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Multiple Myeloma: Front Line Therapy and Autologous Stem Cell Transplantation

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ABSTRACT

Prognosis of multiple myeloma (MM) has improved during the past two decades. This has been attributed to the better understanding of the biology of disease leading to introduction of two new classes of molecules, namely immune-modulators (e.g. thalidomide, lenalidomide), and proteasome inhibitors (e.g. bortezomib), use of high dose chemotherapy and autologous stem cell transplantation (ASCT) and better supportive care. Current management of myeloma for young patients (≤65 years) includes initial induction therapy followed by consolidation with ASCT followed by maintenance therapy with low dose thalidomide or lenalidomide or bortezomib for 1-2 years.

The choice of initial therapy for patients of MM is based upon their eligibility for ASCT which in turn is based on their age and major co-morbid conditions pertaining to cardiac and renal systems. Patients who are ≤65 years of age (or 65 to 70 years) with no major co-morbid conditions are considered potential candidates for ASCT. Four cycles of induction therapy are administered; a combination of 3 drugs (bortezomib, thalidomide, and dexamethasone (BTD) or bortezomib, lenalidomide, and dexamethasone (BLD) or bortezomib, cyclophosphamide and dexamethasone (BCD) is associated with higher complete response (CR) (approx. 30-40%) and very good partial response (VGPR) and better progression free survival (PFS). Further consolidation with ASCT results in CR rates of 50%–70%; patients who achieve CR, have improved event-free and overall survival. Our initial experience with 225 ASCT supports these observations.

It is now possible to individualize therapy in a given patient. For example, for patients with renal failure (present in 20-30% of patients at diagnosis) —bortezomib, dexamethasone and/or doxorubicin combination could be an option; for patients with pre-existing peripheral neuropathy—lenalidomide and dexamethasone is preferred; for patients at high risk of venous thrombo-embolism bortezomib-based regimens can be used safely. Treatment with bortezomib or bortezomib + lenalidomide for patients with poor cytogenetics (chromosome deletion t(4;14), t(14;16), 17p–) appears to result in an outcome similar to that in patients without these abnormalities.

In conclusion, from being incurable, myeloma is now a chronic illness. Along with earlier diagnosis, improved treatment and better management of complications have resulted in longer disease control and survival with a better quality of life. Novel agents have provided an opportunity to tailor therapy in an individual patient. Further research is needed to improve outcome for patients who fail to achieve complete response, those with ISS stage III, and extra-medullary disease. Availability of oral proteasome inhibitors and monoclonal antibodies (e.g. IL-6 receptor) are likely to expand choice of agents for maintenance therapy in future.

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Introduction

Multiple myeloma (MM)- a disease of malignant plasma cells accounts for 1% of all malignant disorders and 10-15% of haematological malignancies. While incidence of myeloma is lower in Asia and in India compared to West, there is evidence that in metropolitan cities, incidence of MM is gradually rising (1). Some of key differences seen in presentation in India compared to western population include- younger age at presentation (median 55-60 years compared to 65 years), delay in diagnosis, lower proportion of asymptomatic patients (1-2% Vs 10-20%), higher proportion of patients with anaemia (Hb <10g/dL) , ISS stage III (30 to 50%), renal failure (eGFR <40 ml/mt in 25%) and higher proportion of patients with extra-medullary disease (10-20%) (2). Limited data suggest that proportion of high risk cytogenetics [17p del, t(4;14), t(14;16)] is similar (10-15%) (unpublished data).

Survival of MM patients has improved significantly during the past 2 decades. This has been attributed to novel agents based induction, autologous stem cell transplantation (ASCT) in eligible patients, and use of maintenance therapy (3). Prior to year 2000, initial therapy for myeloma patients included cytotoxic chemotherapy – melphalan and prednisolone or VAD (vincristine, adriamycin, and dexamethasone) as continuous infusion. Treatment was associated with low complete response rates (5-15%), and short progression free and overall survival (2.5 to 3.5 years). Introduction of immunomodulators (thalidomide, lenalidomide), proteasome inhibitors (bortezomib) and dexamethasone confirmed higher response rates, and improved progression free and overall survival (PFS/OS). Currently, these are the back bone of myeloma treatment.

Treatment

Current management of myeloma is based on the initial assessment for transplant eligibility. Patients who are ≤65 to 70 years of age, in good ECOG performance status and without significant co-morbidities are considered transplant eligible. Such patients receive 3 to 6 cycles of induction therapy followed by ASCT followed by maintenance therapy. Goal of induction therapy is to reduce plasma cells burden and improve depth of response. Patients who are 'transplant ineligible' or elderly are advised induction therapy (9-12 cycles) followed by maintenance therapy. In addition all patients should receive supportive care in the form of bisphosphonates, initially 3 monthly for 1-2 years then at longer intervals (4).

Induction Therapy

Initial studies have used 2 drug-based induction in the form of thalidomide plus dexamethasone, lenalidomide plus dexamethasone or bortezomib plus dexamethasone. In last five years -3 drug combination – one immunomodulator (thalidomide or lenalidomide), one proteasome inhibitor (bortezomib) and dexamethasone are being used for induction. Three drug combinations are associated with higher response rate (complete and very good partial response), and better PFS and OS. Commonly used combinations include- bortezomib, thalidomide plus dexamethasone (VTD), bortezomib, lenalidomide plus dexamethasone (VRd), or bortezomib, cyclophosphamide plus dexamethasone(VCd) or bortezomib, liposomal doxorubicin plus dexamethasone (PAd). There is no head to head comparison between these combinations. A number of randomized trials (5-10) have confirmed high response rates (Table 1).

AIIMS Experience: In a randomized study (11), we compared lenalidomide–dexamethasone (n=97) versus thalidomide-dexamethsone (n=96). Response rate was 72.2% versus 68.7%, p=0.34. At a median follow-up of 70 months, median overall survival was not reached in len-dexa arm versus 63 months in thal-dexa arm (p=0.50). Subsequently, in

Table 1: Novel agents based induction therapy prior to transplant
(Adapted from ref 5 : Moreau *et al*, Blood 2015)

Study (Ref)	Treatment scheme	No of Pts	Response rate (%)		Post transplant CR+ VGPR (%)	Long term outcome
			ORR	CR+VGPR		
IFM (5)	VADx4±DCEP x2-ASCT VDx4±DCEP x2-ASCT	242 240	63 78	1+15 6+38	9+37 16+54	PFS 30 months PFS 36 months
GIMEMA (6)	VTDx3-ASCT-VTD x2-TDx3-ASCT-TDx2-Dexa maintenance	236 238	93 79	≥62 VGPR ≥28 VGPR	≥82VGPR ≥64VGPR	3Yr PFS:68, OS:86mo 3 Yr PFS:56,OS:84mo
PETHEMA (7)	TDx6-ASCT-IFNm/Tm/VTmx 3Y VTDx6-ASCT-IFNm/Tm/VTmx 3Y VBMCP/VBADx4-Vx2-ASCT-IFNm/Tm/VTmx3Y	127 130 129	62 85 75	≥29VGPR ≥60VGPR ≥36VGPR	CR: 40 CR:57 CR:48	PFS 28 mo, OS 65% @4 Yr PFS:56 mo, OS 74% PFS:35 mo, OS:70%
IFM (8)	VDx4-ASCT VTDx4-ASCT	99 100	81 88	≥36VGPR 49≥VGPR	58≥VGPR 74≥VGPR	PFS : 30 mo PFS:26 mo
HOVON-65 (9)	VADx3 -CAD-ASCT-Tmx2Y PADx3 -CAD-ASCT-Vmx2Y	414 413	54 78	14≥VGPR 42≥VGPR	36≥VGPR 62≥VGPR	PFS:28mo,OS 55% @5 Yr PFS:35 mo, OS 61% @5 Yr

Abbreviations: CAD: cyclophosphamide-doxorubicin-dexamethasone; DCEP: dexamethasone-cyclophosphamide-etoposide-cisplatin; Dm: dexamethasone maintenance; GIMEMA: Gruppo Italiano Malattie Ematologiche dell'Adulto; HOVON: Dutch-Belgian Hemato-Oncology Group; IFM: Intergroupe Francophone du Myélome; IFNm: interferon maintenance; NR: not reported; ORR: overall response rate; PAD: bortezomib-doxorubicin-dexamethasone; PETHEMA/GEM: Programa para el Estudio y la Terapéutica de las Hemopatías Malignas/Grupo Español de Mieloma; PR: partial response; TD: thalidomide-dexamethasone; Tm: thalidomide maintenance; V: bortezomib; VBAD: vincristine-BCNU-doxorubicin-dexamethasone; VBMCP: vincristine-BCNU-melphalan-cyclophosphamide-prednisone; Vm: bortezomib maintenance; VTD: bortezomib-thalidomide-dexamethasone; VTm: bortezomib-thalidomide maintenance.

another study (12) a combination of bortezomib-lenalidomide and dexamethasone (VRd) was compared to lenalidomide plus dexamethasone (Rd). Overall response rates (sCR+CR+VGPR +PR) was 78.4% vs 73.9% in VRD and Rd arms, respectively, p=0.6; sCR + CR 21 (28.4%) and 21 (30.4%), respectively, p=0.86. At a median follow-up 17.1 months (range 1 to 33), median OS is 30.2 months (95% CI 28.2 to 32.2) and 28.6 months (95% CI 26 to 31.3) in VRD and Rd arms, respectively, p=0.3. Median PFS was 27.8 months (95% CI 25.4 to 30.2) and 28 months (95% CI 24.6 to 31.4), respectively, p=0.3. Estimated one-year OS is 88% vs 85% in arms A and B, and PFS 83% vs 72%, respectively (12).

Table 2 :High dose chemotherapy and autologous stem cell transplantation with novel agents based induction therapy: Randomized trials
(adapted from ref. 17 Dhakal *et al*, 2018)

Author (Ref)	No of Pts	Induction	Conditioning Vs standard therapy	Maintenance	Follow-up (in months)	Comments
Palumbo *et al*, 2014 (13)	273	Rd	Mel 200 mg x2 Vs MPR	Len Vs observation until progression	51.2	Median PFS 43 mon Vs 22.4 mon, p<0.001 OS @4 Yr 81.6% vs 65.3%,p<0.02
Gay *et al*, 2015 (14)	256	Rd	Mel 200 x2 Vs CRd	Len +P vs Len until progression	52	median PFS 43.3 mo vs 28.6 mo,p<0.0001
Attal *et al*, 2015 (15)	700	RVd	Mel 200x1 Vs RVd x 8 cycles	Len for one year	44	Median PFS 50mo vs 36 mo,p<0.001 OS @ 4 Yr 81% vs 82%,p=ns
Cavo *et al,* 2016 (16)	1192	CyBord	Mel200x 1 or 2 VsVMPx4 cycles	Len until progression	26	VGPR 84% vs 74%,p<0.0001 PFS better with HDCT, p<0.01

Rd: lenalidomide-dexamethsone; RVd: bortezomib, lenalidomide and dexamethsone; Len: lenalidomide; MPR: melphalan, lenalidomide- prednisolone, CRd: cyclophosphamide; lenalidomide: pdexamethasone; Mel: melphalan; VMP: bortezomib, melphalan, prednisolone; PFS: progression free survival; mo: months; HDCT: high dose chemotherapy.

Autologous Stem Cell Transplantation (ASCT)

Post induction therapy, transplant eligible patients undergo ASCT. A number of randomized studies have confirmed superiority of ASCT over conventional cytotoxic chemotherapy in these studies conducted before the year 2000. These studies confirmed superiority of high dose chemotherapy and stem cell transplant over conventional chemotherapy. With availability of novel agents from year 2000 onwards, four randomised studies (13-16) have been reported. Data from these studies have been summarized (17) in Table 2. High dose chemotherapy (HDCT) was associated with superior CR rates and improved PFS, confirming that even in novel agents era- HDCT followed by ASCT is the standard of care for transplant eligible myeloma patients.

Procedure

Prior to transplant all patients were evaluated for their fitness for transplant- for organ function, performance status and disease status. For peripheral blood stem cell mobilization patients receive inj G-CSF 10 mcg/day in 2 divided doses for 5 days followed by aphaeresis. Target is to collect 2-2.5x10(6) CD34+ cells. About 10-20% patients may have poor mobilization. These can be identified by

Table 3 : Maintenance therapy following ASCT : Phase 3 trials
(Adapted from ref. 5 Moreau *et al*, Blood 2015)

Study (Ref)	**No of Pts**	**Initial Dose**	**Response Vs comparator**	**Median FU in months**	**EFS or PFS Vs Comparator**	**OS Vs comparator**
Thalidomide						
Attal *et al* (18)	597	400 mg	CR+VGPR 67% Vs 55%	30mon	3 Yr EFS 52% Vs 36%	87% Vs 77% @ 4 Yr
Barlogie *et al* (19)	668	400mg	CR: 64% Vs 43%	72mon	Median EFS 6.0 vs 4.1 Yr	57% Vs 44% @ 8 Yr
Spencer *et al* (20)	269	200mg	CR+VGPR 63 % Vs 40%	36mon	PFS 42% Vs 23% @ 3Yr	86% Vs 75% @3 Yr
Lokhorst *et al* (21)	556	50mg	CR:31% Vs 23%	52mon	Median PFS 34 Vs 25 mon	Median OS 73 Vs 60 mon
Morgan *et al* (22)	492	50mg	NR	38 mon	Median PFS 30 Vs 23 mon	75% Vs 80% @ 3yr
Steward *et al* (23)	332	200 mg	NR	4.1 Yr	PFS : 32% Vs 14% @ 4 Yr	68% Vs 60% @ 4 Yr
Lenalidomide						
Attal *et al* (24)	614	10 mg	CR+VGPR: 84% Vs 76%	45 mon	Median PFS: 41 Vs 23 mon	73% Vs 75% @ 4 Yr
Mc Carthy *et al* (25)	460	10mg	NR	34 mon	Median TTP: 46 Vs 27 mon	88% Vs 80% @ 3 Yr
Bortezomib						
Sonneveld *et al* (10)	827	1.3mg/m2	CR+VGPR:76% Vs 56%	41 mon	Median PFS:35 Vs 28 mon	61% Vs 55% @ 5 Yr
Rosinol (26)	266	1.3mg/m2	NR	24 mon	2 Yr PFS 78% Vs 63% Vs 49%	NR

CR: complete response; VGPR: very good partial response; EFS: event free survival; NR: not reported; PFS: progression free survival; OS: overall survival; TTP: time to progression.

Table 4 : Induction therapy for transplant ineligible patients : Phase 3 studies and meta analysis results
(Adapted from ref. 5 Moreau *et al*, Blood 2015)

Study (Ref)	Scheme	No of pts	Median FU	Best response	PFS in Months	OS in months
MPT meta analysis (27)	MPTx8 vs 12 vs until relapse	1685	Not available	VGPR25%	20.3	39.3 mo
MPT First trial (28)	MPTx12 cycles	547	37 mon	CR9.3%	21.2	51.4% @ 4 Yr
CTD (29)	CTD -9 cycles	426	44	CR13.1%	13	33.2
VMP (30) VISTA trial	VMP -9 cycles	344	60.1	CR30%	21.7	56.4
MPR-R (31)	MPRx9 cycles followed by R until progression/relapse	152	30	CR9.9%	31	59%@4 Yr
VMPT-VT(32-33)	VMPTx9 followed by VTx 2 yrs or until progression/relapse	254	54	CR38%	35.3	61%@5 Yr
VMP/VTP -VT(34-35)	VMP or VTPx6 f/b VT up to 3 Yrs	91	46	CR46%	39	69%@5Yr
Rd continuous (36)	RD until disease progression	535	37	CR15.1%	25.5	59.4% @4 Yr

Abbreviations: CAD: cyclophosphamide-doxorubicin-dexamethasone; DCEP: dexamethasone-cyclophosphamide-etoposide-cisplatin; Dm: dexamethasone maintenance; GIMEMA: Gruppo Italiano Malattie Ematologiche dell'Adulto; HOVON: Dutch-Belgian Hemato-Oncology Group; IFM: Intergroupe Francophone du Myélome; IFNm: interferon maintenance; NR: not reported; ORR: overall response rate; PAD: bortezomib-doxorubicin-dexamethasone; PETHEMA/GEM: Programa para el Estudio y la Terapéutica de las Hemopatías Malignas/Grupo Español de Mieloma; PR: partial response; TD: thalidomide-dexamethasone; Tm: thalidomide maintenance; V: bortezomib; VBAD: vincristine-BCNU-doxorubicin-dexamethasone; VBMCP: vincristine-BCNU-melphalan-cyclophosphamide-prednisone; Vm: bortezomib maintenance; VTD: bortezomib-thalidomide-dexamethasone; VTm: bortezomib-thalidomide maintenance.

doing peripheral blood CD34 counts on day 4 of G-CSF. Patients with CD34 + cells <20/cmm are likely to have poor mobilization. Options for such patients include- chemo-mobilization using cyclophosphamide 2-4 g/m^2 or Plerixafor, a CXCR4 –chemokine nhibitor. Patients with prior melphalan or radiation are poor mobilizers and therefore these should be avoided during induction in transplant eligible patients. Once adequate number of stem cells are harvested these can be cryopreserved at -80 degree Cels or in liquid nitrogen for long term storage. At our centre, we collect stem cells electively, keep at 4 degree Cel. This is followed by high dose chemotherapy with melphalan 200 mg/m^2 IV followed by stem cell infusion 24 hours later. This practice of keeping stem cells at 4 degree is cost effective and stem cells are viable (>90%) up to 96 hours. Twenty four hours after stem cells, patients are started on G-CSF 5 mcg/kg once daily until engraftment. Once stable, patients are then discharged and followed-up in the out patients department with reassessment for response on day 100. Our current policy is to give 2 more cycles of VRd regimen as consolidation from day 100 (±7 days) onwards followed by maintenance therapy using lenalidomide 10 mg daily for 21 days every 28 days for 2 years. Patients intolerant to lenalidomide receive inj bortezomib 2 mg subcutaneously every 2 weeks. In earlier period we have used low dose thalidomide (50 mg daily).

Post transplant consolidation

A number of studies have suggested that 2-3 cycles of consolidation using VRd or VTd may further improve CR rate and more patients have 'nil' minimal residual disease. In an ongoing prospective study at our centre among 58 patients CR rate improved from 81.3% (post ASCT at day 100) to 89.8 % post consolidation, 32 of 58 were MRD negative at day +100, 26 were MRD +ve, of these 16 (61.5%) became MRD negative post-consolidation as assessed by 8 colour flow cytometry) (unpublished data).

Maintenance therapy

Initial studies have used thalidomide 100 to 200 mg per day; among six randomized studies (18-23) 3 had shown improved PFS and OS. Neuropathy was the main toxicity. Subsequent studies have used lenalidomide 5-10 mg daily 15-21 days every 28 days. These studies have shown improved PFS. Second malignancy has been reported in 4-6% of patients. Inj Bortezomib 2 mg every two weeks has been used in studies from Europe. Currently, Lenalidomide 10 mg daily for 21 days out of 28 days for two years is recommended (Table 3).

Induction therapy for transplant ineligible or elderly patients

Initial studies confirmed superiority of melphalan- thalidomide and prednisolone (MPT) combination over MP alone as regards to response rate, PFS and OS (Table 4). VISTA trial compared VMP (bortezomib, melphalan and prednisolone) with MP; VMP was superior in terms of response rate, CR rate, median time to progression (24.4 months vs. 16.6 months) and OS. In a recent update at 60 months, these results still hold; median OS 56 months versus 43 months (32-33). Recent studies have used a combination of MP-lenalidomide (MPR) (31). Another phase 3 study has compared lenalidomide plus dexamethasone (Ld) as continuous therapy or 18 cycles to MPT. At a median follow-up of 37 months; continuous Ld was better compared to Ld 18 cycles and MPT regimen (36). For patients who are frail or have significant co-morbidities- two drug combinations is a reasonable choice.

Conclusions

Survival of patients with myeloma has improved significantly in the past two decades. Compared to median survival of 3-to 3.5 years prior to year 2000, presently median survival is 5.5 to 6 years. For patients undergoing ASCT median survival is 8 to 9 years. Recently a number of newer agents have been added with

significant activity and have been approved for the treatment of relapse. These include- carfilzomib, ixazomib, pomalidomide. In addition, two monoclonal antibodies- daratumab -anti CD38 and elotuzumab (anti SLAM F7) have been moved to front line. These are now being compared in combination with bortezomib, carfilzomib, or lenalidomide based combinations. Other strategies currently being explored include- vaccination against MM antigens, along with immunomodulatory agents such as IMiDs or the anti-PD-1 antibody and CAR-T cell therapy. It is hoped that these strategies would lead to further improvement in response and long-term control of the disease in near future.

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