

INDIAN COUNCIL OF MEDICAL RESEARCH



CONSENSUS DOCUMENT FOR MANAGEMENT OF MULTIPLE MYELOMA

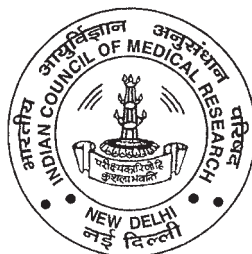
*Prepared as an outcome of ICMR Subcommittee on
Multiple Myeloma*



Indian Council of Medical Research
2017

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Indian Council of Medical Research,
Ansari Nagar, New Delhi – 110029
2017

Disclaimer

This consensus statement represents the ICMR's current thinking on the topic based on available evidence. This has been developed by national experts in the field and does not in any way bind a clinician to follow this guideline verbatim. The physician can use an alternate mode of therapy based on the discussions with the patient and with reference to institution, national or international guidelines. The mention of pharmaceutical drugs for therapy does not constitute endorsement or recommendation for use but is a guidance for clinicians in complex decision –making

Dr. Soumya Swaminathan
Secretary,
Department of Health Research
and Director General, ICMR

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Foreword

I am glad to write this foreword for Consensus Document for Management of Multiple Myeloma. The ICMR had constituted sub-committees to prepare consensus document for management of various cancer sites. This document is the result of the hard work of various experts across the country working in the area of oncology.

This consensus document on management of multiple myeloma summarizes the modalities of treatment including the site-specific anti-cancer therapies, supportive and palliative care and molecular markers and research questions. It also interweaves clinical, biochemical and epidemiological studies.

The various subcommittees constituted under Task Force project on Review of Cancer Management Guidelines worked tirelessly in formulating site-specific guidelines. Each member of the subcommittee's contribution towards drafting of these guidelines deserves appreciation and acknowledgement for their dedicated research, experience and effort for successful completion. We hope that this document would provide guidance to practicing doctors and researchers for the management of patients suffering from multiple myeloma and also focusing their research efforts in Indian context.

It is understood that this document represents the current thinking of national experts on subject based on available evidence. Mention of drugs and clinical tests or therapy do not imply endorsement or recommendation for their use, these are examples to guide clinicians in complex decision making. We are confident that this first edition of Consensus Document on Management of Multiple Myeloma would serve the desired purpose.



Dr. S Swaminathan
Secretary, Department of Health Research
and Director General, ICMR

Message

I take this opportunity to thank Indian Council of Medical Research and all the expert members of the subcommittees for having faith and considering me as chairperson of ICMR Task Force project on guidelines for management of cancer.

The Task Force on management of cancers has been constituted to plan various research projects. Two sub-committees were constituted initially to review the literature on management practices. Subsequently, it was expanded to include more sub-committees to review the literature related to guidelines for management of various sites of cancer. The selected cancer sites are lung, breast, oesophagus, cervix, uterus, stomach, gall bladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukemia, acute lymphoblastic leukaemia, CLL, Non Hodgkin's Lymphoma-high grade, Non Hodgkin's Lymphoma-low grade, Hodgkin's Disease, Multiple Myeloma, Myelodysplastic Syndrome and Pediatric Lymphoma. All aspects related to management were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects. The published literature till December 2016 was reviewed while formulating consensus document and accordingly recommendations are made.



Now, that I have spent over a quarter of a century devoting my career to the fight against cancer, I have witnessed how this disease drastically alters the lives of patients and their families. The theme behind designing of the consensus document for management of cancers associated with various sites of body is to encourage all the eminent scientists and clinicians to actively participate in the diagnosis and treatment of cancers and provide educational information and support services to the patients and researchers. The assessment of the public-health importance of the disease has been hampered by the lack of common methods to investigate the overall worldwide burden. ICMR's National Cancer Registry Programme (NCRP) routinely collects data on cancer incidence, mortality and morbidity in India through its co-ordinating activities across the country since 1982 by Population Based and Hospital Based Cancer Registries and witnessed the rise in cancer cases. Based upon NCRP's three year report of PBCR's (2012-2014) and time trends on Cancer Incidence rates report, the burden of cancer in the country has increased many fold.

In summary, the Consensus Document for management of various cancer sites integrates diagnostic and prognostic criteria with supportive and palliative care that serve our three part mission of clinical service, education and research. Widespread use of the consensus documents will further help us to improve the document in future and thus overall optimizing the outcome of patients. I thank all the eminent faculties and scientists for the excellent work and urge all the practicing oncologists to use the document and give us valuable inputs.

(Dr. G.K. Rath)
Chairperson
ICMR Task Force Project

Preface

In the western hemisphere, Multiple Myeloma (MM) is the second most common hematological malignancy after non-Hodgkin's lymphoma and accounts for about 15% of all hematological cancers. Even though accurate data from India is not available, the disease is important for a treatment standpoint, because it affects patients in the prime of their life and, with appropriate management, good quality life for several years is possible in the majority of cases.



For optimal outcome, the disease requires careful initial workup, staging and specialized treatment at a center where all the investigative and treatment modalities are available, in addition to experts who are experienced and well versed in the management of the disease and its complications.

There have been major advancement in the treatment of this disease in the past two decades and new and novel drugs have been discovered, tested and launched at regular intervals. Progress in this disease has been so rapid that the ICMR MM subcommittee had a difficult time in concluding this project – whenever we were on the verge of finalizing the report, some new major development would happen, which the team felt should be included in the final report resulting in the need to update the same. Considering the rapid advances and research happening in the field of Myeloma, we intent this document to be a 'living' documents with frequent reviews and up gradations of the same at regular intervals.

In the preparation of this report, the team was cognizant of the resource limitations faced by the majority of the patients in our country and we did attempt to highlight the minimum workup and treatment which should be available to all patients including patients with compromised resources. Another important aspect of this report is the areas of future research in the field of MM as applicable to our country. We feel that research along these lines, will in the near future, provide us level-1 evidence to challenge and change treatment paradigms tailored to MM patients in India.

As Chairman of this wonderful group, I would like to thank each and every member of the team for their timely and highly skilled contributions. I would also like to place on record my most sincere thanks to Dr. Soumya Swaminathan, the Director General of the ICMR for her foresightedness in initiating and supporting this important project. Dr. G.K Rath, the Chairman of this Task Force Project; Dr. R.S. Dhaliwal and Dr. Tanvir Kaur of the NCD section of the ICMR deserve special thanks for constantly helping, supporting and guiding the team for timely submission of the report.

Finally, on behalf of the team, we hope and wish that this document is found to be useful for the practicing clinician in the day-to-day workup and management of the patient of multiple myeloma. We will eagerly await comments, criticisms and suggestion from all stake holders so that we came improve and update the next version of this document.

A handwritten signature in blue ink, appearing to read 'Hemant Malhotra', with a large circular flourish above the name.

Dr. Hemant Malhotra
Chairperson, Sub-committee on Multiple Myeloma

Preface

Cancer is a leading cause of death worldwide. Globally Cancer of various types effect millions of population and leads to loss of lives. According to the available data through our comprehensive nationwide registries on cancer incidence, prevalence and mortality in India among males cancers of lung, mouth, oesophagus and stomach are leading sites of cancer and among females cancer of breast, cervix are leading sites. Literature on management and treatment of various cancers in west is widely available but data in Indian context is sparse. Cancer of gallbladder and oesophagus followed by cancer of breast marks as leading site in North-Eastern states. Therefore, cancer research and management practices become one of the crucial tasks of importance for effective management and clinical care for patient in any country. Hence, the need to develop a nationwide consensus for clinical management and treatment for various cancers was felt.



The consensus document is based on review of available evidence about effective management and treatment of cancers in Indian setting by an expert multidisciplinary team of oncologists whose endless efforts, comments, reviews and discussions helped in shaping this document to its current form. This document also represents as first leading step towards development of guidelines for various other cancer specific sites in future ahead. Development of these guidelines will ensure significant contribution in successful management and treatment of cancer and best care made available to patients.

I hope this document would help practicing doctors, clinicians, researchers and patients in complex decision making process in management of the disease. However, constant revision of the document forms another crucial task in future. With this, I would like to acknowledge the valuable contributions of all members of the Expert Committee in formulating, drafting and finalizing these national comprehensive guidelines which would bring uniformity in management and treatment of disease across the length and breadth of our country.



(Dr. R.S. Dhaliwal)
Head, NCD Division

Acknowledgement

The Consensus Document on Management of Cancer is a concerted outcome of effort made by experts of varied disciplines of oncology across the nation. The Indian Council of Medical Research has constituted various sub committees to formulate the document for management of different cancer sites. The Task Force on Management of Cancers has been constituted to formulate the guidelines for management of cancer sites. The sub-committees were constituted to review the literature related to management and treatment practices being adopted nationally and internationally of different cancer sites. The selected cancer sites are that of lung, breast, oesophagus, cervix, uterus, stomach, gallbladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukaemia, ALL, CLL, NHL-high grade, NHL-low grade, HD, MM, MDS, and paediatric lymphoma. All aspects related to treatment were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects.



This document represents a joint effort of large number of individuals and it is my pleasure to acknowledge the dedication and determination of each member who worked tirelessly in completion of the document.

I would like to take this opportunity to thank Dr. GK Rath, chairperson, ICMR Task Force on Guidelines for Management of Cancer for his constant guidance and review in drafting the consensus document. The chairperson of subcommittee, Dr Hemant Malhotra, is specially acknowledged in getting the members together, organizing the meetings and drafting the document.

I would like to express gratitude to Dr. Soumya Swaminathan, Secretary, Department of Health Research and Director General, Indian Council of Medical Research, for taking her special interest and understanding the need of formulating the guidelines which are expected to benefit the cancer patients.

I would like to acknowledge here the initiative undertaken with the able guidance of Dr. Bela Shah. I would like to thank Dr. R.S. Dhaliwal for his support and coordination in finalizing this document. I would like to acknowledge the assistance provided by administrative staff. This document is the result of the deliberations by subcommittees constituted for this purpose. The guidelines were further ratified by circulation to extended group of researchers and practitioners drawn from all over the country. It is hoped that these guidelines will help the practicing doctors to treat cancer patients effectively and thus help them to lead a normal and healthy life.

The ICMR appreciatively acknowledges the valuable contribution of the members for extending their support in formulating these guidelines. The data inputs provided by National Cancer Registry Programme are gratefully acknowledged.



(Dr. Tanvir Kaur)
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1 INTRODUCTION

Multiple myeloma represents a malignant proliferation of plasma cells derived from a single clone. It's the most important of the class of diseases included under the plasma cell dyscrasias. Multiple myeloma is the second most common hematological malignancy after non hodgkins lymphoma and it accounts for 15% of all hematological malignancies.

The incidence of this disease increases with age in a spectrum of 4/lac in the general population to around 30/lac in over 25 years population. Even though lots of advancements have been made in the pathogenesis and etiology of this disease, it has still not made its way into the category of curable diseases.

Initially successfully started with melphalan, which incidentally still remains to be the main stay of therapy, other agents like cyclophosphamide, vincristine, doxorubicin, and others have also been tried. With the advent of Bone Marrow Transplant and Stem Cell Transplant, these have taken up an important place in the treatment protocols. But still, chemotherapy or induction therapy is essential before and later for transplant eligible and only therapy for transplant ineligible.

Melphalan still remains the main stay of chemotherapy but, other agents like cyclophosphamide, vincristine, doxorubicin, are also used. With the use of stem cell transplant, the outcomes have improved in a select group of patients but induction chemotherapy is essential before and later as maintenance or consolidation therapy.

Better awareness regarding the pathogenesis of myeloma, the marrow micro environment and the myeloma cell—marrow stromal cell interactions, have led to newer drugs coming up with better results. Latest among these being the Immunomodulatory drugs like Thalidomide and Lenalidomide, the proteasome inhibitors like Bortezomib and their congeners. Many more are in various phases of research.

HISTORY OF THE DISEASE

Descriptions of diseases very similar to multiple myeloma were obtained in Egyptian mummies. In 1844, Samuel Solley reported a case of myeloma in Sarah Newbury. He described it as “mollitis ossium”. Together with Bence Jones, he found that the urinalysis of the patient showed a protein with the heat properties often observed for urinary light chains. It later on came to be known as the Bence Jones Protein.

MacIntyre and Dalrymple described the properties of the affected bone in the same patient and MacIntyre called it Mollitis and Fragillis ossium^{1,2}.

Rustizky in 1873 gave the term multiple myeloma (MM) after his observation in a similar patient with multiple bone lesions.

Kahler published a detailed description of multiple myeloma in 1889; it was appreciated so much that in Europe the term Kahler's disease for MM is often still used.

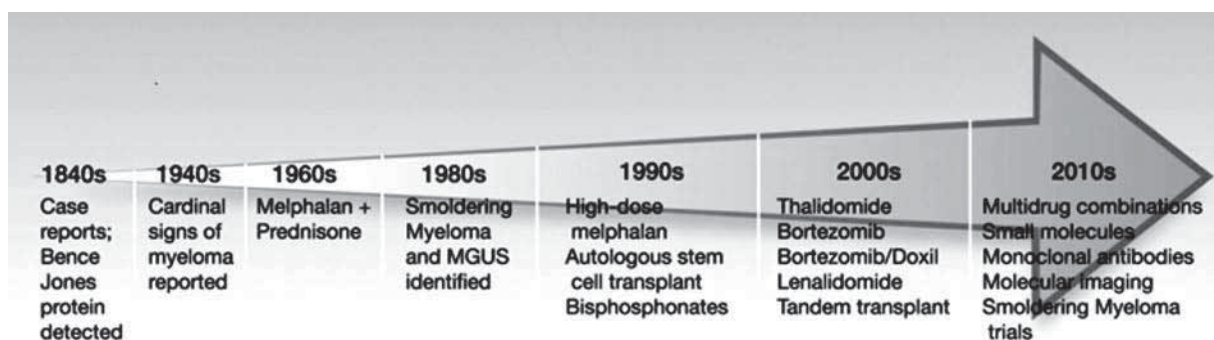
Ellinger in 1899 was the first one to describe in detail about the increased serum proteins and ESR in multiple myeloma.

The close relation between plasma cells in bone marrow and the myeloma cells was first recognized by Wright in 1900. He and Weber in 1898 were the pioneers in providing the X-ray features of the disease which is still used in diagnosing the disease.

Magnus Levy described amyloidosis in MM in 1938. By the 3rd and 4th decade of the 20th century first bone marrow aspiration and then electrophoresis techniques improved the way this disease was diagnosed.

Grabar in 1953 identified heavy and light chains in the monoclonal protein by immunoelectrophoresis and confirmed the monoclonality of Immunoglobulin(Ig) in this disease. In the second half of last century much came to be known regarding the pathogenesis of MM; important among them were the role of the bone marrow microenvironment in myeloma cell growth, survival and antiapoptosis properties of plasma cells and development of drug resistance through cell–cell interaction and activation of cytokine networks.

Timelines in the major events in the understanding of the Myeloma³:



The worldwide Age Standardized Rate (ASR) for incidence of MM as per the GLOBOCAN/IARC data is 1.4/1,00,000 population accounting to 1,00,000 new cases every year. In the US as per the SEER data, the ASR for incidence is higher at 5.8/1,00,000 population accounting for 21,000 new cases each year. The ASR for MM incidence in India is 0.7/1,00,000 population amounting to about 6,800 new cases a year^{4,5}.

Worldwide the 5 year prevalence of the disease is 2,10,697 or 4.3/1,00,000 population. In India it is 11,602 or 1.4/1,00,000 population. As per the SEER data the complete prevalence of MM in USA is around 71,000 cases⁶.

The estimated mortality rate from MM worldwide is 72,453 which accounts for 1% of all cancer related deaths. In India it accounts for around 5,900 deaths every year⁸. The USA SEER data shows that the Age Adjusted Death Rate was 3.4/1,00,000 population.

The disease is slightly more prevalent in males with an M:F ratio of 1.2:1(SEER data) and 1.1:1 worldwide. In India it is 1.3:1. But other single institution studies from India showed a higher M:F ratio of 2.2:1

The disease is more common among the black Americans than the white in USA(14.3 vs. 6.9/1,00,000 new cases every year.

The median age in USA is 74 years as per SEER data, whereas in various single institute data across India it is 1-2 decades lower at around 52-61 years.

The incidence of MM increases with age. More than 75% cases occurring between the age group of 55-85 years. There are only few cases reported below 20 years of age.

The Annual Percentage Change (APC) of Incidence of MM from 2000 to 2009 is an insignificant -0.1% indicating very minimal change, whereas the APC in mortality over the same period is a very significant -1.8% indicating better survival from newer modalities of treatment.

Who Classification of Plasma Cell Neoplasms

Monoclonal gammopathy of undetermined significance (MGUS)^{11, 13-17}

Multiple Myeloma

- Symptomatic
- Asymptomatic (Smoldering)
- Nonsecretory
- Plasma Cell Leukemia

Plasmacytoma

- Solitary plasmacytoma of bone
- Extra medullary plasmacytoma

Deposition Disease

- Primary Amyloidosis,
- Systemic Heavy and Light Chain Disease

Osteosclerotic Myeloma (POEMS Syndrome)

Durie-Salmon Staging²⁶**Stage I**

- Hemoglobin value 10 g/dL
- Serum calcium value normal or =12 mg/dL
- Bone x-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only
- Low M-component production rate (IgG value <5 g/dL; IgA value <3 g/dL; Bence Jones protein <4 g/24 hr)

Stage II*

Neither stage I nor stage III

Neither stage I nor stage III

Stage III

On or more of the following:

- Hemoglobin value 12 mg/dL
- Advanced lytic bone lesions (scale 3)
- High M-component production rate – IgG value >7 g/dL; IgA value >5 g/dL; Bence Jones protein >12 g/24 h

Durie-Salmon sub classifications (either A or B)

A: Relatively normal renal function (serum creatinine value <2.0 mg/dL)

B: Abnormal renal function (serum creatinine value =2.0 mg/dL)

International Staging System for Myeloma (2005)

Stage	Criteria	Median Survival (months)
I	Serum β_2 -microglobulin < 3.5 mg/L	62
	Serum albumin \geq 3.5 g/dL	
II	Not stage I or III	44
III	Serum β_2 -microglobulin \geq 5.5 mg/L	29

Standard Risk Factors for MM and the new proposed R-ISS (Revised International Staging System) by the International Myeloma Working Group (2015)³⁶

Prognostic Factor	Criteria
ISS stage	
I	Serum β_2 -microglobulin < 3.5 mg/L, serum albumin \geq 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2 -microglobulin \geq 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

[CA- cytogenetic abnormality, iFISH – interphase florescent in situ hybridisation, ISS – International Staging System, LDH – lactic dehydrogenase, MM – multiple myeloma]

4

DIAGNOSIS

Plasma cell disorders are a spectrum of disease that vary from a phenotypically benign MGUS to the malignant form of multiple myeloma. The diagnostic criteria that is currently accepted and followed is the International Myeloma Working Group Classification published in 2003¹¹. Unlike other malignancies definition of multiple myeloma is clinicopathological; needs overt clinical manifestations of serious end organ damage and patient cannot be benefited by early therapy to prevent organ damage. So IMWG revised the diagnostic criteria in 2014. The International Myeloma Working Group recommends these criteria for routine practice and future clinical trials³⁶.

Revised diagnostic criteria:

Multiple myeloma

Bone marrow plasma cells 10% or bony or biopsy proven extramedullary plasmacytoma and any one or more of myeloma defining events including:

- **Myeloma defining events:**
 - Evidence of end organ damage due to underlying plasma cell proliferative disorder
 - ◆ Hypercalcemia: >1 mg/dl higher than upper limit or >11 mg/dl
 - ◆ Renal insufficiency: serum creatinine >2mg/dl or creatinine clearance <40 ml/min
 - ◆ Anemia: Hb<10 gm/dl or >2gm/dl below the lower limit of normal
 - ◆ Bone lesion: one or more osteolytic lesions skeletal radiography, CT or PET-CT
 - Any one or more biomarker of malignancy including:
 - ◆ Clonal bone marrow plasma cells 60%
 - ◆ Free light chain ratio 100
 - ◆ >1 focal lesions on MRI

Smouldering multiple myeloma

This is an intermediate during the transition from MGUS to frank symptomatic MM. The monoclonal plasmacytosis and gammopathy has increased to MM levels but the end organ damage that defines MM has not yet occurred.

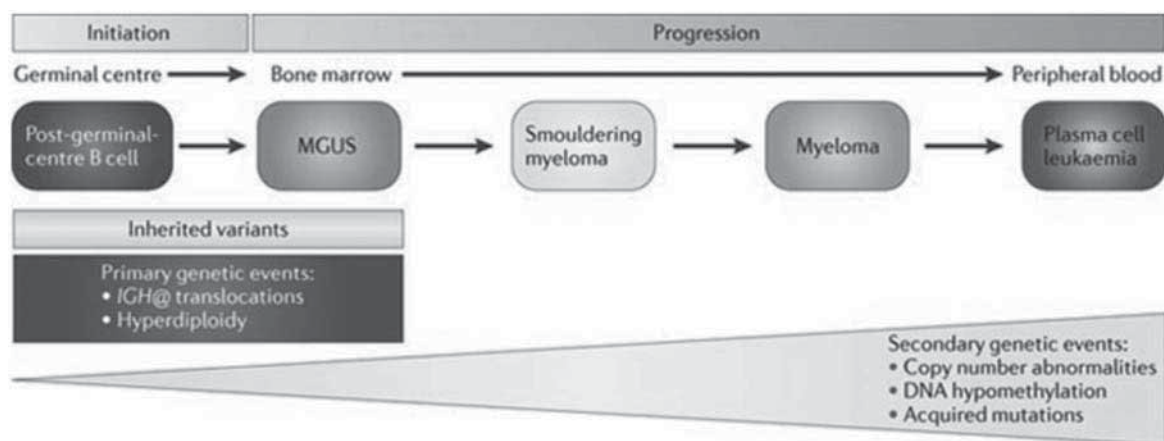
The accepted diagnostic criteria for SMM is:

- Serum monoclonal protein (IgG or IgA) 3gm/dl or 24 hr urinary monoclonal protein 500 mg and/or bone marrow plasma cells 10-60%
- Absence of myeloma defining event or amyloidosis

Monoclonal Gammopathy of Undetermined Significance (MGUS)

In almost all cases multiple myeloma is preceded by a premalignant asymptomatic stage termed as monoclonal gammopathy of undetermined significance. In population over the age of 50 year MGUS is present in 3-4% cases. MGUS can progress to multiple myeloma at the rate of 1% per year¹³. Diagnosis of MGUS requires the absence of hypercalcaemia, renal failure, anaemia, and bone lesions (referred to as CRAB features) that can be attributed to the underlying plasma cell disorder.

Progression of MGUS to MM^{12,28,29}



Diagnostic criteria for MGUS¹¹

All three criteria must be met:

- _ Serum monoclonal protein <3 gm/dL
- _ Clonal bone marrow plasma cells <10%,
- _ Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder; or in the case of IgM MGUS no evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder.

Considering this high risk of plasma cell disorder, persons found to have MGUS should be monitored stringently lifelong.

Various studies from Asian countries have documented a similar percentage (varying from 2.3-6.3%) of MGUS among the general population but are yet to publish their results regarding progression to Plasma cell dyscrasias (PCD). Data from India regarding MGUS is not available. There was an increased incidence of MGUS among people exposed to radiation after the Nagasaki atom bomb explosion especially those living within 1.5 km of the epicentre. But this study did not reveal an increased rate of progression to PCD¹⁵⁻¹⁹.

Solitary Plasmacytoma of Bone:

This occurs around a decade younger than MM and is more common in males. The sites commonly affected are the axial skeleton more than the appendicular skeleton. It should be accompanied with a normal skeletal radiograph. SPEP is ideally negative but in around 50% patients a low level of M protein might be present. BM should not show increased plasma cells. Care should be taken not to do a BM biopsy from an iliac crest or sternum if they are the involved area for the plasmacytoma. MRI might show

other asymptomatic lesions, but still it needs to be taken as a solitary plasmacytoma if X-ray doesn't show any other lesions.

Rate of progression to multiple myeloma is 10% in 3 years.

Solitary plasmacytoma is diagnosed by:

- Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells
- Normal bone marrow with no evidence of clonal plasma cells
- Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion)
- Absence of end-organ damage such as hypercalcaemia, renal insufficiency, anaemia, or bone lesions (CRAB) that can be attributed to a lymphoplasma cell proliferative disorder

Extramedullary Plasmacytoma¹¹

The common sites of involvement are the nasal cavity, nasopharynx, larynx and sinuses. It can happen in any location in the body and is commonly of the IgA subtype. Other evidence of systemic MM should not be present.

The diagnostic criteria is:

- No M-protein in serum and/or urine
- Extramedullary tumour of clonal plasma cells
- Normal bone marrow
- Normal skeletal survey
- No related organ or tissue impairment (end organ damage including bone lesions)

Multiple Solitary Plasmacytomas¹¹:

This entity constitutes less than 5% of all PCDs. The diagnostic criteria for this entity are as follows:

- No M-protein in serum and/or urine
- More than one localized area of bone destruction or extramedullary tumour of clonal plasma cells which may be recurrent
- Normal bone marrow
- Normal skeletal survey and MRI of spine and pelvis if done
- No related organ or tissue impairment (no end organ damage other than the localized bone lesions)

* Small elevation of M protein may be seen

Plasma Cell Leukaemia (PCL):

PCL occurs when there is more than 20% abnormal plasma cells in the differential WBC lineage or if there is an absolute number of more than $2 \times 10^9/L$ of plasma cells. This might be primary or secondary. Primary (approx. 60%), if the patient presents with PCL and secondary is if the patients progresses to PCL from MM.

Symptomatology²²

- Around one third of patients may have another PCD before the diagnosis of MM, in the form of MGUS(20%), SMM(9%), and the rest being plasmacytomas and amyloidosis
- Bone pain, Fatigue and recurrent infections are the most common symptoms of MM.
- Bone pains are present in around 60-90% of patients.
- Anaemia and fatigue was present in about 70% of the patients with the median Hemoglobin (Hb) of around 10gm%.
- Mild elevation of Serum Creatinine is found in around 50% patients while levels above 2mg/dl are found in 20% patients.
- Hypercalcemia is found in 25%. Conventional skeletal survey is abnormal in about 80% patients.

Diagnosis

Diagnosis of MM is based on the following tests¹¹:

- Detection and quantification of the monoclonal (M-) component by serum and/or urine protein electrophoresis; characterisation of the heavy and light chains by immune-fixation; and serum-free light-chain (FLC) measurement;
- Evaluation of bone marrow (BM) plasma cell infiltration by BM aspiration and/or biopsy.
- BM for cytogenetic/fluorescence in situ hybridization (FISH) studies
- Evaluation of lytic bone lesions: a radiological skeletal bone survey, including spine, pelvis, skull, humeri and femurs. MRI or computed tomography (CT) scan may be needed to evaluate symptomatic bony sites, even if the skeletal survey is negative and the patient has symptoms suggesting bone lesions. MRI provides greater detail and is recommended whenever spinal cord compression is suspected. FDG PET scan is currently under evaluation and should be used for evaluation of all patients
- Complete blood cell count, with differential; renal function testing including serum albumin and calcium
- Serum beta2 Microglobulin (for staging)

These tests are used to differential diagnosis between symptomatic MM, SMM and MGUS.

The diagnosis of symptomatic MM requires:

- 10% clonal plasma cells on BM examination or a biopsy proven plasmacytoma; and
- evidence of end-organ damage, the so-called CRAB criteria (hypercalcaemia, renal insufficiency, anaemia or bone lesions) that is felt to be related to the underlying plasma cell disorder (Table 1).

DIAGNOSTIC INVESTIGATIONS²⁵

Broadly the investigations for a new case of Myeloma are aimed for the following factors:

- Confirming and quantifying monoclonal protein and establishing the monoclonality of the plasma cells
- Differentiating MGUS, SMM and symptomatic MM

- Prognosticating, and assessing the tumour burden.

Monoclonal Gammopathy:

- The gold standard for demonstrating this is the serum and Urine immunofixation electrophoresis (SIFE & UIFE).
- In practice it is prudent to start with Serum and Urine Protein Electrophoresis (SPEP & UPEP) as further follow ups require only a SPEP. Eighty per cent of MM patients will have a positive SPEP. With SIFE being added this increases to 93%. By adding UIFE the success rate of identifying a monoclonal gammopathy increased to 97%.
- The remaining 3% is conventionally termed as the *Non-secretory myelomas*. This number again drops when Serum Free Light Chain is also added to the investigations. Thus it's always imperative to do both Serum as well as Urine IFE at baseline.
- Up to 20% of patients are considered as Light Chain Disease (LCD) who does not secrete the heavy chain part. They will be missed if only the SPEP is done. In the diagnosis of MM with SPEP it is prudent to differentiate the Monoclonal M spike from polyclonal gammopathy which can be present in various benign conditions. The M spike of MM is usually present in gamma region but at times may be present in the beta 2 region also.

Serum Free Light Chain (SFLC) assay

- It detects the levels of κ and λ light chains in the serum. The FLC assay measures free κ (reference range, 0.33-1.94 mg/dL) and free λ (reference range, 0.57-2.63 mg/dL) light chains.
- These might together be elevated in polyclonal gammopathy conditions. Hence to prove the monoclonality of the LC, the ratio of κ to λ is taken.
- The normal ratio is 0.26 to 1.65. Values < 0.26 indicates a λ LC disease whereas > 1.65 indicates a κ LC disease.
- SFLC is also to be normal in order to claim a Stringent Complete Response. Thus it is prudent to consider SPEP, SIFE and SFLC as investigations with increasing sensitivity to detect monoclonal gammopathy.

Serum Assays of Immunoglobulins are also another way to quantify monoclonal gammopathy, this also helps in monitoring the follow up. In around 90% of MM patients corresponding to the increase in a specific monoclonal Ig, there will be a reduction or suppression of levels of the other proteins.

So to summarize, among 100 patients of MM, 50-60% will be of IgG subtype, 20% of IgA, 2% of IgD and $< 1\%$ of IgM subtypes. Around 15-20% will be having FLC only. The LC component in total is almost equal or κ might have a slight preponderance, but κ is more common in IgG type (1.7:1) whereas λ is more common in IgD (1.9:1).

Bone Marrow (BM)

- Bone marrow plasmacytosis is to be proven by BM aspiration and Biopsy from both iliac crests.
- Bilateral BM Biopsy is recommended as it is proven that MM can have a patchy affection of the BM.
- BM involvement is found in about 95% patients.

- In around 40% patients the levels might be below 10%^{20,21}.
- Hence in the presence of end organ damage, the absolute percentage of BM plasmacytosis is not significant, rather it only needs to be demonstrated that they are malignant, either morphologically or by flowcytometry. Monoclonality of these plasma cells can be proven by Immuno Histochemistry (IHC) using stains against κ and λ LC.

Test for Organ Involvement

- Anaemia is present at initial presentation in around two thirds of patients while during the course of the disease almost everyone will have this. The cut-off level of Hb for diagnosis of MM is <10gm% or 2gm% less than the normal. The anaemia is usually normocytic, normochromic in nature.
- Hypercalcemia is present in around 10-15% patients at presentation and is a major cause of reversible renal insufficiency at presentation, usually responding to hydration and steroids.
- Serum Creatinine elevations above normal values are found in about one third of patients at presentation but requirement of dialysis is much lesser, most of them responding to correction of dehydration and hypercalcemia. Creatinine elevation at baseline is a poor prognostic indicator, and even poorer if it doesn't become normal on treatment.

Imaging^{24,25}

- Skeletal abnormalities in conventional skeletal survey in MM can manifest in various ways like osteopenia, osteoporosis, lytic lesions and collapse fractures.
- In around 70-80% patients there will be some bone changes evident in baseline and another 15-20% will develop it during the course of the disease.
- Sclerotic lesions in MM are extremely rare and should prompt investigations in line for POEMS syndrome or alternate diagnosis.
- Bone scan is not a preferred modality for assessing skeletal lesions in MM since it shows areas of bone formation only.
- The drawbacks with conventional radiology are that it has a high false positivity of around 30-70%, and it can't distinguish age related osteopenia from MM related osteopenia or osteoporosis.
- Whole body CT scans have a better sensitivity than x-rays, but the drawback is the excessive amount of radiation exposure and poor visualisation of the marrow. But it gives a better estimate of fracture risk.
- Role of MRI is coming up in a large scale now. This is better in detecting spinal lesions more accurately where urgent local treatment is required to save impending neurological complications. MRI also gives a better understanding of the marrow and soft tissue components and also helps in prognostication. Hazard of radiation is not present with MRI.
- PET might be helpful in detecting active lesions from inactive ones and thus differentiate between MGUS and MM. It is also helpful in the follow-up of non-secretory MM. Various serum and Urine assays are being tested to quantify and qualify the bone disease in MM, but none of them are of proven significance and are hence not recommended²³.

To summarize, Whole Body Skeletal survey is imperative in the initial workup of MM. for localised lesions or if only single lesions (like solitary plasmacytomas) are present or if some form of local therapy like

Radiotherapy or surgery is urgently required, a better imaging modality like MRI or PET CT or CT scan can be used. Routine use of PET CT is not recommended. Again bone scan is also not a recommended modality for work up of MM.

Other investigations required for prognostication

Serum $\beta 2$ microglobulins: this is one of the back bones of the International Staging System (ISS) and is a marker of tumor burden.

Serum LDH: has an independent prognostic significance in various studies.

ESR is elevated in most cases of MM but the values correlate neither with tumor burden nor with treatment response. Hence its importance is uncertain.

C-Reactive proteins are elevated in MM and might be of value when infections are a presenting feature of MM.

Molecular testing²⁷

Conventional cytogenetics and Fluorescent In situ Hybridisation (FISH) are being used recently. As per the available data researchers from Mayo Clinic have devised a stratification system based on cytogenetics which is as follows,

Standard-risk

Hyperdiploidy

t (11;14)

t (6;14)

Intermediate-risk

t (4;14)

Deletion 13 or hypodiploidy by conventional karyotyping

High-risk

17p deletion

t (14;16)

t (14;20)

High-risk gene expression profiling signature

Even though efforts are being made to tailor treatment according to these features, consensus is still lacking and especially in India, lack of quality test centres precludes its routine use.

MINIMUM BASELINE DIAGNOSTIC WORKUP

The initial panel of diagnostic investigations of a case of MM should contain at least the following:

- Complete blood count and differential; peripheral blood smear, ESR
- Kidney function tests and Liver function tests including calcium and LDH levels
- Serum protein electrophoresis (including quantification), Immunofixation Electrophoresis
- Routine urinalysis, 24-hour urine collection for electrophoresis, immunofixation (desirable)

- Bone marrow aspirate and/or biopsy
 - ◆ Plasma cell percentage and morphology
 - ◆ Cytogenetics or FISH for risk stratification (desirable)
- Radiologic skeletal bone survey, including spine, pelvis, skull, humeri, and femurs;
 - ◆ Magnetic resonance imaging in certain circumstances
- Serum beta 2-microglobulin
- Measurement of serum-free light chains

INVESTIGATIONS FOR MONITORING³¹

- For monitoring the treatment response, which ever test had documented the monoclonal gammopathy is to be repeated.
- If SPEP was positive, then monitoring the same is only required, there is no need to repeat SIFE and UIFE.
- In non-secretory MM, if SFLC was positive, it has to be used for monitoring.
- Bone marrow need not be repeated routinely, but needs to be done to document what response has been attained at the end of treatment.
- Repeating a skeletal survey is not required unless there is new onset of skeletal symptoms.
- Similarly molecular tests need not be repeated.

5

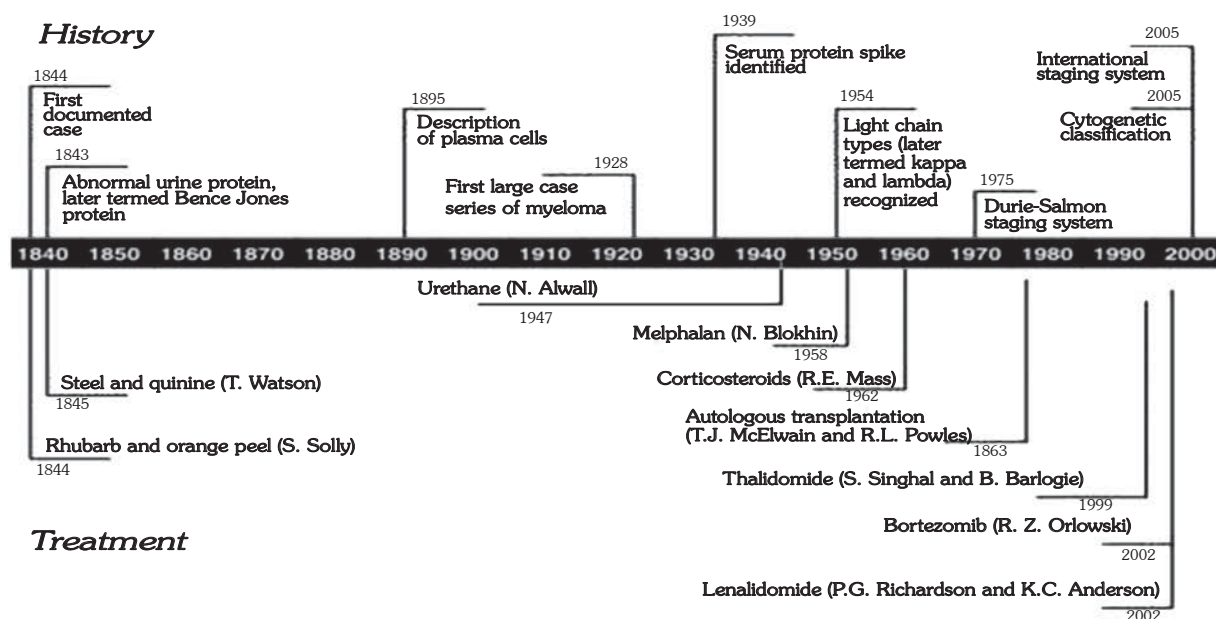
TREATMENT OF MULTIPLE MYELOMA

Transplant eligible patients

After the diagnosis of Multiple Myeloma (MM) has been established for a patient, complete work up as for the relevant prognostic assessment are done so as to decide best treatment options. As has been mentioned previously, asymptomatic plasma cell disorders like MGUS and smoldering myeloma do not require treatment. They are to be kept under strict and regular follow up.

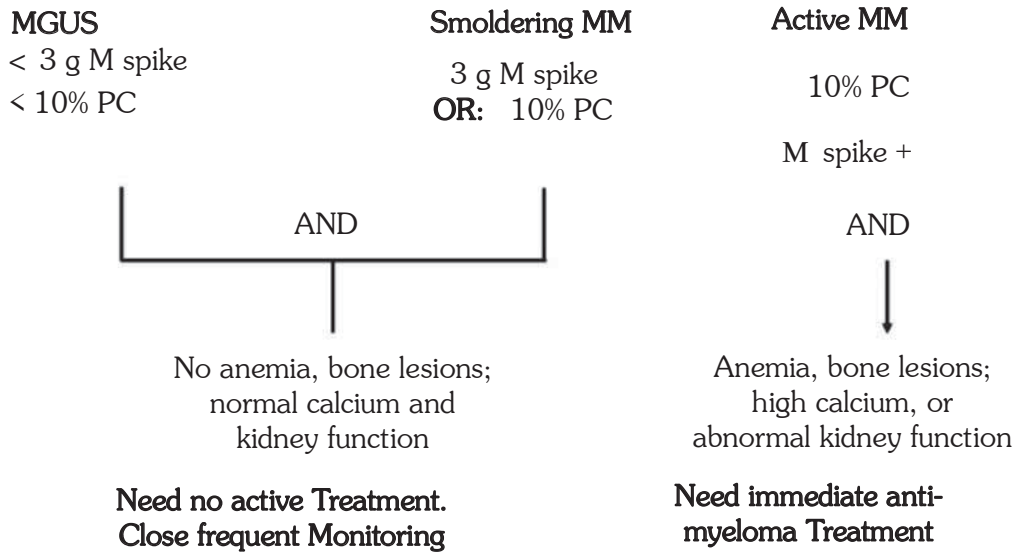
In the last 3 decades major advancements have led to an improved Overall Survival (OS) for patients with MM. Autologous peripheral blood and stem cell transplantation (APBSCT) has evolved into standard of care for transplant eligible candidates. In the last decade, newer drugs belonging to the immunomodulatory group and proteasome inhibitors improved the OS. A study from Mayo clinic demonstrated that in the last decade OS of MM patients almost doubled, after the arrival of these new drugs²⁰.

Historical Time line of major events in the treatment of MM

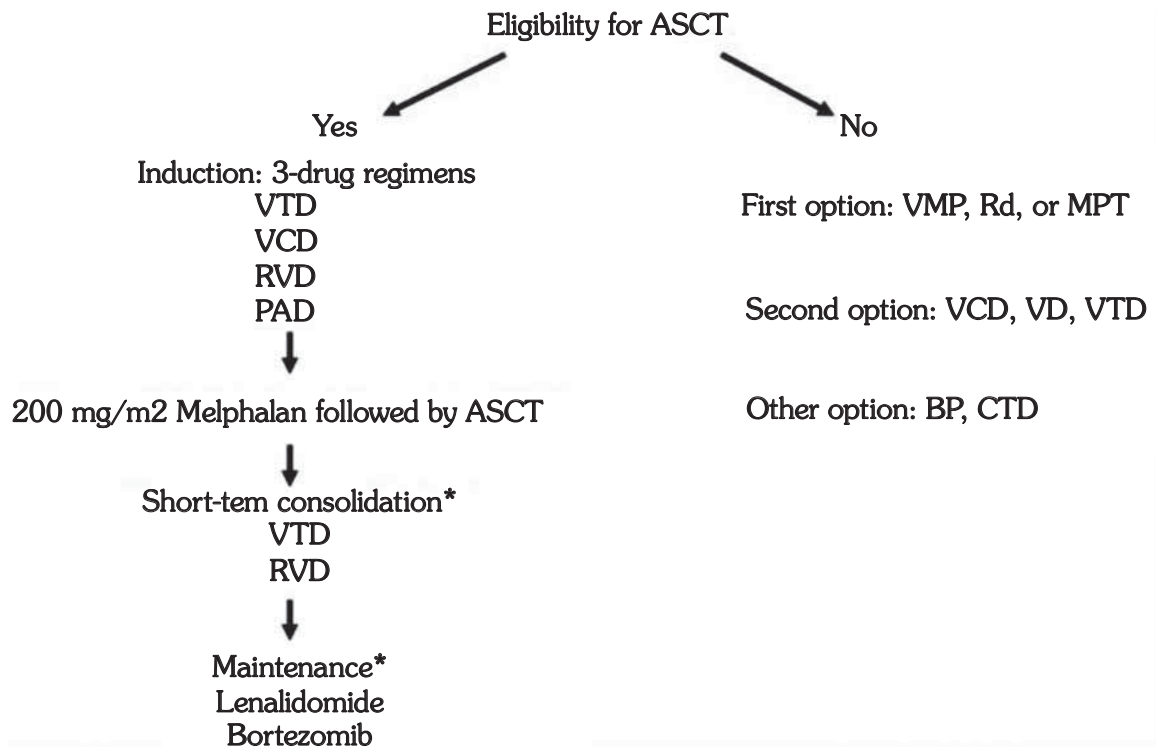


ALGORITHM FOR MULTIPLE MYELOMA

CRITERIA FOR DIAGNOSIS & TREATMENT OF MYELOMA

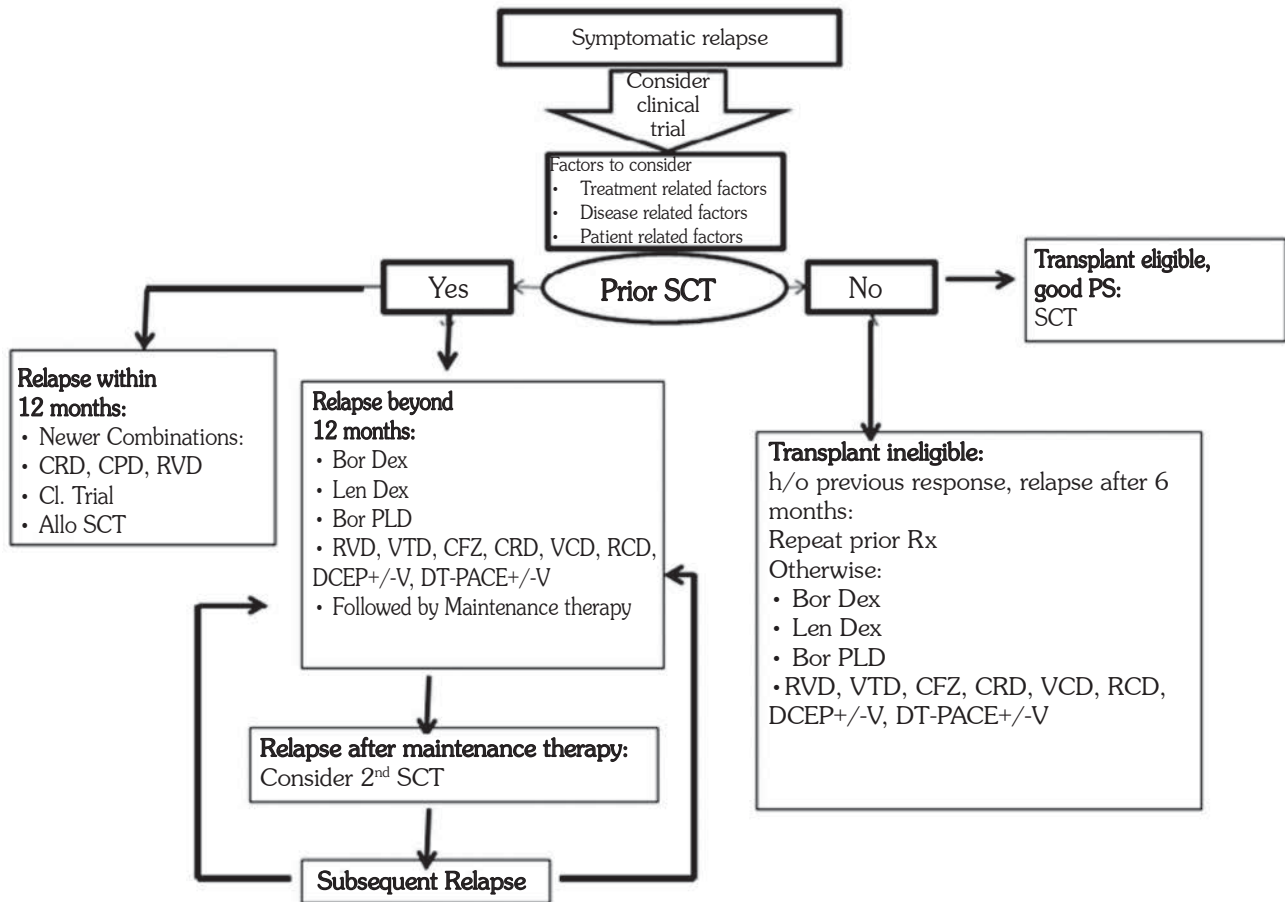


FRONT-LINE TREATMENT OF SYMPTOMATIC MULTIPLE MYELOMA



[ASCT – Autologous Stem Cell Transplant, MPT, melphalan, prednisone, thalidomide; VMP, bortezomib, melphalan, prednisone; CTD, cyclophosphamide, thalidomide, dexamethasone; MP, melphalan, prednisone; VTD, bortezomib, thalidomide, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; PAD, bortezomib, doxorubicin, dexamethasone; RVD, lenalidomide, bortezomib, dexamethasone, BP, bendamustin, prednisolone]

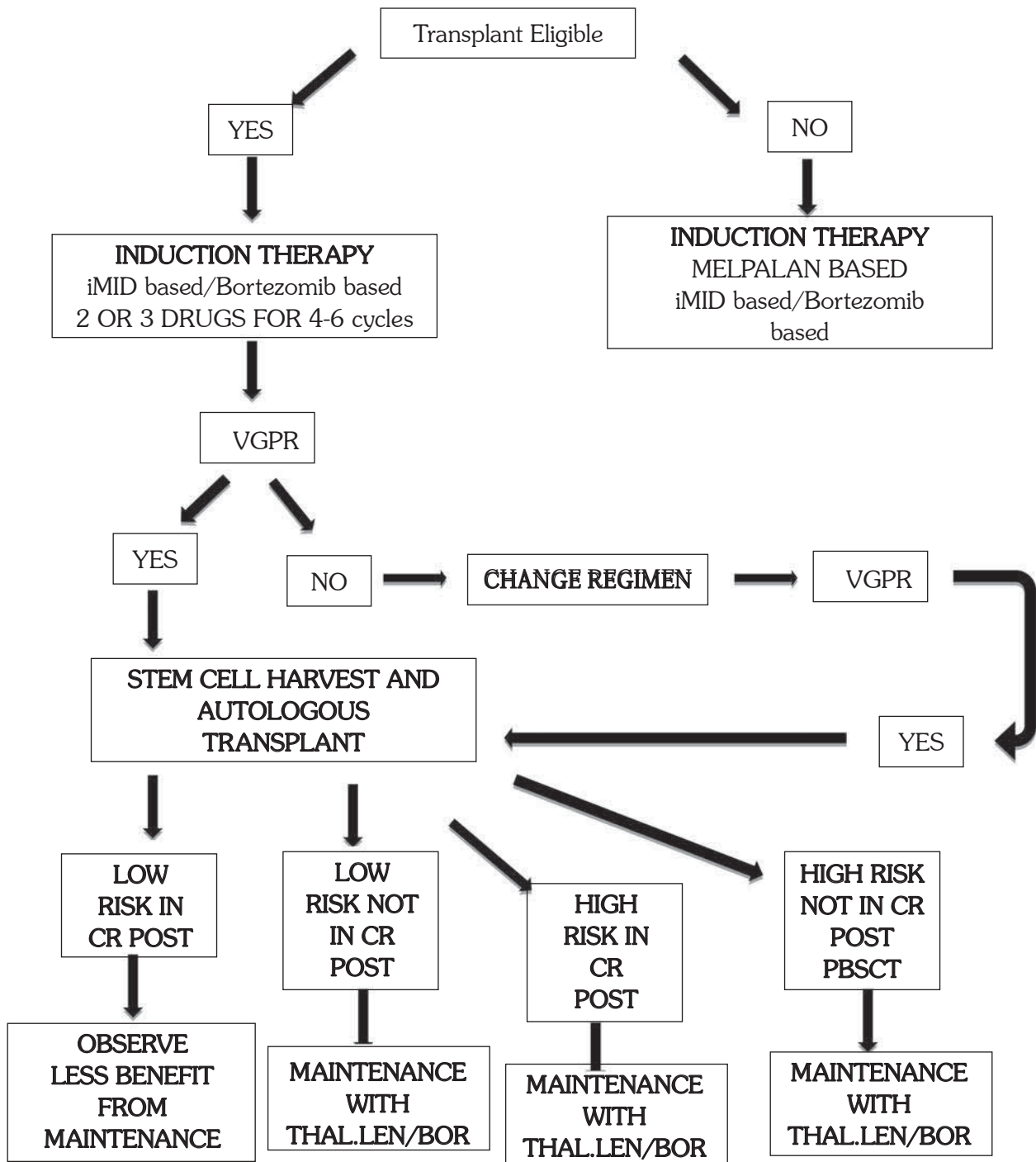
TREATMENT OF MULTIPLE MYELOMA AFTER RELAPSE



[CFZ: carfilzomib; CPD: carfilzomib, pomalidomide and dexamethasone; CRD: carfilzomib, lenalidomide and dexamethasone; DCEP6V: dexamethasone, cyclophosphamide, etoposide, and cisplatin6bortezomib; DT-PACE6V: dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide6bortezomib; Pd: pomalidomide and dexamethasone; PFS: progression free survival; PLD: liposomal doxorubicin; PS: performance status; RCD: lenalidomide, cyclophosphamide and dexamethasone; RVD: lenalidomide, bortezomib and dexamethasone; SCT: autologous stem cell transplant; SCT2: second SCT; Td: thalidomide and dexamethasone; VCD: bortezomib, cyclophosphamide and dexamethasone; VTD: bortezomib, thalidomide and dexamethasone]

For a symptomatic patient with MM the first assessment is whether he is a transplant eligible candidate or not after the induction chemotherapy.

TREATMENT ALGORITHM FOR TRANSPLANT ELIGIBLE PATIENTS



For MM patients Allogeneic Stem Cell Transplant does not carry a benefit over Autologous Peripheral Blood Stem Cell Transplant (APBSCT). Similarly benefit of tandem transplant over single APBSCT is debatable, except in patients who do not attain VGPR. APBSCT is the preferred consolidation therapy for MM patients after attaining the best response.

The selection of a patient for APBSCT depends upon his age, performance status (PS) and co morbid

conditions. Even though there is no exact cut off for age for eligibility for transplant, patients of up to 65 years and an ECOG PS of 0-1 are considered ideal candidates.

In transplant eligible patients, the aim of induction therapy is to attain the best achievable response at the earliest time. Vincristine, doxorubicin, dexamethasone (VAD) was the regimen of choice in the eighties when auto transplant was popularised by Barlogie et al for myeloma. In the last decade with the arrival of newer drugs for MM, popularity of VAD has decreased as first line therapy for MM. This is because of both the better responses and tolerance to these drugs. Cure versus control is an on-going area of debate in myeloma, with some people suggesting for initial multidrug combinations to increase the depth of Complete Remission (CR) and then consolidating it with an APBSCT. Whereas others advocate that sequential disease control approach that emphasizes quality of life as well as OS is appropriate. Efforts are on thus to stratify the disease so that the higher risk patients might be treated more aggressively than the lower risk patients or in other words the lower risk patients may be saved from treatment toxicity of more severe regimens³⁰. The Durie Salmon system was used for many years for this. The International Staging System (ISS) is equally effective and easier to use. Now researchers are trying to use cytogenetics to stratify the disease.

Melphalan containing regimens are better avoided as induction therapy in transplant eligible patients since it reduces the stem cell yield during harvest. Similar concerns are also there for Lenalidomide but are not yet proven. Whether to use 2 drug or 3 drugs for induction is still debated, but where ever tolerance would be good it is preferable to use 3 drug combinations.

TWO DRUG COMBINATIONS

Thalidomide-Dexamethasone (TD):

Thalidomide was the first immunomodulatory drug to be used in MM along with dexamethasone, and had superior activity over dexamethasone alone. One of these trials used a dose of 200mg daily whereas the other trial used escalating doses from 50mg daily to 200mg daily. In India two studies have shown that Thalidomide can be used in similar doses and has shown equal effectiveness as Western studies in frontline or relapsed setting. In the AIIMS study many of the patients received 800mg daily dose for certain period of time, however this dose might not be tolerable for most of the patients especially in combination with Dexamethasone. Again in today's scenario where there are many other options with equivalent or better results, using Thalidomide for more than 200mg doesn't seem acceptable. But in patients presenting with renal failure at initial presentation and not responding to hydration and steroids, thalidomide is a good treatment option, without any dose modifications⁷.

<i>Thalidomide</i>	100-200mg daily
<i>Dexamethasone</i>	40 mg days 1-4, 9-12, and 17-20
<i>Low Dose Dexamethasone</i>	40 mg/day, PO, once per week
<i>Repeated every 4 weeks</i>	
<i>Overall response rate</i>	60-70%
<i>Progression-free survival</i>	22months

Grade 3 or 4 toxicities:

Deep Vein Thrombosis (DVT): 15% (with Steroids)

Constipation: 35%

Peripheral Neuropathy: 60% (any degree, and 5% severe)

Common adverse events with Thalidomide.

Neurologic	
Peri NS	Numbness; paresthesia; pain in the hands, arms, feet, or legs; prickling, burning
CNS	Hangover feeling, loss of coordination, nervousness, tremors, confusion, nausea, aural buzzing, fatigue, mood changes, somnolence, headache, sedation, fluctuation of blood pressure, orthostatic hypotension, bradycardia
Gastrointestinal	Constipation, nausea, gastric pain, increased appetite, xerostomia
Hematologic	Neutropenia, granulocytopenia, deep vein thrombosis
Dermatologic	Red palms, skin rash, toxic epidermal necrolysis, brittle fingernails, pruritus
Genital system	Teratogenicity, phocomelia, menstrual irregularities, decreased libido
Endocrine	Hypothyroidism, edema

NB: Use of thalidomide for MM in ladies of reproductive age group should be extremely cautious. Pregnancy test has to be performed and they should be counselled regarding double contraceptive measures while on thalidomide.

Lenalidomide- Dexamethasone (LD)³⁰

Dexamethasone was initially used at a high dose with Lenalidomide i.e. at 40mg daily on Days 1-4, 9-12, and 17-20 of a 28-day cycle with Lenalidomide at 25mg daily from Days 1-21. But in subsequent study low dose dexamethasone (40 mg weekly) was compared with standard high dose schedule. Result showed that low dose was not only more tolerable but also improved progression free survival (25 vs. 19 months). This was because of a higher death rate in LD (high dose dexamethasone) arm in the first 4 months (12 vs. 2). In fact after this interim analysis, this trial was stopped and patients on LD arm were allowed to crossover to Ld arm. Thus Lenalidomide with low dose Dexamethasone (Ld) is the preferred treatment option now. Stem cell mobilisation is considered to be a problem with Lenalidomide therapy. But this seems to be overcome if cyclophosphamide is used for mobilisation.

<i>Lenalidomide</i>	25mg daily from D1-D21
<i>Dexamethasone</i>	40 mg days 1,8,15,21
<i>Low Dose Dexamethasone</i>	40 mg/day, PO, once per week

Repeated every 4 weeks

<i>Overall response rate</i>	70-80%%
<i>Progression-free survival</i>	25mths
<i>3 year Overall Survival</i>	75%

Grade 3 or 4 toxicities:

Deep Vein Thrombosis (DVT):	26% (LD) vs. 12% (Ld)
Neutropenia:	20%
Infections:	10 to 15 %
Fatigue:	10-15%

In a recent abstract presentation at ASH 2011, Mookerjee et al had compared Ld vs. TD in 56 patients in a randomised controlled manner they showed that both arms had a similar overall response rates (ORR)(74% vs. 84%), but the time to achieve a response was significantly faster in Ld arm (4weeks vs. 11 weeks, $p < 0.002$).

Bortezomib-Dexamethasone: (VD):

VD was tried against the conventional VAD regimen by Harousseau et al. They found a better response rates with VD(38% vs. 15% VGPR) and a modest improvement in PFS(36 vs. 30months) and insignificant difference in OS. Grade 3 or 4 adverse events were similar in both groups (38% vs. 40%). There were more deaths during treatment in VAD arm, (0.8% vs. 2.9%). Neuropathy was more with VD arm (35% vs. 22% and Grade 3 or 4 in 10% vs. 3%). But to summarise this study showed that VD was superior to VAD regimen.

The major drawback of Bortezomib-containing regimens is the risk of neurotoxicity early in the disease course. The neuropathy with Bortezomib can occur abruptly and can be significantly painful and debilitating in a subset of patients. Recent studies show that the neurotoxicity of Bortezomib can be greatly diminished by administering Bortezomib using a once-weekly schedule and by administering the drug subcutaneously(. Bortezomib, unlike Lenalidomide, does not affect stem cell mobilisation.

MULTI DRUG COMBINATIONS:

In last few years, in an endeavour to increase the depth of the initial response so that it might translate into an improved survival, investigators tried multi drug combinations for induction therapy. Various combinations have been tried, most of them having Bortezomib and Dexamethasone as two components and the third component being changed. There are studies that did not use Bortezomib also. The results are of short term follow ups and comparisons between these individual studies are not possible due to varying end points and response parameters used. But it can be safely concluded that these regimens have improved the response rates including CR rates and has shown a trend towards improvement in survival also. Toxicity is obviously more than that for 2 drug regimens. Hence in patients with good performance status, multidrug regimen is an option especially if their disease load is high and baseline prognostic factors are poor.

The various multidrug regimens are summarised below.

BORTEZOMIB–THALIDOMIDE–DEXAMETHASONE (VTD) ref Moreau et al

<i>Bortezomib</i>	1.3 mg/m ² intravenous days 1, 8, 15, 22;
<i>Thalidomide</i>	100–200 mg oral days 1–21;
<i>Dexamethasone</i>	20 mg on day of or after Bortezomib (or 40 mg days 1, 8, 15, 22);
<i>Repeated every 4 weeks × 4 cycles as pre-transplant induction therapy</i>	
<i>Overall response rate:</i>	95%
<i>Estimated CR + VGPR rate:</i>	60%
<i>PFS at 44 months:</i>	61%

Any grade 3–4 non-hematologic adverse events 10%

BORTEZOMIB–CYCLOPHOSPHAMIDE–DEXAMETHASONE (VCD)

<i>Cyclophosphamide</i>	300 mg/m ² orally on days 1, 8, 15 and 22;
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Bortezomib 1.3 mg/m² intravenously on days 1, 8, 15, 22;

Dexamethasone 40 mg orally on days on days 1, 8, 15, 22;

Repeated every 4 weeks

Overall response rate 90%

Estimated CR + VGPR rate 70%

Grade 3 or 4 Adverse Events:

Anaemia 12%

Neutropenia 13%

Thrombocytopenia 25%

Hyperglycaemia 13%

Diarrhoea 6%

Hypokalaemia 9%

Neuropathy 7%

Thrombosis 7%

BORTEZOMIB–LENALIDOMIDE–DEXAMETHASONE (VRD)

Bortezomib 1.3 mg/m² intravenous days 1, 8, 15;

Lenalidomide 25 mg oral days 1–14;

Dexamethasone 20 mg on day of and day after Bortezomib (or 40 mg days 1, 8, 15, 22);

Repeated every 3 weeks

Overall response rate 100%

Estimated CR + VGPR rate 70%

18 month PFS: 75%

Grade 3 or 4 Adverse Events:

Neutropenia 10-35%%

Thrombocytopenia 2-12%

Gastrointestinal toxicity 7%

Infections 2%

Peripheral neuropathy 4-14%%

DVT/thromboembolism 5%

AEs resulting in study discontinuation: 17%

BORTEZOMIB–ADRIAMYCIN–DEXAMETHASONE [PAD]

Bortezomib 1.3 mg/m² days 1, 4,8,11,

Adriamycin 9 mg/m² days 1-4,

Dexamethasone 40 mg days 1-4, 8-11, and 15-18

Repeated every 3 weeks

<i>Overall response rate</i>	95%
<i>Estimated CR + VGPR rate</i>	30%
<i>Progression-free survival</i>	29mths
<i>1 year Overall survival:</i>	100%.
Grade 3 or 4 toxicities:	
Liver function tests	15%,
Psychiatric	10%,
Thrombocytopenia	5%,
Neutropenia	5%
Infection	5%
Neuropathy	5%

BORTEZOMIB, PEGYLATED LIPOSOMAL DOXORUBICIN (PLD), AND DEXAMETHASONE COMBINATION REGIMEN (VDD)

<i>Bortezomib</i>	1.3mg/m ² intravenously (IV) on days 1, 4, 8, and 11;
<i>PLD</i>	30 mg/m ² IV on day 4;
<i>Dexamethasone:</i>	at an initial dose of 40mg orally (PO) on days 1, 2, 4, 5, 8, 9, 11, and 12 during the first cycle and 20 mg PO daily during cycles 2 through 6

Repeated every 3 weeks

<i>Overall response rate</i>	90%
<i>Estimated CR + VGPR rate</i>	55%
<i>1 year PFS:</i>	93%
<i>1 year OS:</i>	98%
Grade 3 or 4 AE	
Neutropenia	10%
Thrombocytopenia	10%
Anaemia	3%
Infections	8%
Thromboembolism	10%
Peripheral neuropathy	3%
Muscle weakness	8%
Fatigue	13%
Glucose intolerance:	13%

Guidelines for Stem Cell Transplant in Multiple Myeloma

Multiple myeloma is a malignant disorder characterized by accumulation of plasma cells which in turn results in a constellation of signs and symptoms that have been addressed earlier in these guidelines. For the most part these are a group of slowly proliferating malignancies where the majority of the malignant population is in a relatively quiescent non dividing state and are hence not susceptible to cell cycle dependent cytotoxic agents. They are hence relatively resistant to most conventional chemotherapy agents and are more susceptible to corticosteroids and alkylating agents such as cyclophosphamide and melphalan. Dose intensification with these drugs is one strategy to overcome intrinsic resistance in these non dividing cells. This forms the basis for high dose melphalan followed by autologous stem cell rescue to reduce the complications that can result from this approach. The role of an allogeneic stem cell transplant is evolving and currently recommended only in the setting of a clinical trial.

Autologous stem cell transplant^{30,35}

The first randomized clinical trial to address the role of an autologous stem cell transplant in the management of myeloma was conducted and reported by the Intergroupe Francophone du Myelome. This study demonstrated the superiority of this approach over conventional therapy in terms of response rates, event free and overall survival. A second such study by the British Medical Research Council 7 years later confirmed these observations. Since then 5 other such randomized controlled trials have been reported. Of these 7 studies in only 3 was there a survival advantage associated with an autologous SCT. Based on the available data it is anticipated that an autologous SCT improves the median survival from 36 months to 50 months. It must be stressed that this procedure is not considered curative in the treatment of myeloma though a small proportion of cases can have functional cure with duration of remission exceeding 10 years. Some of the issues related to autologous SCT in myeloma are:

Age

Most of the randomized clinical trials in myeloma were done in patients less than 70 years of age. Considering that this is not a curative procedure in myeloma it is generally reserved for younger patients without significant co-morbidities in whom it is anticipated that the risk of treatment related mortality will be <5%. In Europe this procedure is generally considered only for those <65 years of age while in the USA there is no formal upper age limit. There is limited data on benefit for patients >65 years though the consensus is that it can be offered for patients >65 years after considering pre-existing co-morbidities and performance status.

Time to stem cell collection after induction therapy

Most patients achieve maximum response to induction therapy after 4 to 6 cycles of the initial induction therapy. While complete remission (CR) is an ideal it is not necessary to achieve this prior to stem cell collection. Assessment of response should be done after every cycle and if there is evidence of disease progression or a less than partial response (PR) after two cycles then the therapy should be changed. At end of 4 cycles if there is less than VGPR it is reasonable to consider additional two cycles of alternative therapy in an effort to improve response prior to stem cell collection though there is little evidence that this contributes significantly to long term outcome. It is also reasonable to proceed with stem cell collection in <PR after 4 cycles of induction therapy if adequate stem cells can be collected. Ongoing studies are addressing the issue of a delayed autologous SCT to time of disease progression after initial therapy. However, based on the available data it is recommended that patients who are transplant eligible should proceed with an autologous SCT after the initial 4 to 6 cycles of induction therapy.

Peripheral blood stem cell (PBSC) collection after cytokine mobilization should be done within 4 to 6 weeks of the last induction cycle of therapy when the decision to proceed with an autologous SCT has been made. While cyclophosphamide plus G-CSF mobilization is widely used, it is reasonable to attempt mobilization with G-CSF alone the first time. However, if induction therapy included at least 4 cycles of lenalidomide based therapy then it would be reasonable to consider chemotherapy followed by G-CSF mobilization up front in view of the higher risk of poor mobilization in this situation. The minimum CD34 cell dose to safely achieve engraftment is considered to be $2 \times 10^6/\text{kg}$.

Conditioning Regimen:

High dose melphalan ($200\text{mg}/\text{m}^2$) remains the standard recommendation. Combination of the above at same or different doses with TBI did not show any advantage while combination with novel drugs such as Bortezomib have shown promise, though this cannot at this time point be considered standard recommendation. Collected stem cells can be infused 12 to 24 hours after the infusion of melphalan dose. There is no need to cryopreserve the stem cells if the stem cell infusion can be timed to within 24 hours of apheresis collection. The collected stem cells can be stored safely at 4°C overnight prior to the infusion. Alternatively the stem cells can be cryopreserved and infused with appropriate monitoring and pre-medication. There is no published data to support any significant advantage of cryopreservation of the stem cell product over infusion of fresh stem cell product.

Need for laminar air flow systems:

The duration of severe neutropenia is usually less than 10 days with this procedure and hence there is no need for a special HEPA room or laminar air flow system required to carry out this procedure. It is reasonable to start G-CSF from the 5th to 7th day following stem cell infusion to hasten neutrophil recovery.

Single versus tandem autologous stem cell transplant:

Tandem autologous SCT was initially reported as a strategy to improve outcome over a single transplant in 1997. A subsequent RCT conducted by the IFM group suggested a small but statistically significant superiority with this approach though it was limited to patients that failed to achieve a CR after the first transplant. More recent systematic review of data from more than 1800 patients does not suggest any significant advantage. After collection of adequate stem cells for two transplants and cryopreservation two strategies can be considered for a second transplant, the first is to proceed with a tandem transplant in those that do not achieve a CR after the first transplant and the second to do a second transplant only after disease progression post transplant. However, a definitive recommendation for a second transplant at the time of disease progression cannot be made at present on the available data but is a reasonable option.

Transplant with renal failure:

High dose melphalan and an autologous SCT are feasible in patients with renal failure and on dialysis though the treatment related mortality with the dose of $200\text{mg}/\text{m}^2$ is unacceptably high. The threshold for dose reduction appears to be a GFR of $<30\text{ml}/\text{min}$. In a young patient it is reasonable to consider this procedure even in setting of irreversible renal failure where the response rates are comparable with matched controls without renal failure.

Assessment of response post transplant and maintenance therapy:

A complete disease response assessment should be done 3 months following the autologous SCT. Achievement of CR at this time point and subsequent loss of CR are the most important prognostic

factors for progression free and overall survival post transplantation. Recent data from a RCT looking at post transplant lenalidomide suggests that there is a survival advantage for those on lenalidomide maintenance. It would be reasonable to consider maintenance therapy with lenalidomide in all patients who can tolerate this regimen post transplantation. Similar data is available with bortezomib and can be considered an option. The best maintenance therapy and the optimal duration of such therapy remain to be defined.

Maintenance Treatment in MM^{30,35}

Maintenance therapy, unlike induction and consolidation therapies, is administered long-term with the objective of prolonging response duration, PFS, and, if possible, OS, with minimal toxicities which impact quality of life.

Thalidomide was the first novel agent examined in this setting. Six randomized studies have been published, with all of them showing a significant benefit for the agent in terms of response and PFS. Three of these studies also show improvement in OS. Peripheral neuropathy and the increase risk of deep venous thrombosis are the main toxicities limiting the long-term use of thalidomide as maintenance treatment.

The other immunomodulator agent, Lenalidomide is currently considered the best candidate for use as maintenance therapy. Results from three randomized trials evaluating lenalidomide maintenance versus placebo following ASCT have been published and both have shown significant improvement in PFS by almost 2 years. This PFS benefit translated into a significantly longer OS in at least one study.

Despite the higher incidence of grade 3 and 4 hematologic adverse events (AEs) in the lenalidomide group, lenalidomide maintenance was considered feasible and manageable, with less than 30% of patients having to discontinue the drug because of AEs.

One of main concerns of long-term Len treatment has been the development of secondary primary malignancies, the cause of which is still not clear. The question of the optimal duration of lenalidomide maintenance is being investigated in several ongoing trials.

Bortezomib as maintenance therapy has been investigated in 2 randomized trials. In spite of variability on the induction regimens used, PFS and OS were statistically improved in the bortezomib arm. Bortezomib toxicity during maintenance was manageable, with a discontinuation and dose-reduction rate of about 35% because of toxicity. Overall, these 2 trials suggest that bortezomib can be an alternative maintenance strategy in patients of myeloma post auto-SCT.

Phase 3 trials of maintenance Therapy following ASCT

Study by Maintenance regimen	No	Initial dose	Response vs comparator	Median follow-up	EFS or PFS vs comparator	OS vs comparator
Thalidomide						
Attal et al	597	400 mg	CR+VGPR:67 % vs 55%	30 months	3-year EFS:52% vs 36%	4-year OS:87% vs 77%
Barlogie et al	668	400 mg	CR: 64 % vs 43%	72 months	Median EFS:6.0 vs 4.1 years	8-year OS:57% vs 44%
Spencer et al	269	200 mg	CR+VGPR:63 % vs 40%	3 years	3-year PFS:42% vs 23%	3-year OS:86% vs 75%
Lokhorst et al	556	50 mg	CR: 31 % vs 23%	52 months	Median PFS:34 vs 25 months	Median OS:73 vs 60 months
Morgan et al	492	50 mg	NR	38 months	Median PFS:30 vs 23 months	3-year OS:75% vs 80%
Stewart et al	332	200 mg	NR	4.1 years	4-year PFS:32% vs 14%	4-year OS:68% vs 60%
Lenalidomide						
Attal et al	614	10 mg	CR+VGPR:84 % vs 76%	45 months	Median PFS: 41 vs 23 months	4-year OS:73% vs 75%
McCarthy et al	460	10 mg	NR	34 months	Median TTP:46 vs 27 months	3-year OS:88% vs 80%
Bortezomib						
Sonneveld et al	827	1.3 mg/m ²	CR+VGPR:76 % vs 56%	41 months	Median PFS:35 vs 28 months	5-year OS:61% vs 55%
Rosinol	266	1.3 mg/m ²	NR	24 months	2-year PFS:78% vs 63% vs 49%	NR

CR, Complete response; VGPR: very good complete response; EFS, event-free survival; NR, not reported; OS, overall survival; PFS, progress-free survival; TTP, time-to-progression;

Management of the Relapsed/Refractory Patient of MM³²

Novel agents such as bortezomib, lenalidomide and thalidomide blunt interactions between clonal myeloma cell and surrounding milieu and overcome resistance to therapy. Introduction of novel agents in relapsed/refractory myeloma has improved response rates and depth of responses resulting in better outcomes. The role of autologous transplant as standard of care in the era of novel agents is now challenged.

- 1. Bortezomib:** Bortezomib is a first-in-class proteasome inhibitor with potent antimyeloma activity. The large randomized APEX trial showed the superiority of bortezomib given intravenously on days 1, 4, 8, and 11 of a 21-day cycle over pulse dexamethasone in MM patients with relapsed and/or refractory disease. Response rate of 43% was achieved with bortezomib and a longer median OS of 29.8 versus 23.7 months for the high-dose dexamethasone treated patients, despite the fact that more than 60% of patients in the dexamethasone arm were allowed to crossover to receive bortezomib. Bortezomib is an attractive agent to use in combination with other drugs, because of its mild and reversible myelosuppression, ease of use in renal insufficiency. Results of a large phase 3 study comparing bortezomib and pegylated liposomal doxorubicin (PLD) with bortezomib alone in 636 relapsed patients showed favorable response rate for the combination (ORR 52%, CR/nCR 17%) versus single-agent bortezomib (ORR 44%, CR/nCR 13%), with a longer duration of response (DOR) (10.2 months vs 7.0 months) and most importantly a survival advantage. Bortezomib based combination combinations generally produce high ORRs, in the range of 50 to 80% with CR and/or near CR (nCR) rates of 15 to 30%, with encouraging duration of response and OS.

The toxicity profile of bortezomib has been well characterized and includes nausea, diarrhea, cyclic reversible thrombocytopenia, fatigue, and peripheral neuropathy. Peripheral neuropathy occurs in about one third of patients and can be painful. Dose modification or discontinuation of bortezomib is required for moderate or severe neuropathy, especially if associated with pain; the neuropathy usually improves or resolves in a high proportion of affected individuals, although often over several months.

- 2. Lenalidomide:** Lenalidomide is an immunomodulatory derivative of thalidomide that shows higher in vitro potency and greater activity than thalidomide in MM cell lines, suggesting that it may be effective in thalidomide-resistant patients. Lenalidomide avoids some of the more troublesome toxicities of thalidomide, such as somnolence, constipation, and significant peripheral neuropathy. However, it is associated with an increased risk of VTE, just like thalidomide, and thromboprophylaxis is required, typically with ASA. Two phase 3 trials comparing lenalidomide plus high-dose dexamethasone to high dose dexamethasone alone have been reported. The dose of lenalidomide administered was 25 mg, days 1 to 21 of a 28-day schedule, with pulse dexamethasone given days 1 to 4, 9 to 12, and 17 to 20 for the first 4 cycles, subsequently, the dose of dexamethasone was decreased to only days 1 to 4 per cycle. The results of the 2 trials were identical, with ORRs of 60 and 61% for lenalidomide and dexamethasone, compared with 20 and 24% with highdose dexamethasone as a single agent. The median TTP was approximately 11 months in both trials, whereas the OS with the combination was not yet reached in the North American trial (MM-090) at the time of last report (85), it was 29.6 months in the European trial. Grade 3 or higher toxicities were neutropenia, DVT (including pulmonary embolism), thrombocytopenia, anemia, pneumonia, atrial fibrillation, fatigue, and diarrhea.
- 3. Thalidomide:** Thalidomide is one of the first novel agents to be evaluated in relapsed/refractory myeloma patients, based initially on its inhibitory effects on angiogenesis. Initial trials used doses ranging from 200 mg/day to 800 mg/day, and demonstrated activity despite a heavily, pretreated refractory patient population. The recent systematic review published by Glasmacher and colleagues

showed that thalidomide alone produced partial remission (PR) or better in 30% of relapsed patients, with a 1-year survival of 60% and median survival of 14 months. Addition of dexamethasone increases the ORR to 50%, with variable remission duration. Combination therapy of anthracyclines or alkylating agents with thalidomide reliably results in ORRs of 60 to 75%, with CR rates of approximately 10 to 20%. Case-matched study by Offidani and colleagues compared thalidomide-dexamethasone-liposomal pegylated doxorubicin (ThaDD) with thalidomide-dexamethasone alone, with ThaDD producing a higher overall and CR rate than thalidomide-dexamethasone (92% and 30% versus 63% and 10%, respectively) and better median progression-free survival and overall survival (OS) with ThaDD (21 versus 11 months, 35 versus 20 months, respectively)

Toxicities included sedation, constipation, and increased risk of venous thromboembolism (VTE), as well as peripheral neuropathy, which occurred more frequently if the daily dose exceeded 200 mg or for durations of therapy 6 months. Individuals with a prior history of VTE should be fully anticoagulated, as should patients with other risk factors for the development of VTE. The use of aspirin, low molecular weight heparin (LMWH), and warfarin have all been evaluated. Equivalence and utility of ASA as a convenient oral antithrombotic agent is now established in patients who are low risk for VTE.

4. Stem cell transplant: High-dose melphalan therapy followed by stem cell replacement can overcome drug resistance in myeloma cells. A clear-cut survival advantage exists for myeloma patients receiving high-dose therapy compared with conventional therapy. However, the nature of the conventional therapy for multiple myeloma has undergone a dramatic change in the past decade and has moved from being based on corticosteroids to being based on novel agents. The role of stem cell transplantation for patients who never achieve PR or have disease relapse immediately before high-dose therapy is not well defined in the era of novel agents. Patients with refractory disease and relapse on induction with novel agents appear to have inherent biologic characteristics that lead to a more rapid regrowth of the myeloma cell population after high-dose melphalan therapy and thus have a modest median time to progression after transplantation of 12.0 to 15.2 months. Induction failure or relapse after combination novel agent therapy, their salvage options are limited and perhaps stem cell transplantation continues to be a treatment of choice because no clear-cut alternatives exist for this poor-risk population.

Combinations of agents in relapsed and refractory MM have improved outcomes of relapsed/refractory myeloma. Advantages of combination therapy include higher ORRs and, in many cases, better depth of responses, as well as the ability to revisit "backbone" agents used earlier in treatment. Second-generation proteasome inhibitor, carfilzomib an irreversible inhibitor of chymotryptic activity of the proteasome, the same site of inhibition induced by bortezomib that is currently being tested in phase I/II trials in myeloma. Complementary to the development of newer proteasome inhibitors, there is the development of the new immunomodulatory agent, pomalidomide. Early phase 1/2 studies have shown encouraging efficacy with an improved safety profile. Additional preclinical studies and derived clinical trials that prove the efficacy of combination therapy are needed to improve outcomes in relapsed refractory myeloma.

Supportive care in Myeloma:

Supportive care is an important but often neglected part of myeloma therapy.

The patient as an individual human being is often forgotten in the quest to eliminate the 'M' band by either chemotherapy or hematopoietic stem cell transplantation.

In a resource limited country like ours treatment of myeloma takes precedence over supportive care.

Supportive care has been shown to reduce Non relapse related mortality and impact EFS and OS after autologous SCT

There are various spheres to the supportive care aspect of myeloma. It is important to comprehend that a given patient may have one or many of these aspects requiring attention and care simultaneously.

The following text deals with these aspects one by one.

Myeloma Bone disease

80-90% myeloma patient have myeloma bone disease. This figure may be higher in Indian patients given the facts that Vitamin D deficiency and post-menopausal osteoporosis incidences are higher in our population.

Also most of our patients present at an advanced stage in myeloma with pathological fractures, vertebral collapse leading to paraparesis and even symptomatic hypercalcemia. (Anecdotal evidence, no reports from India)

Treatment of bone disease includes therapy of the basic disease and Interventional or palliative care of the bone disease. Interventional options are required in cases of unstable fractures/ vertebral collapse/ refractory pain causing immobility or neurological compromise. These interventions are most effective if performed within months of occurrence.

1. Stabilization of long bone fractures with either internal or external fixation.
2. Vertebral fracture/ collapse stabilization with fixation or vertebroplasty
3. Kyphoplasty for spinal deformities
4. Neurosurgery for spinal canal compromise

Vertebroplasty and Kyphoplasty are specialized radiological interventions and should be performed only in centers with expertise and back-up access to spinal surgery services.

Local palliative radiotherapy with 8 Gy can be considered in some situations. This may help in alleviating pain in some patients.

Bisphosphonates

1. **When?** They are recommended for all patients with symptomatic myeloma irrespective of bone lesions on radiology. However, evidence is insufficient in asymptomatic myeloma patients.
2. **Which?** Zolendronate or Pamidronate are the preferred drugs. Zolendronate has evidence showing prolongation of EFS and OS and is the drug of choice.
3. **Precautions before starting:** Dental evaluation. Avoid invasive dental procedures. Renal function assessment (serum creatinine and urine albumin) before starting and before every dose
4. **How frequently?** 4 weekly
5. **Dosing**

Drug	Dose and duration	Dosing frequency	Renal modification
Zolendronate	4mg IV over 15 minutes	4 weekly till 2 years or till CR Or discretion of physician	NR if Cr Cl<30
Pamidronate	90mg IV over 2 hours		Cr Cl=30-60, give over
Ibandronate	6 mg IV		4-6 hours Cr Cl<30, give 30mg

6. **How long?** Generally these are given for 2-years. Decisions sometimes are individualized based on response status of the patient (CR, VGPR, no active bone disease) and renal dysfunction.
7. Oral calcium and vitamin D supplementation is recommended.

Renal Impairment:

It occurs in upto 50% patients during the course of the disease. Only 2-12% of the patients require RRT. Common causes in Indian setting include prerenal AKI, cast nephropathy, tubulointerstitial nephritis, amyloidosis etc

Management

1. Renal failure in myeloma should be managed as a medical emergency because it is reversible in half the patients leading to survival benefit
2. Hydration to maintain urine output >3L/day. Fluids as per CVP if required.
3. Treat precipitating causes aggressively. Manage hypercalcemia with bisphosphonates in renal modified doses, antibiotics for sepsis, allopurinol for hyperuricemia. Stop nephrotoxics/ NSAIDS.
4. Renal biopsy is desirable but not essential. Consult nephrologist if no improvement within 48 hrs of initial interventions. Indications for hemodialysis are standard.
5. High cut off hemodialysis or Plasmapheresis is recommended for patients with light chain myeloma and biopsy proven cast nephropathy.
6. Initiate therapy of myeloma with high dose Dexamethasone 40mg four days on, four days off, for initial few cycles. Treatment to be started urgently pending investigations and decisions about definitive chemotherapy

7. Bortezomib is preferred drug and the dose is to be given after hemodialysis or plasmapheresis.
8. Drugs requiring dose modification in renal impairment

Drug	Renal impairment
Melphalan	25% reduction if Cr Cl<30
Lenalidomide	Crcl 30-60: 10mg, Crcl<30:15mg EOD, HD:5mg

9. Autologous SCT option should not be withheld for such patients as auto-HSCT has been associated with late renal recovery.

Anemia

Almost all Indian patients of myeloma have anemia^{9,10}. Anemia is often multifactorial. Anemia can be attributed to myeloma or renal failure after ruling out hematinic deficiency either by doing iron profile or a therapeutic trial of Hematinics.

Indication: A therapeutic trial of ESA can be considered in cases where significant anemia (Hb<10g/L) is attributed to renal disease/ myeloma. NICE guidelines do not recommend ESA for the treatment of cancer related anemia.

Doses recommended are lowest possible to cause a rise in hemoglobin sufficient to avoid transfusions.

150 U/kg three times a week SC. If no response after 4 weeks can escalate to 300 U/kg three times a week. Darbepoetin 6.25 mcg/kg three weekly.

Target Hb=12g/L. Stop if Hb>12 or no response within 6-8 weeks of trial.

Infections: (all recommendations are grade C/ level IV)

1. Vaccination against Influenza, Streptococcus Pneumoniae, Haemophilus Infuenzae is recommended but efficacy is doubtful, known humoral and cellular immune defects in myeloma.
2. Prophylactic Immunoglobulins is not routinely recommended. But it may be useful in patients with recurrent, severe infections.
3. Prophylactic Acyclovir is recommended for pts receiving Bortezomib, Autologous HSCT, High dose Dexamethasone or recurrent herpes infections.
4. Co-trimoxazole / Azole prophylaxis can be considered in patients receiving high dose Dexamethasone or specifically in elderly patients with poor performance status.

Thrombosis

BCHS guidelines have recommended risk stratification for starting antithrombotic therapy for myeloma patients.

Patients >1 risk factor require therapeutic anticoagulation, while those with 1 or no risk factor can do with Ecosprin (Low dose).

Most Indian patients have more than 1 risk factor for thrombosis (newly diagnosed, have comorbidities, Immobile due to pain, and are on combination therapy or high dose steroids for treatment of myeloma) All such patients on thalidomide or Lenalidomide based chemotherapy need to be started on LMWH

1mg/kg OD or Low dose UFH (5000 U SC BD) or Warfarin dose adjusted to a target INR of 2-3. There is ample evidence to shun use of fixed, low dose Warfarin.

Duration of anticoagulation is till control of disease activity or for 4-6 months. Treatment of established VTE should be for an extended duration.

Pain

There are various causes of pain in myeloma patients e.g. Bone lesions including arthritis and osteoporosis, neuropathy (disease or drug induced), Bone marrow examination, pain related to growth factor use, mucositis, post herpetic neuralgia etc.

The interventional management of bone pains is dealt with in the myeloma bone disease part of this guideline.

The use of various scales to document pain though highly recommended in BCHS guidelines is cumbersome in daily practice. However, a pain VAS Visual Analogue scale (0: No pain and 10: worst pain) Is a simple way to follow the response in the OPD or inpatients. The various analgesics out of the WHO ladder that can be used are

1. Paracetamol (Max 1 gm QID)
2. Tramadol (max 50mg QID or BD sustained release forms)
3. Fentanyl patches (25-50 mcg patch/ 48 hrs)
4. Morphine can be used for severe pain (patients on palliative care for advanced myeloma may be given max morphine upto 120 mg/day)
5. Neuropathic pain: Gabapentin/ Pregabalin/ Amitriptyline

All patients receiving opioid analgesics to be given laxatives. Avoid using NSAIDS

Peripheral neuropathy

PN can be due to myeloma disease per se (M-protein associated), POEMS, AL-amyloidosis, chemotherapy induced (CIPN) or associated with comorbidities viz. type2 diabetes mellitus, CIDP, CKD or nutritional deficiency. The prevalence of PN in newly diagnosed MM (Both clinical and electrophysiological) is to the tune of 62%.NCS is not always necessary in the diagnosis as they do not co-relate with the clinical findings.

Diagnosis of myeloma related or chemotherapy related PN is a diagnosis of exclusion after ruling out all treatable causes of PN mentioned above.

Peripheral neuropathy should be actively screened at initial visit and follow-up by history and clinical examination. National cancer institute common terminology criteria for adverse events can be followed for intervening in CIPN.

Grade of neuropathy	Thalidomide	Bortezomib
1 (paresthesia/weakness, no loss of function/pain)	No action	No action
1 (with pain) 2 (functional impairment)	Reduce dose by 50% or suspend and reintroduce when asymptomatic at 50% dose	Reduce dose to 1mg/m2

2 (with pain) 3 (interfering in activities of daily living)	suspend and reintroduce when asymptomatic at 25% dose	Suspend and reintroduce when asymptomatic at 0.7mg/m ² SC weekly
4 (permanent sensory loss)	Discontinue	Discontinue

Psychosocial rehabilitation:

It is important to understand the unmet needs of the patient and the family by formal questioning and attempts be made to fulfill those as far as possible. Upto 25-50% patients and partners report anxiety about uncertainty in the future and depression. Nutrition, Fatigue and insomnia and sexual concerns are some aspects requiring attention. Such psychosocial screening can be offered in transplant settings by the nursing team. Both patients and their care givers may require psychosocial rehabilitation in consultation with the psychiatrists.

Palliative care

There is paucity of palliative care centers in India and often this burden has to be taken by tertiary care centers. It is best to discuss end of life care with patient’s attendants. (Often, attendants are not willing for these issues be discussed with the patient) It is important that the responsibility during these stages be shared by the general practitioners/ family physicians, primary health care centers and nursing homes, with the hematology team continuing to provide supervised care. Blood transfusions can be taken care of by local centers of care. Pain should be managed adequately and invasive procedures be kept to a minimum. End of life care decisions and withdrawal of treatment must be in accordance with institutional guidelines.

One third of the myeloma patients in CR at 11 years achieve a plateau in survival. With current treatment approaches the 10 year survival rate has increased from 24.5% to 41.3%. However there is a problem in using CR rates and PFS as the end points in current day trials as they correlate poorly with overall survival in diseases like myeloma with long survival. Long term survival is also possible without achieving CR. The debate of cure versus control will always be there with increasing depth and durability of responses with newer agents.

The newer treatment approaches in ongoing clinical trials are testing the role of consolidation and maintenance with or without ASCT. Consolidation therapy aims at improving the response post induction. The strongest proponent for consolidation, the Arkansas total therapy group have shown increase in 5 year survival from 57% in TT1 to 73% in TT3. In terms of maintenance, bortezomib has shown a survival benefit. Despite lenalidomide showing a survival benefit in one out of two trials, the higher rate of secondary malignancies has offset this advantage.

Despite all the advances, myeloma remains an incurable disease. Most patients will eventually relapse and here comes the role of the newer agents. The most promising of these appear carfilzomib and pomalidomide.

Carfilzomib is a second generation proteasome inhibitor that was recently approved by FDA for relapsed myeloma on the basis of following phase II studies.

MLN9708 is the first oral proteasome inhibitor that has entered clinical trials.

Trial	Type	N	Dose Schedule	Results	Serious AE
Siegel et al	Phase II	257	Day1,2,8,9,15,16 (20mg/m ² cohort 1; 27mg/m ² cohort 2-12)	>PR 24% median DOR=7.4 months	Anemia, Thrombocytopenia, neutropenia
Vij et al	Phase II Bortenaive	129	20/20mg/m ² cohort 1; 20/27mg/m ² cohort 2	Cohort1: ORR 42% Cohort2: ORR:52%	As above
Wang et al	Phase II	52	CFZ 20/27mg/m ² + L 25mg D1-21, D 40mg D1,8,15,22	ORR: 78% (PR 38%, VGPR 22%, CR/sCR 18%)	As above
Kumar S et al	Phase II	50	MLN9708: 4mg D1,8,15 + L 25mg D1-21+ D 40mg/wk	ORR 90% (CR 23%, VGPR 58%, PR32%)	Less neurotoxic than Bortezomib

Pomalidomide is the newest of the immunomodulatory agents which received accelerated FDA approval earlier this year in view of the following phase II studies in relapsed/refractory myeloma.

Trial	Type	N	Dose Schedule	ORR
Richardson et al	Phase II	221	POM 4mg D1-21 q 28 days POM 4mg + D 40mg/wk	13% 34%
Shah et al	Phase II	30	POM 4mg D1-28 + D 40mg/wk + CFZ escalating dose	50%
Richardson et al	Phase II	15	POM 1-4mg D1-14 q 21 D 20mg day on and after V V 1-1.3mg/m ² D1,4,8,11	73%

Other agents that have been studied include HDAC inhibitors. Panabinostat has demonstrated encouraging response rates of 34.5% in combination with bortezomib rather than as a single agent. Trials involving Monoclonal antibodies targeting various antigens on myeloma cells are summarized below³⁴. Elotuzumab (HuLuc63) is a potent CS1 antibody which is relatively plasma cell specific and requires NK cell help for its function. Other antibody targets include CD138, CD56, anti-BAFF and anti DKK-1.

Trial	Type	Drug	Target	ORR	
Lonial et al ³³	Phase I	Elotuzumab	Anti CS1	82%	
Richardson	Phase II	Elotuzumab	E 10mg/kg vs 20mg/kg + Len + Dexa	20mg/kg: 18m (PFS) 10mg/kg: NR (PFS)	
Plesner et al	Phase I	Daratumumab	Anti CD38	80-100% reduction in BM plasma cells	

Allogeneic stem cell transplantation is probably the only treatment with a curative potential in myeloma. This is likely due to graft versus myeloma effect proven after achievement of durable complete remissions by donor lymphocyte infusions. However, the role of alloHSCT in myeloma is still debated due to the high morbidity and mortality associated with the procedure. The results of comparison between donor versus no donor cohorts have been mixed. Recent meta-analysis have shown no OS benefit for auto-allo in the upfront setting. The future of alloHSCT in myeloma depends on reducing morbidity and mortality and novel approaches to boost GVL effect in prospective studies.

The future trials are more likely to focus on immunotherapeutic approaches to target the stem cell pool that is non-proliferating and resistant to chemotherapy. Strategies targeting idiotype specific antibodies have been tested in preclinical studies but clinical effects are insignificant. Vaccination with Dendritic cell & tumor fusions to induce antitumor immunity has shown transient responses and marginal clinical benefit. Modulation of inhibitory and activating NK receptor ligands on tumor cells represents another promising therapeutic approach. Until we have more phase I/II studies with these immunotherapeutic approaches, it will be difficult to predict their role in the current scheme of ASCT and established chemotherapeutic agents.

New Drugs in MM:

Pomalidomide:

Pomalidomide is a new drug belonging to the IMiD class which has been recently approved for the treatment of patients with multiple myeloma who have received at least two prior therapies, including lenalidomide and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy.

The approval was based on the results of multicenter, randomized, open-label study of 221 patients with relapsed and refractory multiple myeloma who had previously received lenalidomide and bortezomib

and were refractory to the last myeloma therapy. Pomalidomide alone was compared to pomalidomide plus low-dose dexamethasone. The trial showed an overall response rate of 7% in patients treated with pomalidomide alone, and 29% in those treated with pomalidomide plus low-dose dexamethasone. The median response was 7.4 months in the pomalidomide plus low-dose dexamethasone arm. The most common side effects included fatigue and asthenia, neutropenia, anemia, constipation, nausea, diarrhea, dyspnea, upper respiratory tract infections, back pain, and pyrexia. Pomalidomide can cause embryo-fetal toxicity and venous thromboembolism.

Carfilzomib

Carfilzomib is a second-generation proteasome inhibitor with different functional capacities. It is able to irreversibly inhibit the chymotryptic activity of the proteasome. In 2012, the US Food and Drug Administration approved carfilzomib for the treatment of patients with MM who have received at least 2 prior therapies, including bortezomib and IMiDs, and have demonstrated disease progression on or within 60 days of the completion of the last therapy.

In December 2014 results of phase III ASPIRE trial were presented at the 2014 American Society of Hematology (ASH) annual meeting. This trial showed that addition of carfilzomib to lenalidomide and dexamethasone resulted in prolonged PFS and better quality of life for patients with relapsed multiple myeloma. Patients who received carfilzomib/lenalidomide/dexamethasone had median PFS of 26.3 months compared with 17.6 months in control arm ($P < .001$)

Panobinostat:

Panobinostat is a histone deacetylase inhibitor that was approved by FDA in February 2015 in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent. Panobinostat is a histone deacetylase inhibitor that inhibits the enzymatic activity of HDACs at nanomolar concentrations. Black box warning for severe diarrhea. Other common side effects of this drug are fatigue, nausea, peripheral edema. Severe and fatal cardiac ischemic events, severe arrhythmias may occur rarely.

Monoclonal antibodies:

Use of monoclonal antibodies in multiple myeloma is the areas in which a more extensive investigation is being made.

Elotuzumab is the best evaluated monoclonal antibody in MM. It is directed against a glycoprotein CS1, that is highly specific to plasma cells, Although the results in monotherapy

were modest (with stable disease as best response) the combination with lenalidomide and dexamethasone has given excellent results with 48% PR in relapsed patients and, what is more important, prolonged PFS (33 months in the last update)³³.

Daratumumab: is another monoclonal antibody against CD38.

Multiple myeloma vaccine:

1. PVX vaccine is a tri-peptide vaccine for multiple myeloma.
2. This vaccine recognizes three different proteins that are present in on multiple myeloma cells.
3. It recognizes CD38, CS1 (also targeted by monoclonal antibody elotuzumab) and XBP1. So foreign and try to reject them.

8

RESEARCH PRIORITIES

- Toxicity of drugs
- Bone health
- Early versus Late Auto SCTw

SUMMARY OF INDIAN PUBLISHED LITERATURE ON MULTIPLE MYELOMA

Indian Data
Indian Data (2011-2015)

Author/Institute/Group	Study Subjects	Results	Comments
<i>Gupta N, Khan R, Kumar R et al / Versican and its associated molecules: potential diagnostic markers for multiple myeloma / Clin Chim Acta. 2015 Mar 10;442:119-24 / AIIMS</i>	Expression of VCAN and its associated molecules (β -catenin, β 1 integrin and FAK) were investigated in 60 subjects to evaluate their usefulness as diagnostic marker. Circulatory and molecular levels of above molecules were analyzed in their BM and Blood using ELISA, Q-PCR and western blotting along with their ROC curve analysis.	Circulatory levels of VCAN, β -catenin and FAK were significantly higher in patients with varying significance in each stage. β -Catenin and FAK intracellular levels were significantly elevated in patients. mRNA levels of all molecules were significantly higher in BMMNCs while VCAN and β -catenin also showed increase in PBMCs. Upregulation of these molecules was also observed at protein level. ROC curve analysis for VCAN showed absolute combination of sensitivity and specificity for diagnosis in serum.	Significant elevation of VCAN and its associated molecules imply their role in MM. Optimal sensitivity and specificity of VCAN might utilize its importance as potential marker for active disease.
<i>Khan R, Gupta N, Kumar R et al / Augmented expression of urokinase plasminogen activator and extracellular matrix proteins associates with multiple myeloma progression n / Clin Exp Metastasis. 2014 Jun;31(5):585-93 / AIIMS</i>	Protein levels of urokinase plasminogen activator (uPA) and fibulin 1, nidogen and laminin in plasma and serum respectively and mRNA levels of these molecules in peripheral blood mononuclear cells were determined in 80 subjects by using ELISA and quantitative PCR and data was analyzed with severity of disease.	A statistical significant increase for ECM proteins (laminin, nidogen and fibulin 1) and uPA at circulatory level as well as at mRNA level was observed compared to healthy controls.	Augmented expression of urokinase plasminogen activator and extracellular matrix proteins associates with multiple myeloma progression.
<i>Kaur P, Shah BS, Baja P / Multiple myeloma: a clinical and pathological profile / Gulf J Oncolog. 2014 Jul;1(16):14-20. / Giansagar Medical College and Hospital, Banur, Punjab</i>	This study included all cases of MM diagnosed at Dayanand Medical College and Hospital, Ludhiana, India from March 2003 to August 2004. Clinical findings were recorded and relevant investigations done	Multiple myeloma comprised 11.1% of all hematological malignancies. The mean age was 58.8 years. Bony pain was the most common presenting complaint. Other findings were anemia, raised serum creatinine levels, high serum lactate dehydrogenase and C-reactive protein levels. Plasmablastic morphology was seen in 60% patients with diffuse marrow involvement being the most common pattern.	The percentage incidence of Multiple Myeloma, out of all hematological malignancies reported in this study is comparable with other studies as regards to the median age of incidence, male to female ratio, clinical presentation and percentage of M band positivity. However, a higher percentage of patients had hypercalcemia, higher Serum LDH levels and CRP positivity and more lytic lesions. This corresponds with a higher tumor cell burden and a more frequent diffuse pattern of bone marrow involvement in this study group probably due to the smaller size of study group, or due to late referral of patients to this tertiary care hospital.

<p><i>Chakraborty B, Vishnoi G, Gowda SH et al / Interleukin-6 gene-174 G/C promoter polymorphism and its association with clinical profile of patients with multiple myeloma / Asia Pac J Clin Oncol. 2014 Oct 31 / Dr. D.Y. Patil Medical College, Navi Mumbai, Maharashtra</i></p>	<p>One hundred three patients with MM and 117 age- and sex-matched healthy controls were staged by International Staging System. IL-6 genotypes were evaluated by polymerase chain reaction and restriction enzyme analysis. Serum levels of IL-6 were assessed by ELISA.</p>	<p>Frequency of GG, GC and CC genotypes did not differ significantly between cases (GG 52%, GC 40%, CC 9%) and controls. The median serum level of IL-6 was significantly higher among the GC genotype versus other genotypes (24 ng/mL, P=0.007) as compared with the GG versus other genotypes (12 ng/mL, P=0.001). GC was associated more with stage 3 disease (27%) than was GG (11%) or CC (22% P=0.001).</p>	<p>At position 174 of the IL-6 promoter, patients with GC genotype had higher serum levels of IL-6 and presented with more severe disease compared with patients with GG or CC genotype.</p>
<p><i>Kayal S, Sharma A, Iqbal S et al / High-dose chemotherapy and autologous stem cell transplantation in multiple myeloma: a single institution experience at All India Institute of Medical Sciences, New Delhi, using non-cryopreserved peripheral blood stem cells / Clin Lymphoma Myeloma Leuk. 2014 Apr;14(2):140-7 / AIIMS</i></p>	<p>Ninety-two patients with MM were given high-dose melphalan and rescued with granulocyte colony stimulating factor (G-CSF) mobilized noncryopreserved autologous PBSC, in our hospital during the past 18 years. Stem cells were mobilized with 4 days of G-CSF, harvested (median CD34 dose, 2.9 10(6)/kg) and then stored at 4 C in a refrigerator for a median of 2 days (range, 1-5 days) before reinfusion.</p>	<p>Median time to neutrophil (> 500/mm(3)) and platelet (> 20,000/mm(3)) engraftment were 10 and 14 days respectively. There was no graft failure. Mucositis grade 3/4 was seen in 66 patients (72%). Transplant-related mortality at 100 days was 3.2%. The overall response to transplant was 88% and improvement compared with pretransplant status was seen in 48%. The median overall survival (OS) and progression-free survival (PFS) were 61.7 months and 35.4 months respectively; independent predictors of survival were Eastern Cooperative Oncology Group Performance Status and hemoglobin for OS and chemosensitive disease and remission status after transplant for PFS.</p>	<p>High-dose chemotherapy and autologous transplant with noncryopreserved PBSC is a simple, effective, and safe method for MM with equivalent results, and that cryopreservation is not necessary. It reduces the cost of transplant and avoids dimethyl sulfoxide toxicity.</p>
<p><i>Kumar L, Iqbal N, Mookerjee A et al / Complete response after autologous stem cell transplant in multiple myeloma / Cancer Med. 2014 Aug;3(4):939-46 / AIIMS</i></p>	<p>Evaluated long-term outcome of patients achieving complete response (CR) after autologous stem cell transplantation (ASCT) for multiple myeloma amongst 191 patients who underwent ASCT between April 1990 and June 2012.</p>	<p>The median follow-up for the entire group was 85 months (range, 6-232.5 months). Following transplant 109 (57.1%) patients achieved CR. Median progression-free survival (PFS) for patients with CR was higher compared to those with VGPR and PR, (107 vs. 18 vs. 18 months, P < 0.001).</p>	<p>Achievement of CR post transplant is associated with longer OS and PFS. Among complete responders, those who receive one line of induction therapy pretransplant have superior outcome.</p>
<p><i>Kashyap R, Singh A, Kumar P / Prevalence of autoimmune hemolytic anemia in multiple myeloma: A prospective study / Asia Pac J Clin Oncol. 2014 Sep 22 / SGPGI</i></p>	<p>Sixty-six patients were diagnosed to have MM. Seventeen of these patients who had severe anemia (hemoglobin < 6 g/dL) requiring frequent blood transfusions with or without features of hemolysis were screened for AIHA by performing direct and indirect antiglobulin (Coombs') test</p>	<p>Seven (10.6%) of these 17 patients were found to be complicated with AIHA and carried autoantibodies in their sera. Patients with primary disease showed remission of AIHA with therapy, whereas both the patients with relapsed disease showed no response to treatment and remained positive for antiglobulin test.</p>	<p>AIHA should be suspected in MM patients with severe anemia requiring frequent blood transfusions.</p>
<p><i>Shafia S, Qasim I, Aziz SA et al / Role of vitamin D receptor (VDR) polymorphisms in susceptibility to multiple myeloma in ethnic Kashmiri population / Blood Cells Mol Dis. 2013 Jun;51(1):56-60 / Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar, Kashmir</i></p>	<p>Case control study where 75 multiple myeloma cases were studied for VDR polymorphisms (ApaI, BsmI and FokI) against 150 controls taken from general population. The polymorphisms of VDR gene were investigated using PCR-RFLP method.</p>	<p>No significant association was found between ApaI and BsmI polymorphisms and multiple myeloma risk (P>0.05), but FokI polymorphism was significantly associated with increased risk for multiple myeloma. A significant association was also found between the ff variant genotype with creatinine levels, albumin levels, and Durie-Salmon stage III.</p>	<p>Findings suggest that the FokI polymorphism is involved in the increased susceptibility to development and progression in multiple myeloma in the ethnic Kashmiri population. Furthermore these results suggest that ff genotype is associated with higher risk for developing multiple myeloma.</p>

<p>Khan R, Sharma M, Kumar L et al / Interrelationship and expression profiling of cyclooxygenase and angiogenic factors in Indian patients with multiple myeloma / Ann Hematol. 2013 Jan;92(1):101-9 / AIIMS</p>	<p>Circulatory and mRNA levels of angiogenic factors and cyclooxygenase were determined in 125 subjects (75 MM patients and 50 healthy controls) by using enzyme-linked immunosorbent assay and quantitative PCR.</p>	<p>It was observed that significant increase for angiogenic factors (Ang-1, Ang-2, hepatocyte growth factor, and VEGF) and COX at circulatory level, as well as at mRNA level, as compared to healthy controls except insignificant increase for Ang-1 at circulatory level. Significant positive correlation of all angiogenic factors with cyclooxygenase was also observed.</p>	<p>The strong association found between angiogenic factors and COX-2 in this study may lead to the development of combination therapeutic strategy to treat MM. Therefore, targeting COX-2 by using its effective inhibitors demonstrating antiangiogenic and antitumor effects could be used as a new therapeutic approach for treatment of MM.</p>
<p>Bhaskar A, Gupta R, Vishnubhatla S et al / Angiopoietins as biomarker of disease activity and response to therapy in multiple myeloma / Leuk Lymphoma. 2013 Jul;54(7):1473-8 / AIIMS</p>	<p>mRNA expression and circulating levels of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), angiopoietin-1 (Ang-1), angiopoietin-2 (Ang-2), hypoxia inducible factor (HIF)-1, circulating endothelial progenitor cells (cEPCs) and bone marrow microvessel density (MVD) were evaluated in multiple myeloma (MM).</p>	<p>Compared to healthy controls, the levels of VEGF, bFGF, Ang-2, HIF-1 and cEPCs were significantly higher and Ang-1 and Ang-1/Ang-2 were lower in MM (p < 0.01). cEPC numbers correlated with Ang-1 (p = 0.03), Ang-2 (p = 0.01) and VEGF (p = 0.002). On multivariate analysis, reduced Ang-1/Ang-2 ratio (p = 0.005) at baseline was an independent predictor for response to therapy. After therapy, a decrease in Ang-2 (p < 0.001) and an increase in Ang-1/Ang-2 ratio (p = 0.003) were observed in responders.</p>	<p>This study highlights the role of angiopoietins in MM which may, thus, be evaluated as potential targets for anti-angiogenic therapy in future.</p>
<p>Kumar L, Cyriac SL, Tejomurtula TV et al / Autologous stem cell transplantation for multiple myeloma: identification of prognostic factors / Clin Lymphoma Myeloma Leuk. 2013 Feb;13(1):32-41 / AIIMS</p>	<p>Results of 170 consecutive patients (121 male and 49 female) of MM who underwent ASCT were determined</p>	<p>Post ASCT 44.7% of patients achieved CR, 24.7% had very good partial response (VGPR), and 21.2% had partial response (PR). Patients who responded to transplant (CR, VGPR, and PR) had a longer OS and EFS. Additionally, patients who achieved CR post transplant had a longer OS and EFS.</p>	<p>Outcome after ASCT is better for myeloma patients with pretransplant chemosensitive disease and those who achieve CR after transplant.</p>
<p>Bhaskar A, Gupta R, Sreenivas V et al / Synergistic effect of vascular endothelial growth factor and angiopoietin-2 on progression free survival in multiple myeloma / Leuk Res. 2013 Apr;37(4):410-5 / AIIMS</p>	<p>Investigated the levels of angiogenic cytokines such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), angiopoietin (Ang)-1, Ang-2 and hypoxia inducible factor-1 alpha (HIF-1) in 71 patients of MM and their association with treatment outcome.</p>	<p>In multivariate Cox regression analysis, serum levels of VEGF 756 pg/ml (HR 2.2, 95% CI 1.02-4.91; p=0.045) and relative mRNA expression levels of Ang-2 0.93 (HR 21.0, 95% CI 6.27-70.45; p<0.001) were predictive of inferior progression free survival (PFS) and patients with concomitant increase in VEGF and Ang-2 had poor outcome compared to the rest of the patients (HR 32.6, 95% CI 7.20-148.36; p<0.001)</p>	<p>These results suggest that VEGF and Ang-2 act in synergy and their expression levels at presentation are predictive of PFS in MM.</p>
<p>Padhi S, Varghese RG, Ramdas A et al / Cyclin D1 expression in multiple myeloma by immunohistochemistry: Case series of 14 patients and literature review / Indian J Med Paediatr Oncol. 2013 Oct;34(4):283-91 / Pondicherry Institute of Medical Sciences, Puducherry</p>	<p>Formalin fixed, decalcified, bone marrow trephine sections from 14 symptomatic patients of MM (13 newly diagnosed and one relapsed) were subjected to cyclin D1 IHC by using a rabbit monoclonal antibody to cyclin D1 (clone EPR2241).</p>	<p>Ten of 14 (71.5%) showed a favorable response (follow-up; 7 days to 34 months) to thalidomide and/or bortezomib based chemotherapeutic regimen. Four of eight cyclin D1-patients showed complete response, two had a partial response (PR) and two died of the disease; whereas 4/6 cyclin D1 - patients had PR, one refused definitive therapy and one was lost to follow-up</p>	<p>IHC may be a feasible tool for the demonstration of cyclin D1 expression on adequately processed trephine biopsy specimen in MM patients in a resource poor setting. Negative IHC results should be correlated with molecular techniques for prognostication.</p>

<p>Tripathy S / The role of serum protein electrophoresis in the detection of multiple myeloma: an experience of a corporate hospital / J Clin Diagn Res. 2012 Nov;6(9):1458-61 / Narayan Medical College, Rohtas, Sasaram, Bihar</p>	<p>Serum samples from 150 suspected cases of M.M were subjected to serum protein electrophoresis on cellulose acetate strip. M band detected visually and estimation of M protein was done by densitometer. Bone Marrow biopsy and clinical profile were correlated in M band positive cases.</p>	<p>Out of 150 cases 10.66% cases had monoclonal gammopathy. Ten percent cases were diagnosed to be multiple myeloma and one case was found to be Monoclonal gammopathy of undetermined significance.</p>	<p>SPEP is an easy to perform laboratory test which can be used for detection and quantification of monoclonal gammopathy and should be recommended as preliminary test for suspected cases of multiple myeloma.</p>
<p>Lodh M, Goswami B, Gupta N et al / Assessment of oxidative stress and inflammatory process in patients of multiple myeloma / Indian J Clin Biochem. 2012 Oct;27(4):410-3 / Mission Hospital,Durgapur,WB</p>	<p>To evaluate the role of inflammation and oxidant-antioxidant dynamics in the etiology of MM. The study population comprised of 20 cases of multiple myeloma and 20 healthy controls. The parameters evaluated were serum malondialdehyde (MDA), superoxide dismutase (SOD) and ferritin levels</p>	<p>The serum MDA levels were 1.9 ± 0.96 nmol/ml in cases as compared to 0.98 ± 0.55 nmol/ml in the controls. Similarly, a statistically significant difference was noted in the SOD and ferritin levels between the cases and controls (93.2 ± 23.8 vs. 210.1 ± 190.5 U/ml and 285.8 ± 216.4 vs. 131.8 ± 30.1 ng/ml respectively).</p>	<p>Highlights the imbalance in the oxidant-anti oxidant mechanism and the role of smoldering inflammation in the etiology of multiple myeloma.</p>
<p>Bhaskar A, Gupta R, Kumar L et al / Circulating endothelial progenitor cells as potential prognostic biomarker in multiple myeloma / Leuk Lymphoma. 2012 Apr;53(4):635-40 / AIIMS</p>	<p>In this study, circulating endothelial progenitor cells (cEPC) numbers were assessed and correlation with clinical and laboratory parameters was determined in 75 patients with multiple myeloma (MM).</p>	<p>Higher numbers of cEPCs (defined as CD45-/dim CD34+CD133+CD31+cells) were observed in MM as compared to healthy controls ($n = 10$; $p < 0.001$), which increased progressively from stage I to stage III ($p < 0.001$). A significant decline in cEPC numbers after therapy was observed in patients who attained at least a partial response ($n = 47$; $p < 0.001$). cEPCs correlated with response duration, at a baseline cut-off value of 19.6 cEPCs/μL ($p = 0.006$) and 6.5 cEPCs/μL after therapy ($p < 0.001$).</p>	<p>This study suggests that cEPC numbers and changes in their levels may serve as a potential biomarker of disease severity, response to therapy and treatment outcome in MM</p>
<p>Jena RK, Swain TR, Kansurkar SS et al / Lenalidomide induced intrahepatic cholestasis in newly diagnosed patients of multiple myeloma / Eur J Clin Pharmacol. 2012 May;68(5):881-4 / SCB Medical College and Hospital, Cuttack</p>	<p>Side effects of Lenalidomide assessed in total of 65 newly diagnosed cases of multiple myeloma receiving MPL regimen</p>	<p>One rare adverse effect, i.e., intrahepatic cholestasis related to lenalidomide, in two patients out of a total of 65 newly diagnosed cases of multiple myeloma receiving MPL regimen</p>	<p>As the use of lenalidomide will increase in the future for multiple myeloma and other diseases, clinicians should be aware of Lenalidomide induced intrahepatic cholestasis</p>
<p>Malhotra P, Choudhary PP, Lal V et al / Prevalence of peripheral neuropathy in multiple myeloma at initial diagnosis / Leuk Lymphoma. 2011 Nov;52(11):2135-8. / PGI, Chandigarh</p>	<p>To evaluate the presence of peripheral neuropathy (PN) in newly diagnosed treatment-naive patients with multiple myeloma (MM), 29 patients and 25 age and sex matched controls underwent electrophysiological studies.</p>	<p>Eighteen (62.1%) patients were found to have evidence of PN by history and clinical examination alone (two patients), both clinical and electrophysiological evidence (five patients) and only electrophysiological evidence (11 patients). Out of 25 healthy controls, only two patients had evidence of PN by electrophysiological studies (cases vs. controls, $p < 0.002$).</p>	<p>This information may impact therapeutic and prognostic decision-making in newly diagnosed patients with MM.</p>
<p>Sridhar S, Dutta TK, Basu D / Clinical profile of multiple myeloma and effect of thalidomide based treatment on its outcome / J Indian Med Assoc. 2011 Dec;109(12):880-2, 887-8 / JIPMER</p>	<p>To study the clinical profile of multiple myeloma and the effect of thalidomide based treatment on its outcome in the Indian scenario in 25 multiple myeloma cases</p>	<p>The overall response rate to thalidomide regimen was 72% ($n=18$). Out of these, 10 patients (56%) had complete response and 8 patients (44%) had partial response. The mean bone marrow plasma cell percentage at the end of therapy was 2% compared to 56% before therapy which was significant ($p < 0.0001$). None of the patients developed neutropenia or thrombocytopenia during treatment.</p>	<p>Presently available thalidomide based combination chemotherapy represents an active inductive regimen to improve the outcome and achieve eventual cure.</p>

Summary of INDIAN published literature on multiple Myeloma
Indian Data
Indian Data (Pre 2011)

Author/ Institute/ Group	Study subjects	Results	Comments
Joshi. S et al 2011 / AIIMS	Circulatory levels of angiopoietin-1 & 2 also VEGF in 62 Myeloma patients & 50 healthy controls were determined	Significantly elevated levels of Angiopoietin -2 & VEGF in patients which correlated with severity of disease	Indicated their utility as potential tumor markers
Kumar. L et al 2011 / AIIMS	228 patients undergoing Autologous HSCT among whom 143 were Multiple Myeloma patients	Overall and Event Free Survival were 79 months (95% CI 52.3-105.7) and 30 months (95% CI 22.6-37.4), respectively for Myeloma patients	Provided information regarding complications, pattern of infections, and long-term outcome of patients following high-dose chemotherapy (HDCT) and autologous blood stem cell transplantation
Archana. B et al 2011 / AIIMS	Circulating endothelial progenitor cells (cEPC) assessed in 75 newly diagnosed Myeloma patients	The cut-off value of cEPC at baseline correlated with response duration (p<0.006, n=59); the median response duration was 23 months for the group with 19.6 cEPC/ μ l (n=44) compared to 14 months for the group with >19.6 cEPC/ μ l (n=15)	cEPC numbers correlates with response duration and may serve as prognostic biomarker of treatment outcome in MM.
Rana. C et al 2010 / SGPGI	50 newly diagnosed cases of Myeloma studied for various angiogenesis parameters like micro vessel density (MVD) and total vascular area (TVA) in bone marrow biopsies	Angiogenesis was significantly higher in cases. Patients with residual disease had a higher MVD as compared to the complete responders	Angiogenesis correlates with prognosis and is also a good predictor for complete response in patients with multiple myeloma

Sharma. A et al 2010 / AIIMS	Assessment of Th1 and Th2 derived cytokines in total 112 subjects: 62 patients with MM and 50 healthy controls	Among Th1 cytokines, IFN-gamma was significantly lower while regarding levels of Th2 cytokines, IL-4 and IL-10 were significantly elevated in cases	Indicated that there is marked polarization toward Th2 cytokines in MM while Th1 cytokines remain suppressed
Sharma. A et al 2009 / AIIMS	Circulating levels of antioxidants: superoxide dismutase (SOD), glutathione peroxidase (GPX), catalase, malondialdehyde (MDA), vitamin C and E were estimated using spectrophotometer in 50 patients of MM	Levels of SOD, GPX and catalase and vitamin C and E were significantly declined in patients whereas MDA levels were elevated	MM is closely associated with oxidative stress and reduced antioxidant capacity

Kumar. L et al 2009 / AIIMS	108 patients with multiple myeloma who received High dose chemotherapy (Melphalan) & underwent autologous stem cell transplantation	79.6% of patients responded. At a median follow-up of 70 months, the median overall survival and event free survival (EFS) were 71 and 42 months, respectively	Survival was significantly better for patients with pre-transplant chemo-sensitive disease and for those who achieved complete response following transplant
Subramaniyan. R et al 2009 / JIPMER	55 Cases of MM who underwent bone marrow aspiration & biopsy in whom Plasma cell morphology, percentage infiltrate, pattern of infiltration, fibrosis & mitotic activity were studied	Patients with advanced clinical stage, >50% plasma cells in the marrow, Diffuse pattern of infiltration, High mitosis & increased fibrosis had a shorter median survival	Bone marrow histology correlates well with the clinical stage & also of prognostic importance
Nair. V et al 2009 / Army hospital, New Delhi	35 newly diagnosed cases of MM treated with Lenalidomide & patients earlier treated with thalidomide as controls	95% overall response in Lenalidomide group as compared to 72% in controls. Incidence of VTE, Neuropathy & Constipation were significantly lower in study group	Lenalidomide is a highly effective modality of treatment in newly diagnosed cases of MM
Prakash. J et al 2009 / BHU, Varanasi	50 patients (male 41; female 9) of MM were included in this study	Renal disease was present in 42 of 50 (84%) patients before MM was diagnosed & in only 8 of 50 (16%) patients, diagnosis of MM preceded the detection of renal disease	This study described a spectrum of renal diseases that can precede the diagnosis of multiple myeloma (MM)
Deepak. D et al 2008 / AIIMS	351 patients (176 in lenalidomide plus dexamethasone arm and 175 in placebo plus dexamethasone arm) who had received at least one previous anti myeloma therapy were included	60% in the lenalidomide group achieved significant response compared to 24% in the placebo arm. Time to achieve CR or near CR was 5.1 months compared to 6.9 months and time to progression was 11.3 months in the lenalidomide arm compared to 4.7 months in the placebo arm, p<.001.	Based on these results Lenalidomide plus dexamethasone has been approved for the treatment of relapsed multiple myeloma
Sharma. A et al 2007 / AIIMS	34 patients with MM who are not candidates for ASCT received a maximum of 12 cycles of chemotherapy consisting of oral melphalan 8 mg/m ² on days 1-4 and oral dexamethasone 40 mg on days 1-4 and days 9-12 every 4 weeks	9 patients (26.1%) had complete response/near complete response and 15 (44%) had partial response. overall and progression-free survivals were 58 and 28 months, respectively.	Combination of melphalan and dexamethasone is safe and effective in patients with MM who are not candidates for ASCT

Sharma. A et al 2007 / AIIMS	12 relapsed / refractory MM patients who received thalidomide for more than 2 years	Complete/ near complete response was seen in 50%, partial response in 12% & minimum response in 34%. All patients showed >25-50 % decline in serum M proteins.	Long term thalidomide is safe & effective in relapsed / refractory MM
Bhatti et al 2006 / AIIMS	110 newly diagnosed cases of MM were studied with respect to clinical features, laboratory findings, histological features, angiogenesis parameters, and responses to the treatment on follow-up	Significantly higher angiogenesis parameters in cases when compared with controls. Complete responders" (n = 38) had significant lower angiogenesis than "non responders"	MVD-B (Micro vessel density) is a good predictor for the complete response in patients of MM
Uppal. G et al 2005 / AIIMS	29 patients with refractory or relapsed MM on high dose thalidomide. All hematological and biochemical parameters were monitored at monthly intervals for one year	Hb, TLC, ANC, PC and serum albumin levels showed a significant negative correlation with M proteins & significant positive correlation existed between M proteins on one hand and TP and globulin levels on the other.	Efficacy of thalidomide therapy can be monitored by simple, inexpensive and easily available investigations
Arora et al 2005 / ASCO	108 patients of MM who received thalidomide either alone or in combination with dexamethasone were included.	Prevalence of toxicities were peripheral neuropathy in 44/99 (44.4%), sedation 38/99 (38.4%), constipation 28/99(28.3%), rashes 14/99 (14.1%) and neutropenia 10/99(10.1%)	Analyzed safety profile of Thalidomide & also showed excellent tolerability in the Indian population and has responses similar to that reported in the western literature
Kumar et al 2004 / PGI	Quantitative analysis of DNA ploidy, S-phase fraction % (SPF%), p53 and multidrug resistance (MDR) gene expression in 48 patients of MM	Aneuploidy was found in 5/48 (10.42%), High SPF% was noted in 18/37 (48.65%), p53 Gene product was noted in 8/48 (16.66%) & MDR gene expression was detected in 4/27 (10.81%)	Majority of cases with high SPF% were at advanced stages, indicating the prognostic significance of SPF%
Lalit et al 2003 / AIIMS	50 patients with advanced multiple myeloma undergoing treatment with high dose melphalan followed by autologous stem cell transplantation	Post-transplant, 43 of 50 patients engrafted. 31/46 patients (67%) responded to treatment. Complete response was achieved in 25 (54%) and partial response in 6 (13%)	High dose melphalan followed by autologous stem cell transplantation is an effective treatment for patients with advanced multiple myeloma and achievement of complete response is associated with improved survival

Sakhuja et al 2000 / PGI	Renal involvement in 204 cases with MM was retrospectively studied over a 10-year period in PGI, Chandigarh	Renal involvement seen in 55 cases (27%) of whom 94.5% had presented with renal failure and 7.3% had nephrotic syndrome. Patients with renal involvement had a high tumor burden. Median survival in those with renal involvement was only 4 months.	In unexplained renal failure in an elderly individual with normal sized kidneys, in association with disproportionate anemia even in the absence of skeletal lesions, one should suspect multiple myeloma.
Gupta et al 2000 / AIIMS	42 Patients (of whom 17 were cases of MM) underwent high-dose chemotherapy followed by either autologous bone marrow transplant	32 of the 42 (81%) showed stable engraftment. 8 (19%) died in the early post-transplant period. 7 patients died due to neutropenic infections and 1 due to acute renal failure. The median overall survival for all patients was 17 months and for the 34 engrafted patients it was 27 months	Autologous bone marrow or peripheral stem cell transplantation is a feasible procedure in India with an acceptable morbidity and mortality
Thakar et al 1997 / GMC, Nagpur	Protein electrophoresis of serum for 'M' band and Immunoelectrophoretic analysis of the serum in 72 patients with MM	IgG myeloma seen in 40 patients followed by IgA myeloma (13) & Light chain disease (12).	Immunoelectrophoresis is an essential component of triangular approach to patients with MM
Mohanty et al 1996 / KMC, Manipal	Univariate DNA flow cytometry was done on 13 proved multiple myeloma patients	Patients belonging to advanced clinical stage with more than 60% plasma cells in bone marrow with aneuploidy, especially hyperdiploidy carried a poor prognosis	DNA ploidy assessed with flow cytometry of plasma cells in bone marrow has a role in treatment response of multiple myeloma
Gupta et al 1995 / AIIMS	146 cases of MM studied. Response to a 4 drug combination (Vincristine, melphalan, cyclophosphamide and prednisolone: Group II) was compared to a 2 drug combination (cyclophosphamide or melphalan along with prednisolone: Group I)	The response rate in Group II was better (73 %) compared to Group I (43 %: p less than 0.05). The median duration of response and median survival in Group II (12.5 and 60 months respectively)	
Nair et al 1993 / Regional cancer centre, Kerala	Case records of 142 patients with multiple myeloma were reviewed and abstracted	The mean age of the patients was 61 years and 90 were males. A combination of melphalan and prednisolone was found to be well tolerated and achieved a survival rate of 62% at 5 years.	Melphalan and prednisolone chemotherapy achieves prolonged survival in myeloma

<p>Anand et al 1990 / GCRI</p>	<p>3 patients with MM were treated with recombinant alpha-interferon (r IFN-alpha 2b) along with combination chemotherapy i.e. melphalan and prednisolone.</p>	<p>All three patients experienced improvement in bone pains. Partial response with reduction in the paraprotein level was seen in one patient while there was no radiological, biochemical or hematological improvement in two patients</p>	
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1. NCCN Guidelines: Multiple Myeloma. Version 4.2015. http://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf
2. British Committee for Standards in Haematology - **GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF MULTIPLE MYELOMA 2014**. <http://www.bcsghguidelines.com/>
3. Multiple Myeloma: ESMO Clinical Practice Guidelines. Published in 2013 – *Ann Oncol* 2013; 24 (Suppl 6): vi133-vi137.

5-HT	5- hydroxytryptamine receptors	IV	intravenous
ASH	American Society of Hematology	IF	Immuno Fixation
AuBMT	Autologus Bone Marrow Transplantation	Ig	Immunoglobulin
AuSCT	Autologus Stem Cell Transplantation	LN	Lymph node
BRAF	Proto-oncogene that makes a protein called B-raf	LEN	Lenalidomide
BM	Bone Marrow	SPE	Serum Protein Electrophresis
BJP	Bence Jones Proteins	SFLC	Serum Free light Chain
CAP	Chest abdomen pelvis	THAL	Thalidomide
CT	Computed tomography	MDT	Multi-disciplinary team
CECT	contrast enhanced CT scan	MRI	Magnetic resonance imaging
CT-RT	Chemo-radiotherapy	MM	Multiple Myeloma
CT	chemotherapy	NCI CTCAE	National-Cancer-institute-common-terminology-criteria for adverse-events
D2	Dopamine receptor	NSAID	Non steroidal anti-inflammatory drugs
DR	dose reduction	PET	Positron emission tomography
dMMR	deficient Mismatch repair	PO	per oral
DEXA	Dexamethasone	PPI	Proton pump inhibitor
ESMO	European Society of Medical Oncology	RT	Radiotherapy
FDG	Fluoro-deoxy glucose	SC	Subcutaneous
FNA	Fine needle aspirate	SFLC	Serum Free Light Chains
GABA	gamma-aminobutyric acid receptor	SPE	Serum Protein Electrophoresis
Gy	Gray	SMM	Smouldering Multiple myeloma
ICMR	Indian council of Medical Research	US	Ultrasound
IHC	Immuno-histochemistry	WHO	World Health Organisation
IMiD	Immuno-modulatory drugs		



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