

## Original Research Article

# Treatment outcome of multiple myeloma (MM) based on cytogenetic risk stratification: a single institute experience from south India

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### ABSTRACT

**Background:** To study the epidemiology, incidence and the clinical outcome of multiple myeloma (MM) among the patients based on the cytogenetic risk stratification.

**Methods:** Author retrospectively analysed 50 patients of Multiple Myeloma (MM) with conventional cytogenetics and interphase Fluorescence In-Situ Hybridization (FISH) method and author classified the risk on the mSMART classification. Treatment and outcome were evaluated separately based on the cytogenetic risk stratification for three arms of treatment- Bortezomib, Thalidomide and Dexamethasone (BTD), Thalidomide and Dexamethasone (TD) and Lenalidomide and Dexamethasone (LD).

**Results:** The median age of the patients was 61years (48-74years) and ratio between male to female was 1.5:1. The overall response (OR) rate among high risk patients treated with Bortezomib, Thalidomide and Dexamethasone (BTD) was 100% with Complete Response (CR) being 26.7%. The OR rate and CR rates among standard risk treated with Thalidomide and Dexamethasone (TD) and Lenalidomide and Dexamethasone (LD) were 61%, 11% and 76%, 18% respectively. The two years overall survival (OS) was 53.3% in high risk and 66.7% with Thalidomide and Dexamethasone (TD) and 76.5% with Lenalidomide and Dexamethasone (LD) in low risk group.

**Conclusions:** The present study showed that the high-risk features of cytogenetics portend poor outcome among MM patients. Bortezomib, Thalidomide and Dexamethasone (BTD) based therapy have improved the Overall Response (OR) rate and Complete Response (CR) rates in high risk MM, however overall survival (OS) is poor in this risk strata. The study also showed that cytogenetic risk stratification and the outcome of myeloma do correlated with each other.

**Keywords:** Bortezomib, Cytogenetics, Dexamethasone, Multiple myeloma, Thalidomide

### INTRODUCTION

Multiple Myeloma (MM) constitutes about 1% of malignancies.<sup>1</sup> Multiple myeloma is a haematological malignancy, usually seen in elderly patients in 6<sup>th</sup> or 7<sup>th</sup> decade. Myeloma is an incurable malignancy; however, the last two decades has seen tremendous improvement in median survival from 2-3years initially to 5-8years in current scenario. This is partly because of host of new drugs available since 1999 for treatment (prior to 1999 only melphalan, cyclophosphamide, vincristine and steroids were available, now author have thalidomide,

lenalidomide, bortezomib and recently since last 2years author had pomalidomide, carfilzomib and ixazomib) and as well as safer bone marrow transplant. With better understanding of disease, pathophysiology and insight into cytogenetics, outcome has further improved. Specific cytogenetic abnormalities such as del (13), t (4,14), del (17) and t (14,16) have poor outcome independent of treatment modality used and these have helped to classify disease into high or low risk. The incidence rates from various centres in India ranges from 0.5 to 1.9 per 1,00,000.<sup>2,3</sup> While there is plenty of data in the world literature on MM, there is paucity of data in Indian

patients about the frequency of various cytogenetic risk markers and their outcome.<sup>3</sup> Therefore, author conducted the study to analyse the outcome of MM with standard chemotherapy taking into consideration of the cytogenetic risk stratification criteria.<sup>4</sup>

## METHODS

Author retrospectively evaluate 50 cases of MM, diagnosed and treated from October 2014 to October 2018 who were followed up for a period of four years. Author analyzed the demographic profile, clinical features, treatment and outcome of the treatment.

Diagnosis was confirmed on the basis of pathological examination of bone marrow (showing >10% plasma cells), M spike on serum electrophoresis associated with end organ damage (hypercalcemia, renal failure, anaemia and lytic bone lesion) and examination of wright stained bone marrow aspiration smears. All the patients were tested for conventional and FISH cytogenetic abnormalities.

Cytogenetics: About 2 - 3ml of heparinized bone marrow aspirate was sent immediately at 20-25°C by courier to a lab outside. They were incubated overnight in tissue culture media (RPMI 1640), mitogen colchicine was added for metaphase arrest, glacial acetic acid and methanol were used as fixatives and G-banding done for the chromosomal study.

FISH test: About 2-3ml of heparinized bone marrow aspirate was sent immediately at 20-25°C by courier to a lab outside. FISH test for the panel of del13, del17, t(4:14), t(11:14) and t(14:16) on interphase cells was done using Vysis directly labelled LSI D13S 25 DNA probes of Abbott laboratory, USA.

MM was classified using mSMART risk strata into high risk or low risk group.<sup>4</sup>

High risk patients received BTD based triplet therapy (bortezomib was given as 1.3mg/m<sup>2</sup> weekly on weeks for 4weeks, thalidomide 100mg daily for 28days and oral dexamethasone was 40mg weekly once). In transplant ineligible patients this therapy was given until they achieved maximum response and two cycles after that. In transplant eligible high-risk patients received BTD based triplet therapy till complete remission followed by consolidation with either autologous stem cell transplant or thalidomide maintenance therapy based on patient's preference.

Low risk patients received either TD (Thalidomide 100mg daily for 28days and oral Dexamethasone was 40mg weekly once) or LD (Lenalidomide 25mg daily for 21days of 28day cycle with oral Dexamethasone was 40mg weekly once) based on patient preference and comorbidities. These patients were consolidated with either autologous stem cell transplant or maintenance with

thalidomide alone. Radiotherapy was given for compressive myelopathy or for palliation of pain. All patients were given bisphosphonates for two years duration unless there were contraindications.

These patients were evaluated with serum electrophoresis for quantitative 'M' component every 2months, till it normalized followed by serum free light chain assay and bone marrow evaluation for complete remission.

Evaluation of response was done on basis of International Myeloma Working Group (IMWG) response criteria.<sup>5</sup> The outcome was correlated with cytogenetics (high risk or standard risk). Overall Survival (OS) at 2years was evaluated for all patients using the Kaplan Meier curve (SPSS 19-SPSS Inc, USA).

## RESULTS

The clinical features of these 50 patients are given in Table 1. Median age of presentation was 61years (range 48-74years). Common presentations include lytic bone lesions and anaemia. Majority had ISS stage III at presentation. Nearly half of the patients (N=24) had diabetes, hypertension and ischemic heart disease as comorbidities and 10 of them had symptomatic neuropathy as complication.

Conventional cytogenetics detected high risk feature hypodiploidy in 2 patients while FISH detected abnormality in 13 patients. Deletion 13 was the most common abnormality seen in 7 (14%) cases and remaining abnormalities in 6 patients (Table 2). The cut off percentage of plasma cells positive for del 13 and del 17 were taken as 74% and 60% respectively as these are found to be prognostic. In the remaining 35 patients, no high-risk cytogenetics was detected by FISH with normal karyotype observed in 24 patients, hyper-diploidy in one and conventional cytogenetics failed in remaining 10 patients.

These patients were classified into 15-high risk patients who received triplet therapy BTD and 35-low risk patients of whom 17 received LD and 18 received TD.

In this study, 40 out of 50 patients either refused transplantation or were ineligible and of which 12 were high risk patients. There were 10 transplant eligible patients of whom 3 were high risk patients. One patient each with high risk del 13 and del 17 underwent autologous bone marrow transplant (ABMT). Three patients each in the standard risk arms were treated with ABMT.

In high risk patients with triplet regimen the OR rate was 100% with 26.7% (4 patients) achieving CR. In low risk patients, the OR rate and CR with LD was 76% (13 patients) and 18% (3 patients), while these were 61% (11 patients) and 11% (2 patients) with TD respectively. The two years overall survival was 53.3% in high risk, 76.5%

with LD and 66.7% with TD in low risk group (Table 3). With bortezomib based triplet therapy (BTD) 26.7% (4 patients) had grade 3/4 neuropathy, 6% (1 patient) had herpes zoster, 6% (1 patient) had DVT, and 2 (13%) patient had febrile neutropenia which required admission. With TD doublet therapy 16.6% (3 patients) had grade 3/4 peripheral neuropathy and 5.5% (1 patient) had DVT. LD was associated with grade 3/4 myelosuppression in 29% (5 patients).

**DISCUSSION**

The median age of presentation was lesser than the western literature but similar to other studies from India.<sup>6</sup> Comparing the clinical features with other studies from India author noted a similar incidence of skeletal abnormalities and renal failure (serum creatinine >2mg/dl), however, a higher incidence of anaemia was noted in this study.<sup>3</sup> This is shown in Table 1.

**Table 1: Clinical profile.**

Clinical features	n (%)	Other studies from India(%) <sup>3</sup>
Age (years)	61 (48-74)	
Males: females	1.5:1	
Bone lesions	48 (96)	93.7
Neurological deficit	8 (16)	11.4
Renal failure	14 (28)	31.3
Anaemia	38 (76)	62.4
Hypercalcemia	8 (16)	10.3
<b>Co-morbidities</b>		
Diabetes	12	Not available
Hypertension	7	Not available
Coronary heart disease	4	Not available
<b>Subtype of myeloma</b>		
IgA	12 (24)	18.5
IgG	31 (62)	67.6
Light chain	8 (16)	12.8
<b>ISS stage</b>		
I	3 (6)	6.4
II	6 (12)	12
III	40 (80)	81.7
Plasma cell leukemia	1 (2)	

In western series on cytogenetics, nearly 25-30% of patients were in high risk category, this accounted for 30% in this cases.<sup>7</sup> By conventional cytogenetics author had noted normal karyotype in 19 cases and hypoploidy in three cases, this discrepancy may be due to low proliferative index of plasma cell.<sup>8</sup> Deletion 13 and t (14, 16) accounts for 15% and 5% of high risk cytogenetics respectively and author noted a similar result.<sup>9</sup> This is shown in Table 2.

Comparing the outcome with triplet regimen (BTD) the overall response (CR+PR) rate was more than 95% in other series which was comparable to this data.<sup>12</sup> With

TD doublet and LD, this response is 60-70% and 70-80% respectively in published series which is similar to this study.<sup>10,13,14</sup> Comparing the CR rates, these were 35%, 7-12%, 17-22% with triplet therapy (BTD), TD and LD regimens respectively in larger series.<sup>9,15</sup>

Similar outcome with CR rates of 26.7%, 11% and 18% was noted in this study. The overall survival (OS) at two years shown in their study by Bergsagel PL et al, only 50% of high-risk group survived compared to nearly 75-90% in the low risk group.<sup>16</sup> Author have observed a similar outcome as shown in Table 3.

**Table 2: Cytogenetics in myeloma.**

Cytogenetics	No (%)	Western series <sup>10</sup>	AIIMS, India <sup>11</sup>
<b>High risk (30%)</b>			
Hypodiploidy	2 (4)	Not available	5 (4%)
Deletion 13	7 (14)	15%	51 (56%)
Deletion 17	2 (4)	5%	
t (14:16)	1 (2)	2-10%	
t (4;14)	3 (6)	Undetected -15%	
<b>Standard risk (70%)</b>			
Hyper-diploidy	1 (2)		16 (17%)
Normal	24 (48)		

**Table 3: Outcome based on risk and therapy.**

	Present study	Other studies
<b>High risk response rate: triplet</b>		
OR rate	100%	>95% <sup>12</sup>
CR rate	26.7%	35% <sup>15</sup>
<b>Low risk response rate: doublet</b>		
Thalidomide-dexamethasone		
OR rate	61%	60-70% <sup>12,13</sup>
CR rate	11%	7-12% <sup>9,12,13</sup>
Lenalidomide-dexamethasone		
OR rate	76%	70-80% <sup>14</sup>
CR rate	18%	17-22% <sup>9</sup>
<b>Overall survival (High risk)</b>		
Triplet: BTD	53.3%	56% <sup>17</sup>
<b>Overall survival (Standard risk)</b>		
Lenalidomide-dexamethasone		
	76.5%	91% <sup>14</sup>
Thalidomide-dexamethasone		
	66.7%	72-82% <sup>16</sup>

BTD- Bortezomib, Thalidomide and Dexamethasone, CR- Complete Response, OR- Overall Response.

In reported incidence of grade 3-4 neuropathy with bortezomib based therapy (BTD) was 20% while lenalidomide was associated with incidence of febrile neutropenia in 10-25% cases, author noted a higher rate of 26.7% (4 patients) with grade 3/4 neuropathy and 29% (5 patients) grade 3/4 myelosuppression probably due to advanced age and higher incidence of co-morbidities.<sup>18,19</sup>

## CONCLUSION

Author study showed that the high-risk features of cytogenetics portend poor outcome among myeloma patients. Bortezomib (BTD) based therapy have improved the overall response rate and CR rates in high risk myeloma, however even then overall survival is poor in this risk strata. Newer therapies like carfilzomib and pomalidomide might probably help these patients with high risk cytogenetics features.

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## REFERENCES

- Jemal A, Siegel R, Ward E, Hao Y, Xu J, et al. Cancer statistics. *Cancer J Clin*. 2009;59(4):225-49.
- Nair MK, Varghese C, Krishnan E, Sankaranarayanan R, Nair BA. Survival in multiple myeloma in Kerala. *National Med J India*. 1993;6(1):7-10.
- Kumar LA, Vikram P, Kochupillai V. Recent advances in the management of multiple myeloma. *National Med J India*. 2006;19(2):80.
- Dispenzieri A, Rajkumar SV, Gertz MA, Lacy MQ, Kyle RA, Greipp PR, et al. Treatment of newly diagnosed multiple myeloma based on mayo stratification of myeloma and risk-adapted therapy (mSMART): consensus statement. In: *Mayo Clinic Proceedings*. Elsevier. 2007;82(3):323-341.
- Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;20(9):1467.
- Agarwal N, Kumar P, Rai M, Singh RG, Seth M, Saraf SK. Myeloma in young age. *Ind J Pathol Microbiol*. 2005;48(3):314-7.
- Decaux O, Lodé L, Magrangeas F, Charbonnel C, Gouraud W, Jézéquel P, et al. Prediction of survival in multiple myeloma based on gene expression profiles reveals cell cycle and chromosomal instability signatures in high-risk patients and hyperdiploid signatures in low-risk patients: a study of the Intergroupe Francophone du Myelome. *J Clin Oncol*. 2008;26(29):4798-805.
- Sawyer JR, Waldron JA, Jagannath S, Barlogie B. Cytogenetic findings in 200 patients with multiple myeloma. *Cancer Gen Cytogen*. 1995;82(1):41-9.
- Dimopoulos MA, Terpos E. Multiple myeloma. *Ann Oncol*. 2010; 21(7):143-50.
- Rajkumar SV, Hayman S, Gertz MA, Dispenzieri A, Lacy MQ, Greipp PR, et al. Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. *J Clin Oncol*. 2002;20(21):4319-23.
- Verma R, Kumar L, Gupta R, Halder A, Sharma A, Saxena R. Impact of cytogenetics on clinical outcome in multiple myeloma: a risk stratification model. *J Clin Oncol*. 2011;29:e18576.
- Cavo M, Pantani L, Petrucci MT, Patriarca F, Zamagni E, Donnarumma D, et al. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy following autologous hematopoietic stem-cell transplantation in patients with newly diagnosed multiple myeloma. *Blood*. 2012;9.
- Weber D, Rankin K, Gavino M, Delasalle K, Alexanian R. Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. *J Clin Oncol*. 2003;21(1):16-9.
- Jacobus SJ, Kumar S, Uno H, Van Wier SA, Ahmann GJ, Henderson KJ, et al. Impact of high-risk classification by FISH: an eastern cooperative oncology group (ECOG) study E4A03. *Brit J Haematol*. 2011;155(3):340-8.
- Rosiñol L, Oriol A, Teruel AI, Hernández D, López-Jiménez J, de la Rubia J, et al. Superiority of bortezomib, thalidomide and dexamethasone (VTD) as induction pre-transplantation therapy in multiple myeloma: a randomized phase III PETHEMA/GEM study. *Blood*. 2012:1589-96.
- Bergsagel PL, Mateos MV, Gutierrez NC, Rajkumar SV, San Miguel JF. Improving overall survival and overcoming adverse prognosis in the treatment of cytogenetically high-risk multiple myeloma. *Blood*. 2013;121(6):884-92.
- San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *New Eng J Med*. 2008;359(9):906-17.
- Argyriou AA, Iconomou G, Kalofonos HP. Bortezomib-induced peripheral neuropathy in multiple myeloma: a comprehensive review of the literature. *Blood*. 2008;112(5):1593-9.
- Palumbo A, Falco P, Falcone A, Benevolo G, Canepa L, Gay F, et al. Melphalan, prednisone, and lenalidomide for newly diagnosed myeloma: kinetics of neutropenia and thrombocytopenia and time-to-event results. *Clin Lymph Myel*. 2009;9(2):145-50.

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