an attenuated CTD regimen (CTDa: cyclophosphamide, 500 mg; thalidomide, 100 mg daily; dexamethasone, 20 mg). Although the CTD regimen was superior in terms of the overall response rate and CR rate, the PFS time was comparable between the two arms.

Lenalidomide-Based Regimens

Lenalidomide, an oral thalidomide analogue, was synthesized to avoid the non-hematologic

toxicity of thalidomide without compromising the efficacy.^[3] The results of MM-009 and MM-010 studies have proven the efficacy of lenalidomide in elderly patients with relapsed/refractory myeloma.^[13,14] Lenalidomide-based regimens may represent an alternative approach in the primary induction of transplant-ineligible patients.

A sub analysis of the phase III ECOG trial examined the efficacy of lenalidomide plus high-dose dexamethasone (RD) versus lenalidomide plus low-dose dexamethasone (Rd) as initial therapy for newly diagnosed myeloma patients more than or equal to 65 years old.^[15] The 1 year survival rate was found to be significantly better for patients receiving Rd than for those receiving RD (94% vs 83%, respectively; $p = 0.004$).

A report from the Gruppo Italiano per le Malattie Ematologiche dell'Adulto (GIMEMA)-Italian Multiple Myeloma Network, studied the combination of oral melphalan, prednisone, and lenalidomide (MPR) as a first-line treatment for elderly myeloma patients.^[16] With the maximum tolerated doses of melphalan (0.18 mg/kg) and lenalidomide (10 mg), 81% of patients achieved at least a PR, 47.6% achieved a VGPR, and 23.8% achieved a complete immunofixation-negative response. The 1-year event-free survival (EFS) and OS rates were 92% and 100%, respectively. At the maximum tolerated dose, grade 3 adverse events included neutropenia, thrombocytopenia, febrile neutropenia, vasculitis, and thromboembolism; grade 4 adverse events were neutropenia and thrombocytopenia.

The results of the MM-015 study confirmed MPR followed by lenalidomide maintenance as a new therapeutic option for patients older than 65 years old.^[17] The study randomized patients to one of three arms: MP with no maintenance; MPR followed by no maintenance; and MPR followed by lenalidomide maintenance (MPR-R). The trial was terminated early on recommendation from the data monitoring committee, and early results have demonstrated a superior response rate in the lenalidomide arms (77%, 67%, and 49% for MPRR, MPR, and MP, respectively). In addition, the trial demonstrated an approximately 50% improvement in PFS for patients treated with MPR-R compared with MP and MPR. Overall survival data remain immature.

In addition, the HOVON, the Nordic Myeloma Study Group and ECOG are conducting a phase III trial in elderly patients comparing MPT plus maintenance thalidomide with MPR followed by maintenance with lenalidomide, which will further clarify the role of lenalidomide in such patients. ^[18]

Bortezomib-Based Regimens

In an attempt to improve outcomes in newly diagnosed patients with myeloma ineligible for transplant, a combination of MP with bortezomib has been studied (Table -2). In a phase I/II trial in 60 elderly (median age 75, range 65-85) previously untreated myeloma patients, bortezomib-melphalan-prednisone (VMP) achieved complete and overall response rates of 32 and 89%, respectively with 16 months with EFS and OS rates of 83 and 90%, respectively.[19] Bortezomib-melphalan-prednisone also appeared to overcome the poor prognosis conferred by 13q deletion and IgH translocations. The principal toxicities were hematologic, gastrointestinal, and peripheral neuropathy, which were more evident during early cycles and in patients aged 75 years or more.

On the basis of these promising results, VMP was compared with MP in an international, phase III randomized trial [Velcade as Initial Standard Therapy in Multiple Myeloma : Assessment with melphalan and prednisone (VISTA)] in patients at least 65 years, ineligible for transplant.[20] In this prospective trial comparing VMP with MP, following a median follow-up of 16.3 months, patients treated with VMP had significantly longer median TTP (24 vs 17 months; $p < 0.001$) when compared with those treated with MP. The proportions of patients with a partial response or better were 71% in the VMP group and 35% in the MP group ($p < 0.001$); CR rates were 30% and 4% ($p < 0.001$), respectively. In an updated analysis, the OS rate at 38 months was 85% with VMP and 38% with MP ($p < 0.0001$). Patients in the VMP arm had a significantly longer time to subsequent therapy (28.1 vs 19.2 months; $p < 0.000001$) and treatment-free interval (16.6 vs 8.4 months; $p < 0.00001$). Fewer patients in the VMP arm (38% vs 57%) required subsequent therapy. Additionally, re-treatment with bortezomib was effective in the VMP arm (6% CR); a 10% CR rate was reported in the MP arm after bortezomib-based therapy.[21,22] It was further noted that adverse cytogenetics, advanced age and renal function did not affect the efficacy of the bortezomib containing regimen. Adverse events were consistent with established profiles of toxic events associated with VMP. Grade 3 events occurred in a higher proportion of patients in the VMP group than in the MP group, but there were no significant differences in grade 4 events or treatment-related deaths. The VMP regimen has now been placed under the National Comprehensive Cancer Network (NCCN), category 1 recommendation for the primary induction treatment of transplant- ineligible myeloma patients.[23]

Recently, the WVIP combination has been compared with non-MP based bortezomib combinations. The Spanish Myeloma Group activated a phase III trial comparing VMP versus Velcade,

thalidomide, and prednisone (VTP) as induction therapy in elderly patients with newly diagnosed myeloma, followed by maintenance treatment with VT vs VP for up to three years.[24] Response rate to induction therapy was similar in both arms: 2 PR in 81 and 79% of patients treated with VMP and VTP respectively, with a CR rate of 22% vs 27% ($p = NS$) and CR+nCR of 36% in both arms. Overall, maintenance therapy was able to increase the CR rate from 25% (mean obtained after induction therapy) up to 42%, with no significant differences between VT and VP arms (46 and 38%). After a median duration of maintenance of 13 months there was a trend in favour of VMP induction followed by maintenance VT in terms of 1-year TTP (84% vs 71%; $p = 0.05$), without differences in 1-year OS (92% for VT vs 89% for VP). There was a clear different toxicity profile (more neutropenia, but less cardiac toxicity and peripheral neuropathy with VMP).

The upfront study, a phase IIIb multicentre study is comparing the safety and efficacy of three highly active bortezomib based regimens for multiple myeloma; VTD, bortezomib and dexamethasone (VD), and VMP, in previously untreated myeloma patients ineligible for high-dose therapy and autologous stem cell transplantation.[25] With early follow-up, all three regimens demonstrated substantial activity. The overall response rate was 60%, 70%, and 52% in the VD, VTD, and VMP arms, respectively (CR/nCR: 13%, 18% and 15%; greater than or equal to VGPR: 15%, 23% and 24%, respectively).

The Italian myeloma group has studied the 4 drug combination of bortezomib, melphalan, prednisone and thalidomide (VMPT) in elderly patients with myeloma.[26] Bortezomib, melphalan, prednisone and thalidomide followed by maintenance with bortezomib and thalidomide was found to be superior to VMP for response rates; PR rate (86% vs 79%, $p = 0.02$), VGPR rate (55% vs 47%, $p = 0.07$) and CR rate (34% vs 21% $p = 0.0008$). After a median follow-up of 17.8 months, the 2-year PFS was better in the VMPT group (70% vs 58.2%; $p = 0.008$). The achievement of CR significantly prolonged PFS in both VMPT ($p < 0.0001$) and VMP ($p = 0.003$) patients. Chromosomal abnormalities, such as del, t(4;14), t(14;16), or del 17, did not affect 2-year PFS in both VMPT ($p = 0.51$) and VMP ($p = 0.41$) patients. The 2-year OS was 89.6% in the VMPT group and 89.0% in the VMP group ($p = 0.84$). An important observation with this setting was that weekly infusion of bortezomib given to a subset of patients significantly reduced the incidence of peripheral neuropathy without affecting outcome.

CONCLUSION

With the introduction of novel agents, new standards of care in patients ineligible for transplantation have emerged. The NCCN

recommendations for primary induction therapy for multiple myeloma in transplant-ineligible patients are listed in table-3 However, no randomized trials comparing MP combinations with Support: Nil

Conflict of interest: None declared

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TABLES

Table - 1									
Summary of Trials Evaluating Melphalan, Prednisone and Thalidomide in Patients Not Eligible for transplantation									
MPT regimen									
Sl No	Study	N	Cycles	Melphalan dose	Thalidomide dose	CR+PR (%)	CR (%)	PFS/EFS/TT P (months)	OS (months)
01	MPT vs MP vs ASSCT MEL - 100 trial) ⁶	447	12	0.25 mg/kg, day 1-4	Thalidomide dose, Up to 400 mg	76 vs 35 vs NR	76 vs 35 vs NR	28 vs 18 vs 19, (p < 0.0001)	51.6 vs 33.2 (p = 0.0006)
02	MPT vs MP + Placebo(IFM 01/01) ⁷	232	12	0.2 mg/kg, day 1-4	100 mg	62 vs 31	7 vs 1	24.1 vs 18.5 (p = 0.001)	44 vs 29.1 (p = 0.028)
03	MPT vs MP ⁸	331	6	4mg/m ² days 1-7	100	76 vs 48	15.6 vs 3.7	21.8 vs 14.5mg (p = 0.004)	45 vs 47.6 (p = 0.79)
04	MPT vs MP + Placebo (Norodic Group) ⁹	362	Until Plate-au	0.25 mg/kg	Up to 400 mg	NR	NR	16 vs 14, (PFS; p NS), 20 vs 14	39 vs 29, (p = NS)
05	MPT vs MP (HOVONM Myeloma group) ¹⁰	344	Until Plate-au	0.25 mg/kg, Days 1-5	200 mg	NR	NR	13 vs 10 (p <0.001)	37 vs 30 (p = NS)

MP: Melphalan and prednisone, MPT: Melphalan, prednisone and thalidomide ASCT: Antilougous stem cell transplant, MEL-100: Melphalan,² CR: Complete remission, PR: Partial remission, PFS Progression –free survival, EFS: Event –free survival, TTP: Time to disease progression, OS: Ovrivall survival, NR Not reported NS: Not significant

Table – 2						
Summary of Bortezomib-based Trials in patients Ineligible Transplantation						
Sl No	Study	Median	CR%	PR (%)	TPT(months)	OS (%)
01	VMP vs (VISTA trils) ^{20,22}	25.9	30 vs 4 (p <0.001)	71 vs 35 (p < 0.001)	28.1 vs 19.2 (p< 0.000001)	72 vs. 59 (3year) (p = 0.0032)
02	VMP vs VTP induction	22	46 vs 38	NR	84% VS 71%	92 VS 89
03	Followed by VT vs VP maintenance	22	46 VS 38 (P = NS)	NR	84% VS 71% (P = 0.05)	92 VS 89 (1year(p=NS)
03	Myeloma Group) ²⁴ VMPZT followed by VT vs VMP (Italian Myeloma Group) ²⁶	17.8	34 vs 21 (p= 0.0008)	86 vs 79 (p 0.02)	NR	89.6 vs 89 (2-YEAR) (P = 0.84)

MP: Melphalan and prednisone VMP: Bortezomib, melphalan and prednisone VMPT: Bortezomib melphanlan, prednisone and thalidomide, OS Overall survival, NS not significant, NR Not reported.

Table - 3	
Sl No	NCCN recommendations for primary Therapy for multiple myeloma
01	Dexamethasone (Category 2B)
02	Lenalidomide/low –dose dexamethasone (category1)
03	Liposomal doxorubicin/vincristine /dexamethasone (Category 2B)
04	Melphalan/prednisone (MP)
05	Melphalan/prednisone bortezomib (Category1)
06	Thalidomide/ dexamethasone (Category 2B)
07	Vincristine/doxorubicin/dexamethasone (Category 2B)

MPV, MPT, and MPR are available, and often the choice of regimen presently is driven by factors like side effect profiles, conveniences and affordability. NCCN Recommendations for Primary Therapy for multiple Myeloma.