IMWG Guidelines for the Management of Multiple Myeloma Patients Ineligible for Standard High-Dose Chemotherapy with Autologous Stem Cell Transplantation[1]

A panel of the International Myeloma Working Group (IMWG) consisting of experts in clinical medicine, clinical research, health services and related disciplines (biostatistics, medical decision-making, patient-physician communication), and a patient representative reviewed all the evidence-based myeloma practice guidelines and randomized controlled trials or meta-analyses published in English between December, 2004 and December, 2008. These trials and meta-analyses compared standard chemotherapy versus experimental new drugs, reported overall survival (OS) or disease-free survival as a main outcome, and were published in peer-reviewed journals or reported in a conference abstract. The following guidelines for the management of myeloma patients who are not candidates for high-dose chemotherapy with stem cell transplant are the result of the panel's findings.

Monitoring and Start of Therapy

- No change from earlier guidelines.[2]
- Systemic anti-myeloma therapy indicated for initial treatment of symptomatic myeloma with myeloma-related organ dysfunction.
- No benefit shown for early intervention in standard-risk asymptomatic myeloma; however there are several ongoing studies evaluating new agents in the context of asymptomatic MM.
- Monitoring of MM during treatment should be done according to the clinical conditions.
- For patients in remission, follow-up monitoring should be every 2 months.
- Criteria for retreatment are the same as those used at diagnosis, with the exception that retreatment should be administered in patients without organ damage if the M-protein has doubled within less than 2 months.

Staging and Prognostic Factors[3]

- Patients with symptomatic myeloma are categorized according to disease stage based on the International Staging System (ISS).
- Further factors, such as serum free light chain ratio, or the bone resorption marker ICTP, incorporated into the ISS may improve risk stratification.

- Cytogenetics and/or FISH should be performed in all newly diagnosed MM patients as well as subsequently at the time of relapse, as patients may acquire new chromosomal abnormalities at the time of progression.
    - Any cytogenetic abonormality is associated with poorer outcome compared to normal karyotype.
    - Among FISH-based abnormalities, patients with isolated del 13 don't have a less favorable outcome, although del 13 associated with 17p deletion or t(4;14) are associated with poorer outcome.
    - t(11;14) by FISH does not have a negative outcome.
    - Hyperdiploidy by FISH is associated with more favorable outcome.
    - Although treatment regimens that include bortezomib or lenalidomide may overcome poor prognosis, no specific alternate therapy is routinely recommended for patients with chromosomal abnormalities.

Overall treatment strategy related to age

- Patients younger than 65 should be considered candidates for induction therapy followed by ASCT.
- Outside the United States, patients over 65 years of age are generally not considered to be candidates for stem cell transplant. However, biological age may differ from chronological age in elderly patients.
- Patients age 65-70 or younger with significant co-morbidities may be considered for reduced-dose intensity autologous transplantation.
- Patients with serious heart, lung, renal, or liver dysfunction should not be considered for transplantation.
- For patients 65-75 years of age, full-dose conventional therapy is suggested.
- For patients over 75 years of age (or younger with significant co-morbidities), the dosages of any therapy should be reduced and a more gentle approach considered.

Front-line therapy

- MPT is considered a standard of care for patients > 65 years; associated with neurologic adverse events, infections, cardiac toxicity, and thromboembolism; antithrombotic prophylaxis is recommended.

- VMP is another standard of care for elderly patients; weekly infusion of Velcade (bortezomib) significantly reduces the incidence of peripheral neuropathy (PN) and should be considered in patients with pre-existing PN.
- Thalidomide + dexamethasone (TD) has inferior OS compared to melphalan + prednisone (MP) in the older patient population and is not recommended as standard therapy.
- Revlimid (lenalidomide) + low-dose dexamethasone (Rd) can be considered a standard of care, especially in patients who wish to postpone ASCT.
- MPR (melphalan, prednisone, Revlimid) is currently being validated in a randomized phase III trial comparing MPR with the accepted standard melphalan, prednisone, and thalidomide (MPT); it is therefore not currently recommended as standard frontline therapy in older patients.

Table 1. Phase III studies in newly diagnosed MM.

Regimen	***N***	***ORR (CR), %***	***Median PFS, months***	***Median TTP, months***	***Median survival, months***
TD vs. D (Rajkumar et al., 2008)	470	63 (7.7) vs. 46 (2.6)	14.9 vs. 6.5	22.6 vs. 6.5	
TD vs. MP (Ludwig et al., 2008)	289	68 (2) vs. 50 (2)	16.7 vs. 20.7	21.2 vs. 29.1	41.5 vs. 49.4
RD vs. D (Zonder et al., 2007)	198	79.4 (22) vs. 26.2 (4)[1]	77% vs. 55% @ 1 year		93% vs. 91% @ 1 year
RD vs. Rd (Rajkumar et al., 2008)	445	82 (52) vs. 70 (42)[2]			87% vs. 75% @ 2 years
MPT vs. MP (Palumbo et al., 2006; 2008a)	255	76 (15.5) vs. 47.6 (2.4)	21.8 vs. 14.5		45.0 vs. 47.6
MPT vs. MP (Facon et al., 2007)	321	76 (13) vs. 35 (2)	27.5 vs. 17.8		51.6 vs. 33.2
MPT vs. MP (Hulin et al., 2007)	232	62 (7) vs. 31 (1)	24.1 vs. 19		45.3 vs. 27.6
MPT vs. MP (Gulbrandsen et al.,	357	42 (6) vs. 28 (3)	16 vs. 14	20 vs. 18	29 vs. 33

2008)					
VMP vs MP (San Miguel et al., 2008)	682	71(30) vs. 35(4)		24 vs. 17	83% vs. 78% @ 16 months
VMP vs. VPT (Mateos et al., 2008)	246	78 (18) vs. 78 (23)			
VMPT vs. VMP (Palumbo et al., 2008b)	393	55 (31) vs. 42 (16)[3]	83.9% vs. 75.7% @ 2 years		89.5% vs.88.7% @ 3 years
MPT vs. MP (Wijermans et al., 2008)	344	66 (2) vs. 47% (2)	14 vs. 10		37 vs. 30

- [1] Percentages reported for ORR include minor response.
- [2] Percentages reported for CR include VGPR.
- [3] Percentages reported for ORR are at least VGPR.
- CR, complete remission; MP, melphalan and prednisone; MPT, MP plus thalidomide; ORR, overall response rate (at least partial remission); PFS, progression-free survival; RD, lenalidomide and high-dose dexamethasone; Rd, lenalidomide and low-dose dexamethasone; TD, thalidomide and high-dose dexamethasone; TTP, time to progression; VMP, MP plus bortezomib; VMPT, VMP plus thalidomide; VPT, bortezomib, prednisone, thalidomide.

Reduced-intensity autologous transplant

- Reduced-intensity (RI) ASCT is designed for patients > 65 years of age and uses melphalan at 100 mg/m2 instead of 200 mg/m2. Two clinical trials were conducted in Europe comparing this regimen with standard MP. In patients age 65-70, RI ASCT was superior to MP. In pts 65-75, PFS and OS were equal to those with MP.
- A third European trial was conducted for pts 65-75 using PAD (Velcade, Adriamycin, and dexamethasone) induction, RI ASCT, followed by consolidation with Revlmid + prednisone and maintenance with Revlimid alone. The data thus far indicate that this is a highly effective regimen.
- Reduced-dose melphalan followed by ASCT can be used in patients age 65-70 or younger with pre-existing co-morbidities. The use of bortezomib-based induction before ASCT is suggested. Consolidation with lenalidomide needs further validation in randomized trials.

Maintenance

- There is insufficient evidence regarding the use of maintenance therapy in older patients.

Therapy at relapse

- Bortezomib with or without dexamethasone or in combination with liposomal doxorubicin (Doxil) is recommended in relapsed/refractory patients.
- Lenalidomide in combination with dexamethasone is recommended in relapsed/refractory patients.
- Both TD and VD remain convenient regimens for relapsing or refractory patients.
- Other approaches, including combinations with chemotherapy or novel agents, should be considered when established salvage regimens have already been used.
- For patients who relapse following a durable response (i.e. longer than the median PFS for the previous therapy), the same treatment should be repeated.
- For patients who relapse following a short response (shorter than the median PFS for the previous therapy), the patient should be sequentially introduced to new regimens.
- Drugs that were used before the re-challenge remain secondary options if there was no evidence of progression under that drug.
- The choice of drug depends on pre-existing co-morbidities.

Table 5. Phase III clinical studies in relapsed and/or refractory patients.

Regimen	***N***	***ORR (CR), %***	***Median response duration, months***	***Median TTP, months***	***Median survival, months***
V vs D (Richardson et al., 2005)	669	38 (6)[1] vs. 18 (0.6)	8.0[1] vs. 5.6	6.2[1] vs. 3.5	80%[1] vs. 66% @ 1 year
V vs. V + PLD (Orlowski et al., 2007)	646	41 (2) vs. 44 (4)	7.0 vs. 10.2	6.5 vs. 9.3	65% vs. 76% @ 15 months
RD vs. D	351	60 (16) vs. 24		11.3 vs. 4.7	Not reached vs.

(Dimopoulos et al., 2007)		(3)			20.6
RD vs. D (Weber et al., 2007)	353	61 (14) vs. 20 (0.6)		11.1 vs. 4.7	29.6 vs. 20.2

- [1]Extended median follow-up of 22 months of the bortezomib arm reported an ORR of 43%, CR of 9%, median response duration of 7.8 months, median TTP of 6.2 months, and median survival of 29.8 months (Richardson et al., 2007).
- CR, complete remission; D, dexamethasone; ORR, overall response rate (at least partial remission); RD, lenalidomide and dexamethasone; TTP, time to progression; V, bortezomib; VD, bortezomib and dexamethasone; V + PLD, bortezomib plus pegylated liposomal doxorubicin.

Table 6. Phase II studies in relapsed or refractory MM.

Regimen	***N***	***ORR (CR), %***	***Median PFS, months***	***Median TTP, months***	***Median survival, months***
TD (Dimopoulos et al., 2001)	44	55 (0)	10[1]	4.2	12.6
TD (Palumbo et al., 2001)	77	41[2] (3)		12	Not reached
TD vs. chemotherapy (Palumbo et al., 2004)	120	46 vs. 42	17 vs. 9		19 vs. 19
TD + doxorubicin (Offidani et al., 2006)	50	76 (26)	22	173	79% @ 1 year
DVd-T (Hussein et al., 2006)	49	75 (20)	15.5		39.9
CTD (Kyriakou et al., 2005)	52	79 (17)	34% @ 2 years[3]	Not reached	73% @ 2 years
CTD (Dimopoulos et al., 2004)	53	60 (5)		8.2	17.5
CTD (Garcia-Sanz et al., 2004)	71	57 (2)	57% @ 2 years		66% @ 2 years
CTD (Kropff et al., 2003)	60	72 (4)	11[3]		19
DVd-R (Baz et al., 2006)	62	75 (15)	12		Not reached
CVD vs. VD (Davies et al., 2007)	36	75 (31) vs. 47 (5)	7 vs. 5		

CVD (Kropff et al., 2007)	54	82 (16)	12[3]		22
CVP (Reece et al., 2008)	37	89 (53)[4]		15	24.3
VTD (Pineda-Roman et al., 2008)	85	63 (22)[5]	6% @ 4 years[3]		23% @ 4 years
VMPT (Palumbo et al., 2007b)	30	67 (17)	61% @ 1 year		84% @ 1 year
VMDT (Terpos et al., 2008)	62	66 (13)		9.3	
VTD vs. MyVTD (Ciolli et al., 2008)	70	81 vs. 59	15 vs. 8	19 vs. 11	
RVD (Richardson et al., 2008)	64	67 (24)[5]	21[6]	Not reached	Not reached
RCD (Morgan et al., 2007)	21	65 (5)		5.7	

- [1] Median TTP for responders not reached, expected to exceed 10 months.
- [2] > 50% decline in myeloma protein.
- [3] Event-free survival
- [4] Patients treated at dose levels 5 and 6 (bortezomib: 1.3 mg/m2 days 1, 4, 8, 11 [level 5] and 1.5 mg/m2 days 1, 8, 15 [level 6]; cyclophosphamide: 300 mg/m2/week; prednisone: 100 mg every 2 days).
- [5] Percentage for CR includes nCR.
- [6] Duration of response.
- CR, complete remission; CVD, VD plus cyclophosphamide; CVP, cyclophosphamide, bortezomib, and prednisone; DVd-T, pegylated liposomal doxorubicin, vincristine, decreased-frequency dexamethasone, and thalidomide; CTD, TD plus cyclophosphamide; DVd-R, DVd and lenalidomide; MyVTD, VTD plus myocet; ORR, overall response rate (at least partial remission); PFS, progression-free survival; RCD, lenalidomide, cyclophosphamide, and dexamethasone; RVD, VD plus lenalidomide; TD, thalidomide and dexamethasone; TTP, time to progression; VD, bortezomib and dexamethasone; VMDT, bortezomib, melphalan, dexamethasone, and thalidomide; VMPT, bortezomib, melphalan, prednisone, and thalidomide; VTD, TD plus bortezomib.

Palliative care

- The primary aim of palliative care is to alleviate symptoms.

- Good supportive care and continuity of care are important.
- Good communication between the patient, palliative care team, and doctor are essential to ensure that the patient's desires and concerns are addressed.

Complications

- Bone disease
    - Bone pain, hypercalcemia, and pathologic fractures are treated with bisphosphonate therapy. Options include IV pamidronate, IV zoledronic acid, and in some countries, oral clodronate. Osteonecrosis of the jaw is an uncommon but potentially serious complication of bisphosphonates. See IMWG guidelines on the use of bisphosphonate therapy.
    - For relief of pain, use of prescribed analgesics following principles of the WHO
    - Kyphoplasty, if appropriate, for local pain relief and bone strengthening. See IMWG consensus statement on the role of vertebral augmentation in myeloma.
    - NSAIDS should be avoided due to potential for gastric irritation and adverse effects on renal function.
    - Use of in-hospital pain clinics should be used in difficult cases.
    - Alternative medical procedures such as relaxation techniques, aromatherapy, and hypnosis may be helpful.
    - Use of radiotherapy should be limited whenever possible as long-term use of radiation can affect hematopoietic reserve and bone healing; when used locally, recommended dose for control of bone pain is 8-Gy single fraction.

- Renal failure
    - Maintain high fluid intake (at least 3 liters per day).
    - Avoid nephrotoxic drugs (aminoglycosides and NSAIDs).
    - Treat hypercalcemia and infection.
    - Thalidomide and bortezomib require no dose modification in the context of renal dysfunction.
    - Lenalidomide can be used, but should be dose modified and hematological function watched closely in early cycles.

- Hematologic toxicity
    - Treatment should be held for grade 4 neutropenia lasting at least 7days despite GCSF administration. When the adverse event resolves to grade 2, reintroduce treatment with dose reduction at beginning of next cycle.
    - Prophylaxis with GCSF is recommended for the prevention of febrile neutropenia in patients at high risk based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen.
    - Erythropoiesis-stimulating agents (ESAs) is generally recommended when the hemoglobin level is less than 9 g per 100 ml unless the patient has heart disease or has trouble performing activities of daily living.
    - ESA dose should be adjusted to avoid the need for blood transfusion, but below 12 g/100 ml.

- DVT
    - Aspirin is only recommended for patients with no risk factors or one individual/myeloma-related risk factor.
    - Low molecular-weight heparin or full-dose warfarin is recommended for patients with at least two individual/myeloma-related risk factors. See IMWG guidelines on prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma.

- Infections
    - Treat fever in all MM patients promptly and with broad-spectrum antibiotics.
    - IV antibiotics are required for severe systemic infection.
    - For patients starting chemotherapy, prophylactic trimethoprim-sulfamethoxazole (Septra) for the first two months or during steroid administration periods.
    - Acyclovir prophylaxis is recommended for all patients receiving bortezomib-based therapy, and may be useful during the induction period in order to reduce the risk of VZV reactivation.

- Peripheral neuropathy (PN)
    - For bortezomib, a dose reduction to 1.0 mg/m^2 is recommended for grade 1 PN with pain or grade 2 PN. Alternatively, administer bortezomib once weekly for grade 1 with pain.

- For grade 2 with pain or grade 3 PN, interrupt bortezomib dose until PN resolves with re-initiation at 0.07 mg/m^2 per week.
- For grade 4 PN, treatment discontinuation.

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[1] A. Palumbo *et al. Leukemia* (2009), 1-15.

[2]Smith *et al*. Guidelines on the diagnosis and management of multiple myeloma 2005. *Br J Haematology* 2005; **132**: 410-451.

[3]See PR Greipp et al. International Staging System for Multiple Myeloma. J Clinical Onc May 20, 2005; 23:15, 1-9.