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MULTIPLE MYELOMA: ETIOPATHOGENESIS, STAGING, DIAGNOSIS, TREATMENT AND RESPONSE ASSESSMENT

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ABSTRACT

Multiple myeloma (MM), also known as Kahler's disease is an incurable haematological malignancy (plasma cell dyscrasia) of clonal B – cells of the plasma cells (a type of white blood cells in the bone marrow). Approximately 6.5% per lakh population are affected with multiple myeloma and is the second most common haematological malignancy. According to Indian Council of Medical Research (ICMR), in 2017 the global burden of MM has increased uniformly in the last 30 years and the global prevalence of MM accounts to 10,000 new cases every year in 1.4% per lakh population. The exact cause of MM is not established. Studies showed that, various factors contribute to the etiology of MM, such as genetic causes, environmental or occupational causes and Monoclonal Gammopathy of Undefined Significance (MGUS) or Smoldering MM (SMM). The first and foremost treatment goals of MM is to achieve a deep and long lasting clinical response, control of malignant cell growth and its spreading, to reduce complications of MM and to improve the quality of life in these patients. The selection of treatment regimen is completely patient specific and depends upon the baseline characteristics of the patient such as cytogenetic, disease stage, age, comorbidities and performance status of the patient. Multiple myeloma response criterias are used for determining the disease status for multiple myeloma and solitary plasmacytomas. To report the Stringent Complete Response (sCR) or Complete Response (CR), the urine studies are performed and should fulfil the International Myeloma Working Group (IMWG) criteria.

KEYWORD: multiple myeloma, response assessment, smoldering multiple myeloma, duries- salmon staging.

INTRODUCTION

Multiple myeloma (MM), also known as Kahler's disease is an incurable hematological malignancy of clonal B – cells of the plasma cells which help to fight against the infections by the activation of immune complementary antigen – antibody response reactions. Multiple myeloma results in the accumulation of malignant plasma cells in the bone marrow which crowds the healthy cells. Increased malignant plasma cells secrete abnormal proteins (known as monoclonal proteins or M – proteins which do not helps to fight infections) rather than helpful antibodies. Over production of these malignant plasma cells leads to end organ damages such as bone destruction and bone lesions and is characterized by symptoms such as bone pain in the spine or chest, hypercalcaemia, renal insufficiency and anemia.

PREVALENCE

Approximately 6.5% per lakh population are affected with multiple myeloma and is the second most common hematological malignancy. In 2016, the prevalence of MM was 2.1% per lakh population. Out of 1,30,000 myeloma cases, a global death of 98,437 people (1.5% per lakh population) were reported. Data from 1990 to 2016 showed that the incident of myeloma has increased by 126% globally and the death rates have increased by 94%.[6] According to Indian Council of Medical Research (ICMR), in 2017 the global burden of MM has increased uniformly in the last 30 years and the global prevalence of MM accounts to 10,000 new cases every year in 1.4% per lakh population. In U.S, it accounts for 21,000 new cases every year in 5.8% per lakh population among which 71,000 cases showed complete prevalence of MM. The global 5 year prevalence of MM is 2,10,697 or 4.3 per lakh populations and the global mortality rate is 72,453 (1% of total deaths related to cancer). Globally, the prevalence of MM is slight greater in males than in females (M:F ratio is 1.2:1) and is more common among the black Americans than the white in U.S (14.3 vs. 6.9% per lakh new cases per year). According to the annual report published by the Regional Cancer Center,

Thiruvananthapuram, Kerala in 2014, there was about 258 MM cases (2% MM cases reported in India).[8] According to the ICMR, in 2017 the 5 year prevalence of MM in India was about 11,602 or 1.4 per lakh population and about 59,000 death cases was reported each year. The M:F prevalence ratio in India was 1.3:1. The incidence of MM in India varies from 1.2 to 1.8 per lakh population. Approximately 50,000 new MM cases are diagnosed each year in India.[7]

ETIOPATHOGENESIS

The exact cause of MM is not established. Studies showed that, various factors contribute to the etiology of MM, such as genetic causes, environmental or occupational causes and Monoclonal Gammopathy of Undefined Significance (MGUS) or Smoldering MM (SMM).[10]

i. GENETIC CAUSES: Genetic mutation is one of the main risk factor of this heterogeneous disease. Chromosomal mutations include translocation in the heavy chain immunoglobulin of chromosome 14, trisomies and anomalies in chromosomes 1, 5, 13 and 17.[10] Some studies pointed out that certain mutation in the oncogenes (cancerous genes), such as c – myc could result in the development of plasma cell tumors. Mutations in the oncogenes such as N – ras and K – ras could result in the development of bone marrow relapse. Mutations in the tumor suppressor gene or anti-oncogenes genes that regulates a cell during cell division and replication) such as TP53 result in the spreading of malignant tumors to rest of the organs.[11]

ii. ENVIRONMENTAL OR OCCUPATIONAL CAUSES: Some studies showed that, there is a significant risk in developing MM in significant individuals with environmental or occupational exposures such as the farmers exposed to the herbicides and insecticides (chlordane), benzene, other organic solvents, food and petro – chemical industrial exposures.[10]

iii. MGUS (Monoclonal Gammopathy of Undetermined Significance) or SMM (Smoldering Multiple Myeloma):[4,10,11] Monoclonal Gammopathy of Undetermined Significance (MGUS) is a condition in which;

a. The serum monoclonal M – protein is < 3 gm/dl.
b. < 10% plasma cells in the bone marrow.
c. No significant evidence of end organ damage.

iv. Smoldering Multiple Myeloma (SMM – an asymptomatic plasma cell disorder) is characterized by;

a. M – Protein > 3 gm/dl.
b. Abnormal Serum Free Light Chain (SFLC) ratio.
c. > 10% plasma cells in the bone marrow. With increase in time and the increased number of risk factors, these MGUS and SMM progress into MM. Progression rate of MGUS into MM is 1% per year and the progression rate of SMM into MM is 10% per year.

PATHOGENESIS

MM – the malignancy of the plasma B cells are caused by the cytogenetic abnormalities in the;

i. Hyperdiploid Chromosomes (trisomy in the 3, 5, 7, 9, 11, 13, 15, 17, 19 and 21 chromosomes) such as mutations in the tumor suppressor gene TP 53 results in the dysregulation of the TP 53 pathway and c – myc dysregulation, mutations in the p18INK 4cRB1 results in the dysregulation of the RB1 pathway, mutations in the TRAF3cIAP1/2 CYLD NIK results in the dysregulation of the NFkB pathway.

ii. Non hyperdiploid Chromosomes such as karyotypic abnormalities in the 11q13, 12q13, primary translocation in the Ig heavy chain genes at 14q32, secondary translocation in the Ig TLC at 6p23, IgH TLC at 16q23, 20q11. Deletion of chromosome 13 at 8q24 and 4p16 results in the mutations of the oncogenes N – ras, K – ras and FGFR3 which results in the dysregulation of MAPK/STAT3 pathway. These cytogenetic abnormalities and the dysregulation of the cyclin D / RB (rectinoblastoma) pathway results in the activation of malignant plasma B cells in the germinal centers of the secondary lymphoid organs which further develops into monoclonal gammopathy of undetermined significance (MGUS) and then with the increase in the number of risk factors it further develops into intramedullary myeloma and finally it worsens into extramedullary myeloma.[10] Malignant plasma B cells express CXCR4 receptor for SDF – 1 α (a chemokine that regulates the clonal malignant plasma B cells) to reside inside the bone marrow where the bone disease develops. Plasma B cells which are ready to act on the B – cell receptor recognizes the antigens presented by the follicular dendritic cells present in the germinal cells of the secondary lymphoid organs. The interaction between the CD4 and helper T cell activates the B cells to differentiate into plasma cells, induces isotypic commutation and affinity mutations. During this process, the abnormal DNA recombination event translocates the heavy and light chain immunoglobulin genes into mutated chromosomes and generates a malignant phenotype. Thus the malignant plasma B cells, continuously produces the mutated immunoglobulins which results in the gammopathy and ultimately the malignant plasma cells reside inside the bone marrow and thus results in the development of the bone disease. RANKL – a necessary activation signal for osteoclasts is secreted along with the other growth factors by the malignant plasma B cells and these activated osteoclasts secretes IL6 which promotes the survival of these malignant plasma B cells. Increased bone resorption activity of multinucleated osteoclasts results in the bone destruction. Bone marrow stromal cells and malignant plasma B cells secretes soluble factors which promotes the formation of new blood vessels that supplies blood and oxygen to the malignant

plasma cells and the blood endothelial cells secrets the growth factors that promotes the proliferation and survival of the malignant plasma B cells.[1]

CLASSIFICATION OF MM BY WHO[6,15]

1. Symptomatic or active myeloma – presence of CRAB features and are as follows;

o C = Elevated Calcium levels
o R = Renal failure
o A = Anemia
o B = Bone leisions

2. Smoldering Multiple Myeloma (SMM – an asymptomatic plasma cell disorder) is characterized by;

o M – Protein > 3 gm/dl.
o Abnormal SFLC ratio
o > 10 % plasma cells in the bone marrow.

3. Non secretory myeloma

o Clonal bone marrow plasma cells >10% or biopsy proven plasmacytomas, evidence of end – organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically hypercalcaemia, anemia, renal insufficiency, bone leisions and lack of serum and urinary monoclonal protein on electrophoresis and immunofixation.

4. Plasma Cell Leukemia

o An aggressive form of MM characterized by high levels of abnormal plasma cells circulating in the peripheral blood.

Signs and symptoms

The main cardinal symptoms of MM are as follows:[5, 11]

C - hyperCalcaemia – increased bone destruction releases calcium into bloodstream and thus results in increased blood calcium levels.

R - Renal problems – high levels of M-protein produced by myeloma cells damages the kidney, increased blood calcium levels cause renal problems (nephrolithiasis).

A- Anemia – increased myeloma cells crowds the normal blood cells in the bone marrow which results in less number of red blood cells.

B- Bone lytic leision – myeloma cells releases chemicals that break down the bone cells leading to bone lysis and damage (especially in spine, hip, bone, ribs, vertebral fractures).

Other symptoms

i. Bruising or Bleeding - too many myeloma cells crowding in the bone marrow leads to decrease platelet count which leads to bleeding.
ii. Frequent infections and fever – increased myeloma cells in the bone marrow results in low level of WBC which produces less antibodies to fight against the infections and thus frequently gets infected.
iii. Excess thirst.

Nausea and vomiting.

iv. Frequent urination.
v. Shortness of breath.
vi. Weight loss.

DIAGNOSIS

According to the National Comprehensive Cancer Network (NCCN) diagnostic criteria;[5, 13]

i. For smoldering (asymptomatic) multiple myeloma, the diagnostic criteria are as follows:

- Serum monoclonal protein ≥3 g/dL, or
- Urine Bence Jones protein ≥500 mg/24 h and/or
- 10%–59% clonal plasma cells in the bone marrow and
- Absence of myeloma-defining events or amyloidosis.

ii. For active multiple myeloma, the diagnostic criteria should meet one or more of the following myeloma defining events:

• Serum calcium level > 0.25 mmol/L (> 1 mg/dL) higher than the upper limit of normal or > 2.75 mmol/L (> 11 mg/dL)
• Renal insufficiency (creatinine > 2 mg/dL [> 177 µmol/L] or creatinine clearance < 40 mL/min)
• Anemia (hemoglobin < 10 g/dL or hemoglobin > 2 g/dL below the lower limit of normal)
• One or more osteolytic bone lesions on skeletal radiography, CT, or FDG PET-CT • Clonal bone marrow plasma cells ≥60%
• Abnormal serum free light chain (FLC) ratio ≥100 (involved kappa) or < 0.01 (involved lambda)
• One or more focal ≥5 mm lesions on MRI scan.

Diagnostic tests

The following are the diagnostic tests for MM;[5,12]

A. General Health Tests – medical history, physical examination

B. Blood Tests – complete blood count tests with differential testing

i. Blood chemistry test - Blood urea nitrogen (BUN), Creatinine, Electrolytes, Calcium, Albumin, Lactate dehydrogenase (LDH), B2 – macroglobulin to assess the kidney function and Uric acid.
ii. Serum Quantitative Immunoglobulin Test – measure each type of abnormal antibodies
iii. Serum Free Light Chain Assay
iv. Serum protein electrophoresis (SPEP)
v. Serum Immunofixation Electrophoresis (SIFE)
vi. Serum Viscosity vii. HLA typing

C. Urine Tests

i. Urine analysis
ii. Urine total protein level – Bence Jones Protein
iii. Urine Protein Electrophoresis
iv. Urine Immunofixation electrophoresis

D. Tissue Testing

Bone marrow aspiration and bone marrow biopsy, Tissue biopsy, Imaging studies – X-ray, MRI, CT and PET scan and Cytogenetic analysis – Karyotyping and Fluorescence In Situ Hybridization (FISH) tests.

STAGING AND PROGNOSIS[14,15]

Staging of MM is done to know the location of malignant plasma B cells, extend of its spreading and

whether it has affected other parts of the body. Staging can be done as;

I. DURIE-SALMON SYSTEM - Traditionally used system for grading of myeloma. It is used for finding out extend of the disease and the size of the tumor. According to Durie – Salmon system, there are 3 stages-1, 2 and 3. Each stage is further divided into A and B according to the renal functioning status of the patient.

Stage I: Most of the patients in stage I does not show symptoms of myeloma as there are very few cancer cells in the body. If the cancer affects the kidney, the prognosis may worsen regardless of the stage if the cancer affects the renal function. According to the Durie – Salmon System the characteristic of stage I include:

- Number of red blood cells is within or slightly below normal range
- Hb 10 gm/dl
- Normal blood calcium levels (upto 12mg/dl)
- Low M protein levels in the serum or urine o M protein 7 g/dL for IgG; >5 g/dL for IgA; >12 g/24 h for urinary light chain.

Stage II: In this stage, the number of malignant cell increases. If the cancer affects the renal function, then the prognosis gets worsens regardless of the stage. Criteria for stage II - neither stage I nor stage III characteristics.

Stage III: Numerous malignant cells are present in the body at this stage. Characteristic of this stage include:

- hemoglobin 7 g/dL for IgG; >5 g/dL for IgA; >12 g/24 h for urinary light chain. Durie-Salmon sub classifications (either A or B)

A: Relatively normal renal function with serum creatinine value ≤ 2.0 mg/dL

B: Abnormal renal function with serum creatinine value ≥ 2.0 mg/dL.

II. INTERNATIONAL STAGING SYSTEM - The International Staging System (ISS) is commonly used to classify multiple myeloma. ISS defines the factors that influence the survival of the patients. It is based on the collected data from MM patients all around the world. According to this system there are 3 stages which are based on the serum albumin levels and serum β2-Microglobulin levels.

Stage I: β2-Microglobulin levels ≤ 3.5 mg/L with a serum albumin level of 3.5 g/dL or more

Stage II: Either of these 2 criteria:

- β2-Microglobulin levels should be between 3.5 mg/L and 5.5 mg/dL
- Serum albumin levels ≤ 3.5 g/dL.

Stage III: β2-Microglobulin level ≥ 5.5 mg/L. The system has been recently revised to include the serum levels of lactate dehydrogenase (LDH) and the high-risk gene abnormalities (defined by the FISH test). The revised system is called the revised-ISS (or R-ISS). This system is commonly used to predict the prognosis of the disease. High levels of serum LDH indicates less prognosis.

Recurrent or relapsed myeloma

Reappearance of the signs and symptoms of the disease after a period of improvement for atleast 60 days from the end of the treatment regimen. If relapse occurs, the cancer needs to be staged again by using one of the systems above and is known as re-staging.

Prognosis of MM[13,14,15,16]

The International Staging System of myeloma describes about the prognosis and predicts whether the person will recover or not. Evaluation of prognosis includes:

- A high level of β2-Microglobulin indicates that a large number of myeloma cells are present and the kidney has been damaged. (advanced myeloma)
- Lower level of serum albumin indicates that lower is the prognosis.
- Higher the blood levels of LDH, lesser are the disease prognosis.
- A cytogenetic abnormality in the cancer cells shows how aggressive is the cancer and is determines by FISH tests.
- A plasma cell labeling index is done by using bone marrow samples to find out how faster, the cancer cells are growing.

TREATMENT

The first and foremost treatment goals of MM is to achieve a deep and long lasting clinical response, control of malignant cell growth and its spreading, to reduce complications of MM and to improve the quality of life in these patients. The selection of treatment regimen is completely patient specific and depends upon the baseline characteristics of the patient such as cytogenetic, disease stage, age, comorbidities and performance status of the patient.[5 6] A patient diagnosed with MM is divided into either Allogeneic Stem Cell transplant (ASCT) eligible or ASCT non eligible according to the frailty and fitness (lack of comorbidities) of the patient and then further treatment regimen is selected for them.

Commonly used drugs for MM are as follows:[5]

1. Alkylating agents – Cyclophosphamide, Melphalan
2. Targeted Therapy i. Proteasome Inhibitor – Bortezomib, Carfilzomib, Ixazomib ii. Angiogenesis Inhibitor – Bevacizumab, Sunitinib, Everolimus iii. Immunomodulator – Thalidomide, Lenalidomide iv. Histone Deacetylase Inhibitor – Panobinostat v. Monoclonal Antibodies – Rituximab, Adalimumab
3. Steroid decreases the amount of swelling or inflammation in the malignant cell regions and also relieves the associated pain and pressure – Dexamethasone, Prednisolone.

Treatments used for symptomatic or active MM include corticosteroids, alkylating agents, proteasome inhibitors

(PIs), immunomodulatory drugs (IMIDs), monoclonal antibodies (mAbs), histone deacetylase inhibitors (iHDACs) and nuclear export inhibitors.[19]

(a) Classical alkylating agents as Melphalan target highly proliferating cells, including malignant plasma cells, by intercalating permanently their DNA, causing cell death later on.

(b) PIs such as Bortezomib, Carfilzomib and Ixazomib block the IkB and/or pro-apoptotic proteins degradation in malignant plasma cells proteasome, overcoming their resistance to apoptotic stimuli.

(c) IMIDs such as Thalidomide, Lenalidomide and Pomalidomide modulate the inflammatory environment of the BM inhibiting the progression of MM [e.g., reduction of Interleukin-6 (IL-6), tumor necrosis factor (TNF) etc.] through inhibition of angiogenesis and other key stromal-MM cell interactions). Some of these drugs target the cereblon protein of the E3 ubiquitin ligase complex blocking the ubiquitination process in malignant plasma cells. This in turn leads to a toxic accumulation of proteins and cell death.

(d) Monoclonal antibodies (mAbs) such as Daratumumab, Isatuximab and Elotuzumab bind to specific antigens on the surface of malignant plasma cells. This will in turn induce MM plasma cell death by antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and/or antibody-dependent cellular phagocytosis (ADCP).

(e) histone deacetylase inhibitors (iHDACs) such as Panobinostat and Vorinostat act on malignant plasma cells by opening the chromatin structure. Consequently, this will activate the expression of tumor suppressor genes, which were previously silenced by aberrant histone acetylation in malignant plasma cells.

(f) Exportin 1 (XP01) inhibitors such as Selinexor act on malignant plasma cells by blocking the export tumor suppressor proteins out of the nucleus by the XPO1 pump while retaining many oncoprotein mRNAs within the nucleus.[19]

Patients eligible for ASCT will be started with the Primary or INDUCTION PHASE THERAPY – a triple combination therapy of Proteasome Inhibitor (Bortezomib, Ixazomib or Carfilzomib) + Immunomodulatory Drugs (Thalidomide, Lenalidomide or Pomalidomide) + Steroids (Dexamethasone) is used. The commonly used combination therapies are Bortezomib (V), Thalidomide (T) and Dexamethasone (D) (VTD) and Bortezomib (V), Lenalidomide (R) and Dexamethasone (VRD). The treatment cycle lasts upto 3 weeks and the patients receive 3 – 4 cycles before ASCT. After the induction therapy most of the patients may achieve remission and the non-progressive patients proceed to high dose chemotherapy followed by ASCT. The disease evaluation is done after the 3 months of the ASCT and further a consolidation or maintenance therapy may be initiated. After ASCT, a short period of treatment (CONSOLIDATION THERAPY) upto 2 – 3 months is given with full dose of chemotherapy. Consolidation therapy is followed by the MAINTENANCE THERAPY – a longer therapy with lower dose of chemotherapy and is given until the next relapse or for a fixed duration. For non-transplant eligible patients,[16, 18]

1. An alkylator based double combination therapy of Melphalan and prednisolone (steroid) – MP is used.
2. Lenalidomide + Dexamethasone (RD)
3. Triple combination – Bortezomib, Lenalidomide and Dexamethasone (VRD)
4. Second generation agents like Carfilzomib, Pomalidomide and Ixazomib can also be used along with above mentioned regimens.

Treatment regimens in practice[5, 6, 17]

- **CyBorD:** Cyclophosphamide + Bortezomib + Dexamethasone – 3 to 4 cycles each of 28 days.

Cyclophosphamide – 300 mg/m2 /day on days 1, 8, 15 and 22, Bortezomib – 1.3 mg/m2 on days 1, 4, 8 and 11, Dexamethasone – 40 mg on days 1-4, 9-12 and 17-20 or Cyclophosphamide – 500 mg/m2 /day on days 1, 8 and 15, Bortezomib – 1.3 mg/m2 on days 1, 4, 8 and 11, Dexamethasone – 40 mg on days 1, 8 and 15 or Cyclophosphamide – 900 mg/m2 over 1hour on day 1, Bortezomib -- 1.3 mg/m2 on days 1, 4, 8 and 11, Dexamethasone – 40 mg on days 1, 2, 4, 5, 8, 9, 11 and 12

Maintenance

Bortezomib 1.3mg/m2 IV push over 3–5 seconds or SC on days 1, 4, 8, and 11 and then repeat cycle every 2 weeks for 2 years or until disease progression or unacceptable toxicity or Bortezomib 1.6mg/m2 IV push over 3–5 seconds or SC on days 1, 8, 15, and 22.

- **VRD:** Bortezomib + Lenalidomide + Dexamethasone – 3 to 4 cycles each of 21 days.

Bortezomib – 1.3 mg/m2 on days 1, 4, 8 and 11, Lenalidomide – 25mg on days 1 – 14, Dexamethasone – 20 mg on days 1, 2, 4, 5, 8, 9, 11 and 12 or 40 mg on days 1, 8 and 15.

Maintenance

Lenalidomide 10mg orally daily for 3 cycles for days 1–28:, followed by 15mg for subsequent cycles; Or Lenalidomide 10mg orally daily for Days 1–21, repeat the cycle every 4 weeks until disease progression or unacceptable toxicity; Or Bortezomib 1.3mg/m2 IV push over 3–5 seconds or SC on days 1, 4, 8, and 11 and then repeat cycle every 2 weeks for 2 years or until disease progression or unacceptable toxicity; Or Bortezomib 1.6mg/m2 IV push over 3–5 seconds or SC on days 1, 8, 15, and 22. Repeat cycle every 5 weeks for 6 months or until disease progression or unacceptable toxicity.

- **VD:** Bortezomib + Dexamethasone – 3 to 4 cycles each of 21 days.

Bortezomib – 1.3 mg/m2 on days 1, 4, 8 and 11, Dexamethasone 40 mg on days 1-4, 9-12 on cycles 1 & 2 and 1 – 4 on cycles 3 & 4; Or i. Bortezomib – 1.3 mg/m2

on days 1, 4, 8 and 11 every 3 weeks ii. Dexamethasone – 20 mg on the day of and the day after bortezomib.

Maintenance
Bortezomib 1.3mg/m2 IV push over 3–5 seconds or SC on days 1, 4, 8, and 11 and then repeat cycle every 2 weeks for 2 years or until disease progression or unacceptable toxicity; Or Bortezomib 1.6mg/m2 IV push over 3–5 seconds or SC on days 1, 8, 15, and 22.

- **RD:** Lenalidomide + Dexamethasone – 3 to 4 cycles each of 28 days.

Lenalidomide – 25 mg on days 1 – 21, Dexamethasone – 40 mg on days 1, 8, 15 and 22 or 1-4, 9-12 and 17-20; Or Lenalidomide – 25 mg on days 1 – 28, Dexamethasone – 40 mg on days 1-4, 9-12 and 17-20.

Maintenance
Lenalidomide 10mg orally daily for 3 cycles for days 1–28:, followed by 15mg for subsequent cycles; Or Lenalidomide 10mg orally daily for Days 1–21, repeat the cycle every 4 weeks until disease progression or unacceptable toxicity.

- **VTD:** Bortezomib + Thalidomide + Dexamethasone – 3 to 4 cycles each of 21 days.

Bortezomib – 1–1.3 mg/m2 on days 1, 4, 8 and 11, Thalidomide – 50-200 mg on days 1 – 21 at bedtime, Dexamethasone – 40 mg on days 1, 2, 4, 5, 8, 9, 11 and 12 or 1-4 & 9- 12 or 1-4 & 8-11. Bortezomib 1.3mg/m2 IV push over 3–5 seconds or SC on days 1, 4, 8, and 11 and then repeat cycle every 2 weeks for 2 years or until disease progression or unacceptable toxicity.

- **TD:** Thalidomide + Dexamethasone – 3 to 4 cycles each of 28 days.

Thalidomide – 200 mg P/O daily, Dexamethasone – 40 mg 1-4 and 15-18 on even cycles and on days 1- 14 on odd cycles of every 28 day cycle.

Maintenance
Thalidomide 50–200mg orally daily at bedtime for days 1–28 and then repeat the cycle for every 4 weeks until maximal response, disease progression, or unacceptable toxicity.

- **Pomalidomide:** 4 mg P/O QID on days 1 – 21 of repeated 28 day cycles until disease progression; may also be given in combination with Dexamethasone.

- **VMP:** Bortezomib + Melphalan + Prednisolone – every 6 weeks for about 4 cycles.

Bortezomib - 1-1.3mg/m2 on days 1, 4, 8, 11, 22, 25, 29 & 32 followed by 10 days of rest period, Melphalan – 9 mg/m2, Prednisolone 60 mg/m2 both on days 1-4.

Maintenance
Bortezomib 1 – 1.3mg/m2 on days 1, 8, 22 & 29 followed by 13 days rest period + Melphalan – 9 mg/m2 + Prednisolone 60 mg/m2 both on days 1-4 both for about 5 weeks for 5 cycles.

- **MPT:** Melphalan + Prednisolone + Thalidomide every 6 weeks upto 42 days.

Melphalan – 0.25 mg/kg, Prednisolone – 2 mg/kg, Thalidomide – 100-200 mg, escalated upto 400 mg on days 1 – 4 every 6 weeks upto 42 days; Or MPT- 28 day cycle of; Melphalan – 0.25 mg/kg P/O on days 1 – 4, Prednisolone – 2 mg/kg on days 1 – 4, Thalidomide – 50-100 mg X. 12, 6 week cycles of Melphalan – 0.25 mg/kg and Prednisolone – 2 mg/kg for 4 days.

- **MRD:** Melphalan + Lenalidomide + Dexamethasone – 28 day cycle

Melphalan – 0.18 mg/kg on days 1-4, Lenalidomide – 10 mg on days 1 – 21, Dexamethasone – 40 mg weekly every 28 days.

RESPONSE ASSESSMENT
Multiple myeloma response criterias are used for determining the disease status for multiple myeloma and solitary plasmacytomas. Immunofixation (IFE) and immunoelectrophoresis (IEP) are essentially used to determine Complete Response. Electrophoresis (SPEP and UPEP) assessments are also done as apart of the response assessment. When both the serum (SPEP) and urine (UPEP) levels are not measurable (NonMeasurable Disease), the difference between free light chain ratios should only be used for determining disease status. If either the SPEP or the UPEP values are measurable (serum M-protein $\geq$ 1 g/dL or urine $\geq$ 200 mg/24 hours), then the disease status should be tracked by using the serum M-protein levels from the SPEP or the UPEP.

To report the Stringent Complete Response (sCR) or Complete Response (CR), the urine studies are performed and should fulfil the International Myeloma Working Group (IMWG) criteria.

- **Stringent Complete Response (sCR):** Follows criteria for CR as defined below;

• Normal free light chain ratio,
• Absence of clonal cells in the bone marrow by immunohistochemistry (confirmation with repeat bone marrow biopsy not needed). (κ/λ ratio $\leq$ 4:1 or $\geq$ 1:2 for κ and λ patients, respectively, after counting $\geq$ 100 plasma cells)
• sCR requires two consecutive assessments (by the same method) made at any time before the institution of any new therapy. If radiographic studies were performed, there must be no known evidence of new or progressive bone lesions. Radiographic studies are not required to satisfy sCR requirements.

- **Complete Response (CR)**

I. Measurable and Non-Measurable Multiple Myeloma; A treatment response where all the following criteria are met:

- Negative immunofixation on serum and urine samples
- Disappearance of any soft tissue plasmacytomas
- ≤ 5% plasma cells in the bone marrow (confirmation with repeat bone marrow biopsy not needed)

II. Light Chain Only Myeloma; A treatment response where all the follow criteria are met:

- Normal serum free light chain ratio
- Negative immunofixation on serum and urine samples
- Disappearance of any soft tissue plasmacytomas
- < 5% plasma cells in the bone marrow (confirmation with repeat bone marrow biopsy not needed)

III. Non-Secretory Myeloma; A treatment response where all the following criteria are met:

- Disappearance of all soft tissue plasmacytomas
- < 5% plasma cells in the bone marrow (confirmation with repeat bone marrow biopsy not needed)

▪ **Very Good Partial Response (VGPR)**

I. Measurable Myeloma; One or more of the following must be present:

- Heavy Chain Myeloma (e.g., IgG kappa, IgG lambda, IgG only, etc.): Serum and urine M-protein detectable by immunofixation but not on electrophoresis and ≥ 90% reduction in serum M-protein and urine M-protein level < 100 mg/24 hours
- Light Chain Only Myeloma (e.g., kappa or lambda only): Serum and urine M-protein detectable by immunofixation but not on electrophoresis and ≥ 90% decrease in the difference between involved and uninvolved free light chain levels (applicable to Light Chain Only Myeloma)

II. Non-Measurable Myeloma; If the serum and urine M-protein are not measurable (i.e., do not meed the following criteria at the time of diagnosis):

- Serum M-protein ≥ 1 g/dL
- Urine M-protein ≥ 200 mg/24 hours
- then a ≥ 90% decrease in the difference between involved and uninvolved free light chain levels is required in place of the M-protein criteria (provided the serum free light chain assay shows involved > 10 mg/dL and the serum free light chain ratio is abnormal). For recipients with non-secretory myeloma, VGPR cannot be reported as a disease response.

▪ **Partial Response (PR)**

I. Measurable Myeloma; Both of the following criteria must be met:

- Heavy Chain Myeloma (e.g., IgG kappa, IgG lambda, IgG only, etc.): ≥ 50% reduction in serum M-protein and Reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 hours
- Light Chain Only Myeloma (e.g., kappa or lambda only) : ≥ 50% reduction in serum M-protein and ≥ 50% decrease in the difference between the involved and uninvolved free light chain levels (applicable to Light Chain Only Myeloma)

II. Non-Measurable Myeloma; If the serum and urine M-protein are not measurable (i.e., do not meet the following criteria at time of diagnosis):

- Serum M-protein ≥ 1 g/dL
- Urine M-protein ≥ 200 mg/24 hours; then a ≥ 50% decrease in the difference between involved and uninvolved free light chain levels is required in place of the M-protein criteria (provided the serum free light chain assay shows involved level > 10 mg/dL and the serum free light chain is abnormal).

III. Non-Secretory Myeloma; The following criteria must be met:

- ≥ 50% reduction in bone marrow plasma cells is required in place of M-protein (provided the baseline bone marrow plasma cell percentage was ≥ 30%) In addition, for recipients who had soft tissue plasmacytoma(s) present at baseline, a ≥ 50% reduction in their size is also required.

▪ **Stable Disease (SD)**

Does not meet the criteria for CR, VGPR, PR, or PD.

▪ **Progressive Disease (PD)**

- Measurable Myeloma; One or more of the following criteria must be met:
- Heavy Chain Myeloma (e.g., IgG kappa, IgG lambda, IgG only, etc.):

--Increase of ≥ 25% from the lowest response value achieved in one or more of the following:

♣ Serum M-component with an absolute increase ≥ 0.5 g/dL (for progressive disease, serum M-component increases of ≥ 1 g/dL are sufficient if the starting M-component is ≥ 5 g/dL)

♣ Urine M-component with an absolute increase ≥ 200 mg/24 hours

♣ Bone marrow plasma cell percentage with an absolute increase of at least 10% plasma cells.

-- Definite development of new bone lesions or soft tissue plasmacytomas, or definite increase in the size of any existing bone lesions or soft tissue plasmacytomas (≥ 50% increase from nadir in size of > 1 lesion, or a ≥ 50% increase in the longest diameter of a previous lesion > 1 cm in short axis); and/or

-- ≥ 50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease.

- Light Chain Only Myeloma (e.g., kappa or lambda only)

--Increase of ≥ 25% from the lowest response value achieved in one or more of the following:

♣ The difference between involved and uninvolved free light chain levels with an absolute increase > 10 mg/dL (applicable to Light Chain Only Myeloma)

♣ Bone marrow plasma cell percentage with an absolute increase of at least 10% plasma cells.

--Definite development of new bone lesions or soft tissue plasmacytomas, or definite increase in the size of any

existing bone lesions or soft tissue plasmacytomas (≥ 50% increase from nadir in size of >1 lesion, or a ≥ 50%. -- ≥ 50% increase in circulating plasma cells (minimum of 200 cells per µL) if this is the only measure of disease.

- Non-Measurable Myeloma: One or more of the following criteria must be met:

• Increase of ≥ 25% from the lowest response value achieved in one or more of the following:
o The difference between involved and uninvolved free light chain levels with an absolute increase > 10 mg/dL
o Bone marrow plasma cell percentage with an absolute increase of at least 10% plasma cells.
• Definite development of new bone lesions or soft tissue plasmacytomas, or definite increase in the size of any existing bone lesions or soft tissue plasmacytomas (≥ 50% increase from nadir in size of >1 lesion, or a ≥ 50% increase in the longest diameter of a previous lesion >1 cm in short axis); and/or ≥ 50% increase in circulating plasma cells (minimum of 200 cells per µL) if this is the only measure of disease.

- Non-Secretory Myeloma: One or more of the following criteria must be met:Increase of ≥ 25% from the lowest response value achieved in one or more of the following:

o Bone marrow plasma cell percentage (irrespective of baselines status) with an absolute increase of at least 10% plasma cells
• Definite development of new bone lesions or soft tissue plasmacytomas, or definite increase in the size of any existing bone lesions or soft tissue plasmacytomas (≥ 50% increase from nadir in size of >1 lesion, or a ≥ 50% increase in the longest diameter of a previous lesion >1 cm in short axis); and/or
• ≥ 50% increase in circulating plasma cells (minimum of 200 cells per µL) if this is the only measure of disease.

Relapse from CR: One or more of the following criteria must be met:
• Reappearance of serum or urine M-protein by immunofixation or electrophoresis; and/or
• Development of ≥ 5% plasma cells in the bone marrow; and/or
• Appearance of any other sign of progression such as:
o Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression)
o Hypercalcemia (> 11mg/dL)
o Decrease in hemoglobin of ≥ 2 g/dL not related to therapy or other non-myeloma-related conditions o Rise in serum creatinine by 2 mg/dL or more from the start of therapy and attributable to myeloma.
o Hyperviscosity related to serum paraprotein Relapse requires two consecutive assessments (by the same method) made at any time before classification as relapse, and/or the start of any new therapy.[6]

CONCLUSION

According to the US Cancer network, the world wide incidence rate of Multiple Myeloma as in the year 2016 was 2.1% per lakh persons and has shown a global increase of 126% during the year 1990 – 2016. Reports of Indian Council of Medical Research (ICMR) states that approximately 50000 new MM cases are diagnosed each year in India with the incidence varying from 1.2 – 1.8% per lakh population and about 59000 deaths cases are reported each year. Kerala reports about 258 MM cases (2% of MM cases reported in India) as quoted from the annual report published by the Regional Cancer Center, Trivandrum. Once the patient is identified as Non – transplant eligible or if the patient is not willing for the transplant, the patient is liable to undergo low dose chemotherapy followed by high dose chemotherapy. According to National Comprehensive Cancer Network (NCCN), there are about 9 chemotherapeutic regimens which are combinations of 6 - 8 cytotoxic drugs including alkylating agents and steroids. Of these regimens CyBorD, VD, TD, RD and VRD are most commonly used novel regimens. A strict and detailed study regarding the clinical response, toxicity profile and survival rate of the these regimens were mandatory to shed light upon the success and survival of MM patients in an Indian setting as the existing published literatures were highly deficient regarding these information.

As the drugs involved in the treatment of MM are cytotoxic in nature, the patients were highly prone to adverse drug reactions which were evident in their laboratory observations. Increased toxic events can decrease the prognosis and as the incidence of MM is increasing in India and the number of Indian studies was less among these patients, a meticulous study was necessary regarding the toxicity profile. Detailed information regarding the toxicity profile of these regimens will help the Practioner to choose the therapeutic regimen with less toxic effects and thereby improve the quality of life of the patient. As such there were no studies available regarding the clinical response, survival rate, toxicity profile and the improvements seen in the laboratory parameters of MM patients to the different therapeutic regimens in a clinical care setting in Kerala in the recent years. Therefore such a study was relevant and desirable in this setting.

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