PLASMA CELL DISORDERS
Region and risk adapted approach.

VELLORE HAEMATOLOGY FORUM
Department of Haematology,
Christian Medical College, Vellore, India
Disclaimer: The details included in this booklet are aimed at standardization of treatment protocols for multiple myeloma in our department. The guidelines presented here are intended to be followed by registrars under close supervision of the consultants in this department. This material is not for wider circulation and cannot be referenced for the management practices elsewhere. This booklet is only for internal circulation in the Department of Haematology of Christian Medical College, Vellore, India.

While all due care has been taken to ensure that data and facts presented in this book are accurate, minor errors and omissions are still possible. The authors do not recommend or intend material in this book to replace standard and accepted guidelines for management.

Foreword

It gives me a great pleasure to write a foreword for this book, the first in a series, from the Vellore Haematology Forum (VHF). At the Department of Haematology in Christian Medical College, Vellore, we have constantly strived to treat all patients with uniform treatment protocols with a focus not only on evidence based medicine but also on the cost effectiveness of a therapeutic approach. This at times requires region specific adaptations to address economic as well as social constraints that may apply to certain subsets. We believe that an effort has to be made to treat even these subsets of patients in a systematic manner rather than to make ad-hoc variations in our treatment approach. In this book on our department’s approach to myeloma, Dr. Anup J. Devasia has comprehensively addressed all the above mentioned issues and made these complex algorithms simple to understand, easy to practice and most importantly relevant to our patients. We believe this book will be a useful handbook for haematologists and oncologists who treat patients with plasma cell dyscrasias in our country.

Dr. Vikram Mathews MD.DM
Associate Director
Professor and Head
Department of Haematology
Christian Medical College
Vellore 632004
India
Dear Dr. Jones,

The tube contains urine of very high specific gravity. When boiled it becomes slightly opaque. On the addition of nitric acid, it effervescences, assumes a reddish hue, and becomes quite clear; but as it cools, assumes the consistency and appearance which you see. Heat reliquifies it. What is it?

Dr William Macintyre
Saturday, November 1st 1845

# INDEX

*Foreword*  
*Index*  

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The Spectrum of Monoclonal Gammopathies</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Monoclonal Gammopathy of Undetermined Significance (MGUS)</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Smouldering Multiple Myeloma (SMM)</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>Multiple Myeloma</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>Autologous Stem Cell Transplantation in Multiple Myeloma</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>Management of Relapsed Myeloma</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>Plasma Cell Leukemia</td>
<td>41</td>
</tr>
<tr>
<td>8</td>
<td>AL Amyloidosis</td>
<td>44</td>
</tr>
<tr>
<td>9</td>
<td>Waldenstrom Macroglobulinemia (WM)</td>
<td>49</td>
</tr>
<tr>
<td>10</td>
<td>POEMS Syndrome</td>
<td>53</td>
</tr>
</tbody>
</table>

*References*  
*Annexures*
# THE SPECTRUM OF MONOCLONAL GAMMOPATHIES

<table>
<thead>
<tr>
<th></th>
<th>MGUS</th>
<th>SMM</th>
<th>MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum M protein</td>
<td>&lt;3gm/dL</td>
<td>≥3gm/dL (or any with BMPC 10-60%)</td>
<td>NA</td>
</tr>
<tr>
<td>Serum free light chain</td>
<td>NA</td>
<td>NA</td>
<td>FLC r &gt;100</td>
</tr>
<tr>
<td>BM plasma cells (BMPC)</td>
<td>&lt;10%</td>
<td>10-60% Or &lt;10% with Serum M protein ≥3gm/dL</td>
<td>&gt;60% without any other criteria Or &gt;10% with one myeloma defining event</td>
</tr>
<tr>
<td>Bone lesions (non-lytic)</td>
<td>NA</td>
<td>NA</td>
<td>&gt;1</td>
</tr>
<tr>
<td>End organ damage (CRAB)</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

*This is only a comparison. For a detailed diagnostic criteria, refer each section.*
MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS)

Diagnosis of MGUS

All 3 criteria must be met:

1. Serum monoclonal protein <3 g/dL
2. Clonal bone marrow plasma cells <10%
3. 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.

Initial investigations in MGUS

1. Complete blood count, serum chemistries – creatinine, calcium, liver function tests
2. Serum protein electrophoresis, serum free light chain, immunofixation electrophoresis

In MGUS with IgG or IgM monoclonal protein <1.5gm/dL or IgA <0.5gm/dL with normal FLC and normal blood counts, a bone marrow at diagnosis can be deferred at diagnosis. A bone marrow examination is mandatory in all cases with unexplained cytopenia or abnormal morphology on peripheral smear.

4. Skeletal survey - Skull, Pelvis, thoraco-lumbar spine, chest, humerus and femur. In affording patients low dose whole body CT scan is recommended.

Role of LDH and Beta 2 microglobulin are unclear in MGUS at this point of time.
If there are symptoms like neuropathy, dyspnoea or clinical examination findings like organomegaly or skin signs, investigations to rule out a concomitant POEMS syndrome/amyloidosis is to be performed.

Risk stratification of MGUS and risk of progression to MM

The risk factors that determine the rate of progression to symptomatic myeloma are:

a. Serum monoclonal protein level >1.5gm/dL
b. Non-IgG MGUS (IgA, IgM, IgD MGUS)
c. Abnormal serum FLC ratio.

The absolute risk of progression to MM over 20 years based on the above risk factors will be as

1. 3 risk factors present (high risk MGUS) – 58%
2. 2 risk factors present (high intermediate risk MGUS) – 37%
3. 1 risk factor present (low intermediate risk MGUS) – 21%
4. No risk factors (low risk MGUS) -5%.

Follow up of patients based on risk of progression

All patients should be followed up in 3 months after their initial diagnosis of MGUS. Subsequently follow up should be annual for life time. Patients with lowest risk of progression like IgG monoclonal protein <1.5gm/dL may be followed up less often at 2-3 year intervals.

Investigations at follow up

1. Complete blood count, serum chemistries – creatinine, calcium
2. Serum protein electrophoresis +/ Serum free light chain based on the initial immunofixation.
SMOULDERING MULTIPLE MYELOMA (SMM)

Diagnosis of SMM

Both criteria must be met:

1. Serum monoclonal protein (IgG or IgA) > 3 g/dL, or urinary monoclonal protein > 500 mg per 24 h and/or clonal bone marrow plasma cells 10%–60%
2. Absence of myeloma defining events or amyloidosis.

Initial investigations in SMM

1. Complete blood count, Serum chemistries – Creatinine, Calcium, liver function tests
2. Serum protein electrophoresis, Serum free light chain, Immunofixation electrophoresis
4. Skeletal survey - Skull, Pelvis, thoraco-lumbar spine, chest, humerus and femur. In affording patients low dose whole body CT scan is recommended.

Role of LDH and Beta 2 microglobulin are unclear in SMM at this point of time.

If there are symptoms like neuropathy, dyspnoea or clinical examination findings like organomegaly or skin signs, investigations to rule out a concomitant POEMS syndrome/amyloidosis is to be performed.
Risk stratification of SMM (Mayo model)

The risk factors that determine the rate of progression to symptomatic myeloma are:

a. Serum monoclonal protein level ≥ 3gm/dL.
b. Non-IgG M protein (IgA, IgM, IgD MGUS).
c. Serum FLC ratio (involved/uninvolved) >8.

The highest risk group i.e. patients with all 3 factors have median time to progression to myeloma of 2 years.

Follow up of patients based on risk of progression

All patients should be followed once in every 3 months at least for the first five years when the risk of progression to myeloma is approximately 10% per year. For the next 5 years, when the risk is approximately 3% per year, follow up can be once in every 6 months. If the patient has not progressed in 10 years, then the risk is identical to that of MGUS and an annual follow up is appropriate.

In patients with low risk SMM (IgG M spike <3gm/dL, inv/univ FLC ratio <8, follow up can be done once in 6 months after the initial 3 month evaluation.

Investigations at follow up

1. Complete blood count, Serum chemistries – Creatinine, Calcium
2. Serum protein electrophoresis +/- Serum free light chain based on the initial immunofixation.
3. Annual immunoglobulin quantification is advisable as development of immunoparesis can be an early marker of progression.
4. Annual skeletal survey / low dose whole body CT is advisable in the first 5 years.
Serial bone marrow examination is not advisable unless there are other clear signs of progression.

**Therapeutic Interventions in MGUS/SMM**

Bisphosphonates or any other anti-myeloma therapy is currently not recommended in MGUS/SMM outside the setting of a clinical trial. In patients with senile osteoporosis, bisphosphonates can be administered as per recommendation for the general population.
MULTIPLE MYELOMA
TREATMENT GUIDELINES FOR NEWLY DIAGNOSED PATIENTS

Diagnosis of Multiple Myeloma – IMWG 2014 updated diagnostic criteria

1. Clonal plasma cells ≥10% in BM or biopsy proven bony or extra medullary plasmacytoma*.

    and

2. Any one or more of the following myeloma defining events.
   a. Hypercalcemia: serum calcium >1 mg/dL higher than the upper limit of normal or >11 mg/dL
   b. Renal insufficiency: creatinine clearance <40 mL per minute or serum creatinine >2 mg/dL
   c. Anaemia: haemoglobin value of >2 g/dL below the lower limit of normal, or a haemoglobin value <10 g/dL
   d. Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography-CT (PET-CT)
   e. Clonal bone marrow plasma cell percentage ≥ 60% **
   f. Involved: uninvolved serum free light chain (FLC) ratio >100 (involved free light chain level must be > 100 mg/L)
   g. >1 focal lesions on magnetic resonance imaging (MRI) studies (at least 5 mm in size)

**If bone marrow plasma cells are ≥ 60%, then no other criteria is required for a diagnosis of myeloma.
*Solitary plasmacytoma with BM > 10% clonal plasma cells is to be considered as Myeloma [1]
Points to note in the diagnosis of Multiple Myeloma

New myeloma defining events

1. Bone marrow plasma cell (BMPC) percentage estimation for diagnosis is based on either conventional bone marrow aspirate or biopsy examination. BMPC estimation should not be based on the proportion of plasma cells reported by flow cytometry; studies are ongoing to determine whether flow-based enumeration is feasible. If a discrepancy exists between BMPC estimation in the biopsy sample and aspirate, the higher of the two values should be used [2]. Bone marrow plasma cells >60% irrespective of the presence/absence of other myeloma defining illness, is to be considered as myeloma. This addition in the diagnostic criteria was based on a pivotal observation made by the Mayo group, that 95% of patients with >60% plasma cells in bone marrow progressed to develop myeloma in 2 years [3]. These patients were previously considered as high risk smoldering myeloma. These findings were subsequently validated by other groups [4].

2. The normal ratio for free light chains FLC (κ/λ) is 0.26–1.65. In clonal plasma cell disorders, excess production of one FLC type (the clonal component referred to as the involved light chain) often results in an abnormal FLC ratio [5]. (FLC) ratio > 100 is another addition as a myeloma defining event. The risk of progression to multiple myeloma within the first 2 years in patients with smoldering myeloma with an FLC ratio of at least 100 was consistently found to be 70-80% across multiple studies [6, 7]. It was hence concluded by the IMWG that an FLC ratio of at least 100 is a predictor of imminent progression in smoldering multiple myeloma and that such patients should be regarded as having multiple myeloma requiring therapy. To reduce possibility of error
the new criteria require a minimum involved FLC level of at least 100 mg/L

3. The presence of more than one focal lesion at least 5mm in size on MRI in smoldering myeloma was found to be associated with a substantial increase in risk of progression. The median time to progression was 13 months, and 70% of patients had progressed at 2 years [8]. It was hence incorporated as a myeloma defining event. In patients with more than one focal lesion on MRI, if such lesions are small (<5 mm) or equivocal, additional imaging with CT or PET-CT should be considered before making the diagnosis of multiple myeloma. A diffuse marrow infiltration pattern is associated with an increased risk of progression, but is not recommended as adequate to establish the diagnosis of multiple myeloma. In patients with diffuse infiltration, solitary focal lesion, or in the presence of equivocal findings, follow-up examinations in 3–6 months are strongly recommended. The IMWG clarifies that clear evidence of one or more sites of osteolytic bone destruction (≥5 mm in size) seen on CT (including low dose whole-body CT) or PET-CT does fulfil the criteria for bone disease in myeloma. Increased uptake on PET-CT alone is not adequate for the diagnosis of multiple myeloma; evidence of underlying osteolytic bone destruction is needed on the CT portion of the examination. When the diagnosis is in doubt, a biopsy of one of the bone lesions should be considered. Furthermore, in view of the incorporation and availability of more sensitive imaging modalities to identify osteolytic bone destruction, IMWG no longer recommends the presence of osteoporosis or vertebral compression fractures alone in the absence of lytic lesions as being sufficient evidence of bone disease for purposes of the diagnostic criteria. However, if vertebral compression fractures are seen in younger patients with monoclonal gammopathy, judgment should be exercised, and additional imaging should
as CT or PET-CT should be done to clarify that the changes are not related to myeloma [1].

Solitary Plasmacytomas

It consists of two distinct entities:

1. Solitary plasmacytoma (no clonal BMPCs)
2. Solitary plasmacytoma with low marrow involvement (<10% clonal BMPCs). These both entities to be treated with local irradiation and should be followed up for progression to multiple myeloma. [7]

By contrast, patients with solitary plasmacytoma and 10% or more of clonal plasma cells are classified and treated as multiple myeloma.

Renal failure in Myeloma

Only renal failure caused by light-chain cast nephropathy (based on typical histological changes or presumptive diagnosis based on the presence of high involved FLC levels, typically >1500 mg/L) is regarded as a myeloma-defining event. Although other forms of renal damage (eg. AL amyloidosis, monoclonal immunoglobulin deposition disease, light chain Fanconi syndrome, monoclonal gammopathy associated membranoproliferative glomerulonephritis) can occur in multiple myeloma, this association is not characteristic of multiple myeloma and can be seen with other types of plasma cell dyscrasias (e.g. MGUS) or lymphoproliferative disorders. Some investigators have collectively referred to these disorders under the term monoclonal gammopathy of renal significance (MGRS). Although they can occur in conjunction with multiple myeloma, in most patients they occur independently without evidence of other myeloma defining events. For this reason, these renal disorders are not regarded as myeloma-defining events, and should not lead to
multiple myeloma diagnosis, unless they meet criteria for multiple myeloma as listed in the panel.

**Investigations at Diagnosis**

Based on the recommended by the IMWG [9] the following investigations are mandatory at diagnosis for all new cases of multiple myeloma

1. Complete blood counts.
2. Liver and renal function tests, serum electrolytes including Ca, Ph, Uric acid, LDH, beta 2 microglobulin

[FISH panel -del17p, t (4; 14) and t (14; 16) – in all patients where finances are permitting.

*In resource constrained patients – del 17p alone has to be done.*

4. Serum electrophoresis** with immunofixation, Urine BJP, quantitative immunoglobulin levels, Serum free light chain assay, 24 hr. urine protein.

5. Imaging* – Skull, Pelvis, thoraco-lumbar spine, chest, humerus and femur.

* An MRI of the spine and pelvis may be considered in all patients with a presumed diagnosis of solitary plasmacytoma [10] and in patients with smoldering myeloma because it can detect occult lesions and, if positive, can predict for more rapid progression to myeloma. But it our scenario this may be applicable only in a set of patients with no restriction in resources.

** In patients with two monoclonal protein bands at the start of therapy, the sum of the two spikes should be used for monitoring of disease [11]
Risk stratification – International Staging System

1. All patients are to be risk stratified based on the International staging system (ISS)[12] or as much as possible based on the revised ISS [13] as follows:

<table>
<thead>
<tr>
<th>ISS Stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>$\beta_2$ microglobulin &lt; 3.5mg/L &amp; albumin ≥ 3.5g/L</td>
</tr>
<tr>
<td>II</td>
<td>Neither I or II</td>
</tr>
<tr>
<td>III</td>
<td>$\beta_2$ microglobulin ≥ 5.5mg/L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R-ISS Stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>$\beta_2$ microglobulin &lt; 3.5mg/L + albumin ≥ 3.5g/L + normal LDH + no high risk cytogenetics</td>
</tr>
<tr>
<td>II</td>
<td>Neither I or II</td>
</tr>
<tr>
<td>III</td>
<td>$\beta_2$ microglobulin ≥ 5.5mg/L, elevated LDH or high risk cytogenetics – del 17p, t(4;14), t(14;16)</td>
</tr>
</tbody>
</table>

Treatment of a newly diagnosed case of Multiple Myeloma.

Every newly diagnosed patient with multiple myeloma needs to be stratified into one of the following groups – transplant eligible and ineligible. Within these groups there will be patients without/with resource constraints. Induction regimens has been chosen based on the transplant eligibility and financial condition. The following groups are possible.

1. Group 1: Transplant Eligible – No financial constraints – Non high risk – No del17p
2. Group 2: Transplant Eligible – No financial constraints – High risk i.e. del17p
3. Group 3: Transplant Eligible – with financial constraints
4. Group 4: Transplant Ineligible – No financial constraints
5. Group 5: Transplant Ineligible – with financial constraints.
The treatment outline for the various groups of patients will be as follows:

**Group 1: Transplant Eligible – No financial constraints**

Transplant eligible patients with no financial constraints and who are negative for del 17p would be given a triplet induction regimen with Cyclophosphamide- Bortezomib- Dexamethasone (CyBorD). Disease assessment would be done after 4 cycles. If they have attained a VGPR or better they would undergo an autologous stem cell transplantation with high dose Melphalan. If the response is a PR, then they would be given 2 more cycles of CyBorD and if the response is <PR the induction regimen would be changed to Bortezomib-Lenalidomide- Dexamethasone (VLD) for 2 additional cycles before transplantation. Post-transplant consolidation would
be administered to patients who has attained <VGPR on day +100 post autologous stem cell transplantation. In patients who were given additional 2 cycles of VLD induction in view of attainment of stable disease after 4 cycles of CyBorD, will be given 2 cycles of VLD consolidation. The other group of patients will receive 2 cycles of CyBorD consolidation. This would be followed by maintenance with Lenalidomide till progression/tolerated.
Group 2: Transplant Eligible – No financial constraints – High risk i.e. del17p

In patients with del 17p we would offer a tandem autologous stem cell transplantation after the initial induction followed by consolidation and maintenance. This is based on compilation of data from European phase III studies which showed a clear survival benefit for patients with del 17p who underwent a tandem autologous stem cell transplantation. In patients who were given additional 2 cycles of VLD induction in view of attainment of stable disease after 4 cycles of CyBorD, will be given 2 cycles of VLD consolidation. The other group of patients will receive 2 cycles of CyBorD consolidation. This is to be followed by maintenance therapy with fortnightly Bortezomib and Dexamethasone till disease progression or till tolerated.
Group 3: Transplant Eligible – with financial constraints

In patients who are transplant eligible but has financial constraints, a triplet regimen consisting of Cyclophosphamide-Thalidomide and Dexamethasone (CTD) will be used in upfront induction for 4-6 cycles and this will be followed by an autologous stem cell transplantation with high dose Melphalan with departmental subsidies. Any patient who has <VGPR on day +100 post transplantation would also receive 2 cycles of CTD as consolidation. All patients will receive maintenance with Thalidomide till they progress or till the drug is tolerated.
Group 4: Transplant Ineligible – No financial constraints

In patients who are transplant ineligible and are having no resource constraints, we would give upfront triplet induction therapy with CyBorD (4-6 cycles) as per response illustrated in the above image. If a favourable response is achieved, they will be started on Bortezomib maintenance till disease progression or till tolerated.

In patients whom only a stable disease is attained or if the disease progresses after 4 cycles of CyBorD, Bortezomib-Lenalidomide-Dexamethasone (VLD) will be given for 2 cycles followed by Lenalidomide maintenance till tolerated or disease progression. If the disease progresses in spite of these, relapse protocols are to be initiated.
**Group 5: Transplant Ineligible with financial constraints**

In patients who are transplant ineligible with resource constraints, we would give upfront triplet induction therapy with CTD (6-9 cycles) as per response illustrated in the above image. If a favourable response is achieved, they will be continued on Thalidomide maintenance till disease progression or till tolerated.

In patients whom only a partial response / stable disease is attained or if the disease progresses after 9 cycles of CTD, Melphanal-Prednisolone- Thalidomide (MPT) will be given for 6-9 cycles followed by Thalidomide maintenance till tolerated or disease progression.
Defining response after induction therapy

After induction therapy every patient has to be assessed for response at specific time points before deciding on consolidation in the form of an autologous stem cell transplant in case of transplant eligible patients or about consolidation in case of transplant ineligible patients. Response evaluation in multiple myeloma has traditionally been based on the assessment of serum and urine monoclonal protein concentrations via protein electrophoresis or serum free light chain (for light chain myelomas) as a surrogate for tumour burden, allowing for the detection of trace amounts of paraprotein [14]. Molecular methods like allele specific oligonucleotide qPCR (ASO-PCR), next generation sequencing (NGS) and multicolour flow cytometry (MFC) has also been incorporated into the recently modified and updated IMWG response assessment criteria [11]. But these newer molecular response assessment parameters and the response called stringent complete response (sCR) are largely confined to the setting of clinical trials and hence we will not be using in our day to day clinical practice.
Response assessment in Myeloma -Modified from IMWG 2006 response assessment [14]

<table>
<thead>
<tr>
<th>SD</th>
<th>PR</th>
<th>VGPR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not meeting criteria for PR, VGPR or CR</td>
<td>&gt;50% reduction in serum M protein</td>
<td>&gt;90% reduction in serum M protein</td>
<td>Negative IFE, Disappearance of plasmacytomas, &lt;5% plasma cells in BM</td>
</tr>
<tr>
<td>&gt;90% reduction in 24 hr. urine M protein or to &lt;200mg</td>
<td>24 hr. urine M protein &lt;100mg</td>
<td>Or M band negative on SPEP and IFE+</td>
<td></td>
</tr>
<tr>
<td>If no measurable serum/urine M protein</td>
<td>&gt;50% reduction of dFLC</td>
<td>&gt;90% reduction of dFLC</td>
<td>Normal FLC ratio</td>
</tr>
<tr>
<td>If no serum/urine M protein or FLC</td>
<td>&gt;50% reduction in the plasma cells from diagnosis provided &gt;30% plasma cells at diagnosis.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If only plasmacytoma at diagnosis</td>
<td>&gt;50% reduction in size of plasmacytoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FLC – free light chain,
dFLC – Difference between involved and uninvolved free light chains.

*Measurable serum M protein – at least 1gm/100ml
*Measurable urine M protein – at least 200mg/24 hrs.
Routine use of FLC for disease monitoring is not recommended. Serum FLC levels should only be used for response assessment when both the serum and urine M-component levels are deemed not measurable. [5] [9]. In patients with two monoclonal protein bands at the start of therapy, the sum of the two spikes should be used for monitoring of disease [11]. Careful attention should be given to new positive immunofixation results appearing in patients who have achieved a complete response, when the isotype is different, it probably represents oligoclonal immune reconstitution and should not be confused with relapse; these bands typically disappear over time and these patients need a close follow up [11].

Approach to Diagnosis and Response Assessment in Multiple Myeloma

The following approach to response assessment would be followed in the department.

<table>
<thead>
<tr>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood counts.</td>
</tr>
<tr>
<td>Liver and Renal function tests, Serum electrolytes including Ca, Ph, Uric acid, LDH</td>
</tr>
<tr>
<td>Beta 2 microglobulin</td>
</tr>
<tr>
<td>Bone marrow – Aspiration, Trephine biopsy, karyotyping &amp; FISH</td>
</tr>
<tr>
<td>FISH panel - del17p, t (4; 14) and t (14; 16) – in all patients where finances are permitting.</td>
</tr>
<tr>
<td>In resource constrained patients who are transplant eligible – del 17p alone has to be done.</td>
</tr>
<tr>
<td>Serum protein electrophoresis, Urine BJP, Immunoglobulin levels, Free light chains (FLC), Immunofixation electrophoresis, 24 hr. urine protein.</td>
</tr>
<tr>
<td>Imaging– Skull, Pelvis, thoraco-lumbar spine, chest, humerus and femur.</td>
</tr>
<tr>
<td>Follow up</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>After 2 cycles of Induction</td>
</tr>
<tr>
<td>After 4/6 cycles of induction</td>
</tr>
<tr>
<td>(Before autologous SCT)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Do Bone marrow &amp; IFE</td>
</tr>
<tr>
<td>If &lt;5% plasma cells, Normal IFE</td>
</tr>
<tr>
<td>and disappearance of</td>
</tr>
<tr>
<td>plasmacytomas</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Then document CR</td>
</tr>
<tr>
<td>Post-transplant follow up</td>
</tr>
</tbody>
</table>

| Stringent complete response (sCR) is largely confined to the setting of clinical trials and hence we will not be using it in our day to day clinical practice. |
MODIFICATIONS IN THERAPY IN SPECIFIC CIRCUMSTANCES

RENAL FAILURE

1. Modifications in 1st cycle in Bortezomib based induction: Bortezomib should be started at a dose of 1.3 mg/m2 on days 1, 4, 8, and 11 of a 3-week cycle (grade A) in patients with renal failure [15]

2. Renal dose modification for antimyeloma drugs: Renal dose modification for antimyeloma therapy has been clearly defined by the IMWG and is as follows [15]. No dose modification is required for Dexamethasone, Bortezomib, Thalidomide and Cyclophosphamide in renal failure.

Dose modifications for various drugs used in myeloma in renal failure

See Chart on page 24

PERIPHERAL NEUROPATHY

Thalidomide & Bortezomib are drugs that can cause or worsen a pre-existing peripheral neuropathy (PN). Bortezomib given as subcutaneous injection has been found to cause less neuropathy compared to the intravenous preparation with equal efficacy [16, 17]. Patients who are on these medications needs to be assessed at frequent intervals and dose adjustments are to be made accordingly based on the severity as per the NCCN toxicity scale.

Dose adjustment for Bortezomib & Thalidomide [18]

<table>
<thead>
<tr>
<th>Severity of PN.</th>
<th>Bortezomib</th>
<th>Thalidomide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (paraesthesias or areflexia without pain or loss of function)</td>
<td>No dose modification</td>
<td>No modification</td>
</tr>
<tr>
<td>Drug</td>
<td>CrCl &gt; 60 mL/min</td>
<td>CrCl, 30-59 mL/min</td>
</tr>
<tr>
<td>-----------</td>
<td>------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>20-40 mg</td>
<td>No dose modification needed</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Oral melphalan 0.15 to 0.25 mg/kg/d for 4-7 days</td>
<td>Oral melphalan reduced 25% (0.11-0.19 mg/kg/d for 4-7 days)</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1.3 mg/m² on days 1, 4, 8, and 11, or weekly regimens</td>
<td>No dose modification needed</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>50-200 mg/d</td>
<td>No dose modification needed</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>25 mg/d</td>
<td>10 mg per d, can be increased to 15 mg/d if no toxicity occurs</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>20 mg/m² cycle 1; 27 mg/m² cycle 2 and 3</td>
<td>No dose modification needed</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>According to regimen</td>
<td>No dose modification needed</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>According to regimen</td>
<td>No dose modification needed</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>4 mg/d</td>
<td>No dose modification needed for CrCl ≥ 45 mL/min</td>
</tr>
</tbody>
</table>

Abbreviation: CrCl, creatinine clearance.
Grade 1 with pain or Grade 2 (Interferes with function but not with ADL) | 1mg/m² | Reduce dose by 50%
---|---|---
Grade 2 with pain or Grade 3 (interferes with ADL) | Withhold till symptoms disappear and start at 0.7mg/m² | Stop thalidomide till symptoms disappear and start at 50% dose
Grade 4 (Sensorimotor neuropathy that significantly interferes with ADL) | Discontinue medication | Discontinue medication

**CYTOPENIA**

**Bortezomib in thrombocytopenia**

The most common hematologic toxicity associated with Bortezomib therapy is transient thrombocytopenia which returns toward baseline in the rest period between treatment cycles. Bortezomib does not appear to be directly cytotoxic to most normal bone marrow cells or to destroy progenitor cells. Platelet budding from megakaryocyte progenitors is thought to be dependent on NF-κB, and Bortezomib may suppress this process temporarily, resulting in thrombocytopenia.

At the diagnosis of myeloma, the thrombocytopenia may be related to the marrow involvement by the disease. In such circumstances, the potential benefits of administering Bortezomib should be balanced against the risks. Prophylactic platelet transfusions may be given in patients who are at high risk of bleeding. In general Bortezomib is to be withheld at the onset of grade III-IV thrombocytopenia and should be restarted at 25% reduced dose (1mg/m²) once the thrombocytopenia recovers [19].

**Cyclophosphamide in Cytopenia**

The standard dose of cyclophosphamide used in the triplet induction would be 300mg/m². No dose escalations would be
done. There are no clear cut recommendations as to the threshold at which cyclophosphamide should be dose adjusted or withheld. One study [20] has done dose reduction only in patients with grade III haematological toxicity (WBC <2000 or ANC <1000). Another area of concern regarding the risk of cytopenia is when there is concurrent irradiation to the spine/pelvis. In such a situation the decision to withhold cyclophosphamide is to be made based on the WBC count, the anticipated severity of cytopenia and the presence of any concurrent infections and is left to the discretion of the treating physician. Cyclophosphamide has to be restarted as soon as the white cell count recovers and close monitoring of blood counts is required henceforth.

**Lenalidomide in Cytopenia**

Lenalidomide is a drug that is prone to cause cytopenia. There are no available recommendations by any group regarding dose adjustment of Lenalidomide in neutropenia secondary to bone marrow involvement by myeloma. Lenalidomide is to be started at 10mg if renal functions are normal. Subsequent dose increments/reductions are to be made by 5mg if patients tolerate the starting dose or experience cytopenia. The dose adjustment for Lenalidomide in cytopenia has to be based on a published Canadian consensus [21]:

<table>
<thead>
<tr>
<th>Neutrophil count</th>
<th>Dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC &lt;1000 on day 1 of a cycle</td>
<td>Delay start of the cycle for a week, until ANC &gt;1000</td>
</tr>
<tr>
<td>ANC &lt;1000 during a cycle</td>
<td>Interruption of Lenalidomide until next cycle</td>
</tr>
<tr>
<td>Returning to ANC &gt;1000 on next cycle.</td>
<td>Continue Lenalidomide at same dose ± addition of G-CSF, if no other significant toxicities needing dose reduction. Reduce Lenalidomide to the first reduction level if other significant toxicities observed</td>
</tr>
<tr>
<td>For each subsequent drop to &lt;1000</td>
<td>Interrupt Lenalidomide treatment</td>
</tr>
<tr>
<td>Returning to ≥ 1000/L on next cycle</td>
<td>Resume Lenalidomide at next dose reduction level</td>
</tr>
</tbody>
</table>
Platelet count | Dose adjustment
---|---
<30000 on day 1 of a cycle | Delay start of the cycle for a week, until platelet count ≥30000
<30000 during a cycle | Interruption of Lenalidomide until next cycle
Returning to ≥30 × 10⁹/L on next cycle | Reduce Lenalidomide to the first reduction level.
For each subsequent drop <30 × 10⁹/L | Interrupt Lenalidomide treatment
Returning to ≥30 × 10⁹/L on next cycle | Reduce Lenalidomide to the next dose reduction level

**Steroids Dose Adjustments**

Corticosteroids are essential part of the antmyeloma armamentarium but will often aggravate diabetes, hypertension, congestive heart failure and even psychiatric illnesses. In patients with suboptimal control of any of the above conditions it is reasonable to attenuate corticosteroids dose (20mg /day ) or even divide the weekly dose over the course of 2 days (20mg on day 1,2, 8,9, 15,16, 22, 23). These patients should be more closely monitored and may require frequent adjustments in the management of the pre-existing comorbidities, such as introduction or increase in dose of insulin therapy etc.

**SUPPORTIVE CARE IN MYELOMA**

**Antimicrobial prophylaxis**

Infections are the most common cause of early mortality in patients with myeloma. However the routine use of antibacterial agents in myeloma is controversial. Emerging drug resistance patterns does not support the routine use of antibacterial agents in myeloma chemotherapy or during the peri-transplant period.

1. **Trimethoprim – Sulfamethoxazole (TMP-SMX):** If 20 mg or more of prednisone per day is administered, the use of TMP-
SMX for Pneumocystis jiroveci prophylaxis is recommended [22]. Standard prophylactic doses of TMP-SMX is to be given to all patients during the first 2 cycles of CyBorD regimen when high dose pulse steroids are used.

Dose: Tab. Septran (DS) 1 tab twice a day on 2 days a week.

*DS - Equivalent to 160mg of TMP+800mg of SMX.

In Renal failure: once a day if CrCl 15-30, Withhold if CrCl <15.

2. **Acyclovir:** Treatment with proteasome inhibitors like Bortezomib has been found to disrupt normal T-cell immunity predisposing MM patients to varicella zoster reactivation [23]. Thus, the use of prophylactic acyclovir or Valacyclovir during the course of therapy is strongly recommended, especially in patients with a prior history of VZV infection during adulthood [24, 25].

Dose: Tab. Acyclovir 400mg twice a day till 6 months from the last dose of Bortezomib.

In Renal failure: 200mg twice a day if CrCl 10-25 or on haemodialysis, 200mg once a day if CrCl <10.

**Intravenous Immunoglobulin**

Intravenous gammaglobulin (IVIG) has not shown to have any improvement in outcomes in newly diagnosed MM patients [26] but has demonstrated efficacy in treated patients in a plateau phase, albeit they did not receive antibiotic prophylaxis [26]. In patients with recurrent bacterial infections in the setting of severe hypogammaglobulinemia (IgG levels below 400 mg/dL), monthly prophylaxis with IVIG may be a reasonable intervention.

**Bisphosphonates**

Bisphosphonates are the cornerstone for management of myeloma-related bone disease and it has also been proven to have antimyeloma
effect. A Cochrane meta-analysis confirmed that Zoledronic acid was the only bisphosphonate that produced superior overall survival compared with placebo [27]. Use of monthly bisphosphonate has been shown to result in the reduction of bone pain [28], hypercalcemia, and pathologic fractures in patients with cancer. The IMWG recommends use of bisphosphonates in all patients with myeloma receiving first-line antmyeloma therapy, regardless of presence of osteolytic bone lesions on conventional radiography [29]. Bisphosphonate use is not recommended in patients with MGUS or smoldering myeloma. Bisphosphonates should be administered for at least 12 months and up to 24 months and then at the physician’s discretion. It should be restarted at the time of relapse. Bisphosphonates can cause acute tubular damage and deterioration in renal function and renal functions are to be monitored. It requires dose modification in patients with renal dysfunction. Another complication of Bisphosphonates is osteonecrosis of jaw (ONJ). Hence patients should be on routine dental check-ups and it has to be stopped at least 3 months before a planned dental procedure except cleaning, scaling or root canal procedure.

Dose: Inj. Zoledronic acid 4mg IV once a month during first yr. then once in 3 months during second yr. Restart at relapse.

In Renal failure: Full dose if CrCl >60, 3.5mg if CrCl 50-60, 3.3mg if CrCl 40-49, 3mg if CrCl 30-39. Contraindicated if CrCl <30.

**Thromboprophylaxis**

The risk of venous thromboembolism (VTE) in cancer patients is more than 7% and those with myeloma has the highest risk [30]. The oral immunomodulatory drugs, Thalidomide and Lenalidomide, further increase that risk. The IMWG recommends thromboprophylaxis in patients with myeloma based on a risk assessment model [31]
Risk factors for VTE in myeloma patients

<table>
<thead>
<tr>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity (defined as body mass index &gt; 30kg/m2)</td>
</tr>
<tr>
<td>Previous venous thromboembolism</td>
</tr>
<tr>
<td>Central venous catheter or pacemaker</td>
</tr>
<tr>
<td>Associated disease - Cardiac disease, chronic renal disease, Diabetes, Acute infection, Immobilization</td>
</tr>
<tr>
<td>Surgery - General surgery, any anaesthesia, Trauma</td>
</tr>
<tr>
<td>Medications - Erythropoietin</td>
</tr>
<tr>
<td>Blood clotting disorders</td>
</tr>
<tr>
<td>Myeloma-related risk factors - Diagnosis per se, hyperviscosity</td>
</tr>
<tr>
<td>Myeloma therapy - High-dose dexamethasone, Thalidomide, Lenalidomide.</td>
</tr>
</tbody>
</table>

If no risk factor, or any one risk factor is present, aspirin 81-325 mg once daily is recommended.

If two or more risk factors are present, LMWH (equivalent of enoxaparin 40 mg once daily) or full-dose warfarin, international normalized ratio (INR) 2-3, is recommended.

If any myeloma therapy-related risk factor is present, then LMWH (equivalent of 40 mg enoxaparin once daily) or full-dose warfarin (target INR 2-3) is recommended.

In the absence of clear data from randomized studies as a foundation for recommendations, many of the following proposed strategies are the results of common sense or derive from the extrapolation of data from many studies not specifically designed to answer these questions. Further investigation is needed to define the best VTE prophylaxis.

In clinical practice the decision on thromboprophylaxis has to be individualised based on the risk factors present and the anticipated risks. It has to be balanced against the risk of bleeding.
ROLE OF RADIATION THERAPY IN MYELOMA [32]

The following are the indications for radiation therapy in Multiple myeloma.

1. Treatment modality in Isolated plasmacytoma

2. Cord compression caused by non-bony lesions. Radiation therapy should be commenced as soon as is possible, preferably within 24 h of diagnosis. A dose of 30 Gy in 10 fractions/ 20Gy in 5 fractions is recommended (Grade B1)

3. Pain control A dose of 30 Gy in 10 fractions/ 20Gy in 5 fractions is recommended (Grade B1)
**AUTOLOGOUS STEM CELL TRANSPLANTATION IN MULTIPLE MYELOMA**

Autologous stem cell transplantation is considered as the gold standard as part of the initial therapy for fit patients with multiple myeloma even in the era of novel agents. All patients with multiple myeloma who are fit and transplant eligible should be offered an autologous stem cell transplantation after the initial induction therapy (4-6 cycles) if they attain some response except a progressive disease (Please see figure attached in each group of patients). The department shall provide financial assistance to transplant eligible and resource constrained patients for autologous stem cell transplantation.

**Mobilization of stem cells**

1. **Cytokine mobilization**
   Mobilization with G-CSF would be the standard mobilization strategy in all patients except in a subset of patients where adequate cell dose is not anticipated. The dose of G-CSF would be 10mcg/kg in 2 divided doses (rounded to the nearest 100mcg) and has to be started on day -4 before the planned day of the stem cell harvest.

2. **Cyclophosphamide mobilization**
   In patients where an adequate cell dose is not obtained with cytokine mobilization, chemotherapy mobilisation with cyclophosphamide is attempted after 10-14 days. The dose of Cyclophosphamide to be used is 4gm/m². Following the administration of cyclophosphamide, G-CSF has to be started from day 4 at a dose of 10mcg/kg in 2 divided doses. Alternate day peripheral blood counts are done and once WBC is >1000/cu.mm, CD34 counts are
sent. Peripheral blood stem cell mobilization is to be done when the peripheral blood CD34 count is >20.

In exceptional cases, where the patient is heavily treated or has been administered > 4 cycles of Lenalidomide based therapy, upfront chemotherapy mobilization or G-CSF with Plerixafor is used.

3. Plerixafor

Dose used is 0.24mg/kg – Single dose to be given 12 hrs before the anticipated time of the harvest. This is given along with standard dose of G-CSF.

**Targeted Stem cell dose**

Target a stem cell dose of at least $4 \times 10^6$ CD34 cells/kg if a single autologous stem cell transplant is planned. If a tandem stem cell transplant is planned, a minimum cell dose of $8 \times 10^6$ CD34 cells/kg has to be targeted and cell dose of $4 \times 10^6$ CD34 cells/kg has to be cryopreserved for the second stem cell transplantation which is done 100 days post first autologous stem cell transplantation.

The stem cell harvest can be completed in 2-3 days depending on the adequacy of the stem cell dose.

**Regimen**

Single dose Melphalan is the standard conditioning regimen in myeloma autologous stem cell transplantation. The dose is 200mg/m² on day -1. Dose has to be reduced to 140mg/m² if creatinine clearance is <60ml/minute. During the infusion of melphalan, it is mandatory that patient chews/sucks ice chips that can act as local cryotherapy which helps in reducing the severity of mucositis. This has to be started 5 minutes before melphalan administration and has to be continued for 15 minutes after the end of melphalan administration. The stem cells are to be infused 12 hrs after the melphalan injection if CrCl is >60 ml/minute or 24 hrs later if CrCl is <60 ml/minute.
Patients with renal failure on renal replacement therapy (dialysis): Melphalan is not dialyzable. The dose of melphalan has to be 140mg/m² which may be split up to 70mg/m² on day -2 and day -1. Stem cell infusion should be preceded by dialysis 24-36 hours after the melphalan administration.

In case a tandem autologous transplantation is planned it has to be done after 100 days from the first autologous stem cell transplantation and the dose of the conditioning remain the same.
MANAGEMENT OF RELAPSED MYELOMA

Despite advances in therapy and the use of upfront autologous stem cell transplant, invariably all patients with multiple myeloma will eventually relapse.

Definition of progressive myeloma [33]

Progression of disease in myeloma can happen either as biochemical progression when an increase in the monoclonal protein/plasma cells in bone marrow is noticed without any associated myeloma related organ injury. Alternatively patients can sometimes experience an overt clinical relapse when they develop new myeloma related tissue/organ injury in association with features of biochemical relapse. Patients who develop biochemical progression may later develop an overt clinical relapse.

Relapse/progression in myeloma can be defined as follows:

Biochemical Relapse

1. 25% increase from the baseline in serum monoclonal protein, or an absolute increase ≥ 0.5gm
2. 25% increase in Urine M protein or an absolute increase > 200 mg/d
3. 25% increase in the bone marrow plasma cells or an absolute increase >10%
4. 25% increase in the dFLC or an absolute increase >10mg/dL

Clinical Relapse: (One or more of the following along with any one of the biochemical parameter)

1. New soft tissue plasmacytoma or bone lesion and / or increase in the size of an existing plasmacytoma or bone lesion
2. Hypercalcemia (serum calcium >1 mg/dL higher than the
upper limit of normal or $>11\, \text{mg/dL}$) that is not secondary to other causes

3. Decrease in haemoglobin to $>2\, \text{gm}\%$ from baseline or haemoglobin $<10\, \text{gm/dL}$

4. Rise in creatinine to $>2\, \text{mg/dL}$ or a creatinine clearance $<40\, \text{mL/minute}$.

All patients who develops anaemia or renal failure while on follow should be evaluated for an alternative cause.

**Definition of refractory myeloma**

Disease that progresses on salvage therapy or that relapsed within 60 days of last treatment in patients who have achieved at least a minimal response to treatment (CR, VGPR, PR or SD).

**Primary refractory myeloma**

Disease that fails to achieve at least a minimal response with any therapy.

**When to treat relapsed myeloma?**

Treatment of relapse in myeloma is indicated in case of

a. Symptomatic/clinical relapse,

b. In case of biochemical relapse - rapidly increasing paraprotein level*

c. Extramedullary disease.

Patients experiencing a biochemical relapse alone need not be treated immediately. In such instance, the pace in increase of the monoclonal protein, a doubling time of 3 months or shorter would suggest initiating therapy*. For asymptomatic biochemical relapse a stringent wait and watch policy with workup every 3 months is recommended. A few patients can develop transient oligoclonal reconstitution following autologous stem cell
transplantation and they should be kept under observation and should not be treated.

**General principles in treating relapsed myeloma**

1. A thorough review of previous and ongoing therapies, duration of prior therapies, and both depth and duration of response to prior treatment is necessary at the time of disease progression.
2. A thorough knowledge of the patient’s performance status, comorbidities is essential before initiating the treatment for relapsed myeloma.
3. A patient who is naïve to an agent (or a class of drugs) is typically treated with a regimen incorporating this agent (or any agent from the drug class).
4. A patient who previously responded to a particular agent with a duration of response of at least 12 months can be retreated at relapse with similar drugs used previously or in combination with other agents.
5. A patient who has previously not undergone an autologous stem cell transplantation should be taken up for autologous stem cell transplantation after salvage.
6. A patient who has previously undergone single ASCT may be eligible for a second course of high dose therapy with autologous stem cell rescue if the progression free survival (PFS) after the first was at least 24 months. If the patient did not receive consolidation/maintenance therapy post initial ASCT, such therapy should be considered following the second ASCT.
7. Relapse in young and fit patients <60 years with a suitable donor can be managed by allogeneic stem cell transplantation after a suitable salvage therapy.
8. Indolent vs aggressive relapse.
Patients with **indolent disease** at relapse are generally treated with regimens that include an agent to which the patient is either naïve or has known sensitivity.

Patients with high risk disease or **aggressive disease** without co-morbidities and adequate performance status should be treated with highly active drug combinations to achieve a maximal response. This has to be further consolidated with a repeat autologous or an allogeneic stem cell transplantation based on the setting (Refer 6 and 7).

The characteristics that define high risk or aggressive disease are any of the following:

a. High risk cytogenetics (upfront or at relapse) – del 17p, t(4,14)

b. High beta 2 microglobulin and/or high LDH

c. Extramedullary disease

d. Shorter duration of response (<1 year) to initial therapy or progression while on therapy

e. Circulating plasma cells.

**There are no standard recommendations as of which is the superior regimen that has to be administered in case of relapsed/refractory MM.** The decision on the salvage has to be made based on the above listed principles. While choosing the salvage regimen, it is important also to consider the potential toxicities associated with the agents that are being tried and to avoid them based on the patients comorbidities/performance status.

The various regimens that can be used in the setting of relapse are:

1. Lenalidomide – Dexamethasone (9-12) cycles followed by Lenalidomide maintenance

2. Other triplet combinations not tried upfront
   a. Cyclophosphamide-Thalidomide-Dexamethasone (CTD)
   b. Bortezomib-Thalidomide-Dexamethasone (VTD)
c. Bortezomib-Lenalidomide-Dexamethasone (VLD)

3. Pomalidomide – Dexamethasone (in patients who are double refractory – refractory to lenalidomide and bortezomib, or patients who have relapsed in less than one year after an autologous SCT)

4. Pomalidomide – Bortezomib-Dexamethasone (in patients who are double refractory – refractory to lenalidomide and bortezomib, or patients who have relapsed in less than one year after an autologous SCT)

5. Carfilzomib-Lenalidomide-Dexamethasone (KRd) – in patients who have failed 2-3 regimens, who had no progression while on bortezomib based therapy and who had no major adverse events/no progression in the first 3 months while on Lenalidomide therapy.[34]

6. VTD-PACE (in young and fit patient or with extramedullary relapse or refractory disease)

7. DCEP (in young and fit patient)

8. Pegylated liposomal Doxorubicin-Lenalidomide-Dexamethasone (preferable in extramedullary relapse)

9. Bortezomib-Bendamustine- Dexamethasone

10. Melphalan-Prednisolone-Thalidomide (in elderly and unfit)

11. Daratumumab (monotherapy and in combination) – In relapsed and refractory heavily pre-treated patients [35] [36, 37]

(Each chemotherapeutic regimen has been detailed in the annexures at the end of this book)
ROLE OF SECOND AUTOLOGOUS STEM CELL TRANSPLANTATION

Retrospective data from Germany have shown that patients who have relapsed more than 18 months after the first autologous stem cell transplantation may benefit from a second autologous stem cell transplantation after appropriate response (PR and above) is obtained after a novel agent (Lenalidomide or bortezomib) based re-induction therapy. The median PFS and OS in these patients were 15.2 months and 42.3 months respectively[38].

This can be a potential salvage strategy in our patients who attains a relapse free survival of atleast 2 years and are unfit for an allogeneic stem cell transplantation.

ALLOGENEIC STEM CELL TRANSPLANTATION IN MULTIPLE MYELOMA

Ever improving outcomes with autologous stem cell transplantation and the high transplant related mortality associated with an allogeneic stem cell transplantation has made it not in contention as an upfront consolidation option in MM. However an allogeneic stem cell transplantation can be considered in a fit patient in the following setting:

1. Relapsed and refractory myeloma
2. Early relapse after autologous stem cell transplantation (<1 yr)
3. Primary plasma cell leukemia in an young and fit patient
4. Myeloma with extramedullary relapse.
PLASMA CELL LEUKEMIA

TREATMENT GUIDELINES FOR NEWLY DIAGNOSED PATIENTS

Plasma cell leukemia is the most aggressive form of monoclonal gammopathies and is characterised by the presence of circulating plasma cells in the peripheral blood.

It can be of 2 types: [39]

1. Primary plasma cell leukemia: de novo plasma cell leukemia (Median survival – 11.2 months)
2. Secondary plasma cell leukemia: terminal phase of pre-existing myeloma (Median survival – 1.3 months)

Diagnosis of plasma cell leukemia [40]

Diagnosis of plasma cell leukemia is based on the presence of

1. Plasma cells >20% in the peripheral circulation and
2. Absolute plasma cell count >2000/cu.mm in the peripheral blood.

[However this diagnostic criteria is restrictive and the degree of peripheral plasmacytosis needs to be reconsidered. Patients with significant treatment exposure (in case of secondary plasma cell leukemia) and poor bone marrow reserve may have baseline leukopenia and may not meet absolute criteria but may meet percentage criteria. Hence probably only one of these criteria is needed for diagnosis. Additional methods including flow cytometry is warranted in indicated cases for a diagnosis of plasma cell leukemia when the peripheral blood criteria is not met and when the index of suspicion is high. These modifications in the diagnostic criteria has been proposed to the IMWG but have not been approved yet]

Investigations at diagnosis (As for myeloma) – Please refer page 11.
Management of plasma cell leukemia

Compared to conventional alkylator based chemotherapy, bortezomib based induction regimen followed by autologous stem cell transplantation has shown significant survival advantage in plasma cell leukemia with respect to improved event free and overall survival. A bortezomib based multidrug induction regimen (4 cycles of CyBorD/VTD-PACE in young and fit patient) is advisable. An allogeneic stem cell transplantation is a reasonable option in young and fit patients when a matched sibling donor is available. In all other cases if the patient is transplant eligible, autologous stem cell transplantation (preferably a tandem autologous stem cell transplantation) followed by consolidation and dual drug maintenance (Bortezomib + Lenalidomide) till progression/tolerated would be the best option in patients with primary plasma cell leukemia.

Patients who are transplant ineligible should be given 6 cycles of CyBorD followed by dual drug maintenance (Bortezomib + Lenalidomide) till progression/tolerated.
The management of plasma cell leukemia can be summarized as follows:

1. Treatment of primary plasma cell leukemia.

   - **Transplant eligible**
     - **No**
       - **Induction** CyBorD (4-6)
       - **VTD-PACE in young and fit**
     - **Yes**
       - **CyBorD (4-6)**
       - **Maintenance** Bortezomib + Lenalidomide (Till progression/tolerated)

   - **Donor available**
     - **Yes**
       - **Tandem autologous transplant**
       - **Consolidation x 4** CyBorD /VTD
       - **Maintenance** Bortezomib + Lenalidomide (Till progression/tolerated)
     - **No**
       - **Age >50 yrs** <50 yrs
         - **Tandem autologous transplant**
         - **Autologous transplant**
           - **RIC - Allo SCT**
           - **MAC - Allo SCT**
           - **Maintenance** Bortezomib + Lenalidomide (Till progression/tolerated)

2. Secondary plasma cell leukemia or relapsed primary plasma cell leukemia.

   - **Fit patient**
     - **No**
       - **Palliation**
     - **Yes**
       - **Bortezomib/Lenalidomide based regimen. (Possibly avoid the agent that was given previously)**
       - **Transplant eligible**
         - **Yes**
           - **MAC/RIC Allo or Auto transplantation based on age and PS**
         - **No**
           - **Maintenance** Bortezomib + Lenalidomide (Till progression/tolerated)
AL AMYLOIDOSIS

The term primary systemic amyloidosis, or AL amyloidosis, refers to a systemic disorder with amyloid deposits consisting of immunoglobulin light chains or their fragments or heavy chains. All forms of systemic AL are associated with a clonal disorder of plasma cells, which may range from a small clonal population of 5% plasma cells or less in the bone marrow (BM) to overt multiple myeloma. Amyloidosis is particularly difficult to diagnose because no single imaging, blood, or urine test is diagnostic for this disorder. The scope of this manuscript is only for primary systemic amyloidosis and its treatment.

Diagnosis of Primary systemic amyloidosis (Systemic light chain – AL amyloidosis)

The diagnosis of AL amyloidosis should be suspected in any patient with

1. non-diabetic nephrotic syndrome;
2. non ischemic cardiomyopathy with “hypertrophy” on echocardiography;
3. hepatomegaly or increased alkaline phosphatase value with no imaging abnormalities of the liver;
4. chronic inflammatory demyelinating polyneuropathy with a monoclonal protein
5. presence of a monoclonal gammopathy in a patient with unexplained fatigue, edema, weight loss, or paraesthesias [41].

Diagnostic tests

1. Complete blood counts, serum chemistries – creatinine, Ca, Ph, LDH, LFT, PT , APTT
2. Biopsy with Congo red staining with apple green birefringence on polarizing microscopy and/or thioflavin T, confirming the diagnosis of amyloidosis from organs – abdominal fat pad, rectal etc. In all cases an immunohistochemistry for light chain restriction is advised though interpretation is difficult because of background staining.

3. Bone marrow aspiration, biopsy and FISH after plasma cell sorting.

4. Serum free light chain assay, quantitative immunoglobulin assay, and 24 hr. urine protein assessment

5. Skeletal survey as in myeloma.

6. ECG, echocardiogram, serum NT-Pro BNP, serum troponin T levels

7. In case there is an associated multiple myeloma, a full myeloma work up needs to be done as per the diagnostic evaluation given under myeloma.

Risk stratification and median survival

Once a diagnosis of AL amyloidosis is made, all patient should be risk stratified on the basis of the Revised Mayo risk criteria – serum NT-Pro BNP, serum troponin levels and serum free light chains at diagnosis being the parameters [42].

1. Serum NT-Pro BNP >1800 pg/mL or >1800ng/L
2. Serum troponin T >25 pg/mL or >0.025ng/mL
3. dFLC > 180mg/L

The median survival of patients is based on the no. of risk factors present at the time of diagnosis

1. Stage 1 - No risk factor - 94 months
2. Stage 2 - 1 risk factor – 40 months
3. Stage 3 -2 risk factor present – 14 months
4. Stage 4 -3 risk factors present – 6 months.
Therapeutic strategies based on risk stratification [43]

1. Transplant eligible:

- **Low risk - All criteria to be met**
  - NT Pro BNP <5000 pg/mL
  - Trop T <60
  - Age <65
  - ECOG PS 0-2
  - Normal renal function
  - NYHA <III
  - Normal cardiac function
  - SBP >100 mm Hg
  - DLCO >90
  - BMPC <10%

- **Low risk with BMPC >10%**
  - Or
  - Any adverse factor present
  - CyBorD* x 4-6
  - CTD x 4-6 **

- **Autologous stem cell transplant with Melphalan 200mg/sq.m**

Consider maintenance therapy with Bortezomib-Dexamethasone if response is <CR after autologous stem cell transplantation even though there is no evidence to support the role of consolidation/maintenance in amyloidosis.

2. Transplant ineligible

- **CyBorD x 4-6**
- Bortezomib + Dexamethasone as maintenance till progression

- **CTD**x 4-6
- Thalidomide till progression

* Bortezomib is preferably given as intravenous in patients who are fluid overloaded where there is a concern about the adequacy of absorption with subcutaneous administration [44]

** In patients with financial constraints.
Localized AL amyloidosis can occur rarely and if there are no systemic involvement or organ dysfunction, local excision/radiotherapy is an option.

**Response assessment in primary systemic amyloidosis [43, 44]**

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haematological criteria</strong></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>Negative serum and urine immunofixation and normal serum FLC ratio</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>dFLC &lt;40</td>
</tr>
<tr>
<td>Partial response</td>
<td>Reduction in FLC &gt;50% compared with baseline</td>
</tr>
<tr>
<td>No response</td>
<td>All other scenario</td>
</tr>
<tr>
<td><strong>Cardiac response</strong></td>
<td>Decrease of NT-pro BNP by &gt;30% and 300 ng/L (if baseline NT-pro BNP &gt; 650 ng/L), or at least 2-point decrease of NYHA class (if baseline NYHA class is III or IV)</td>
</tr>
<tr>
<td><strong>Renal response</strong></td>
<td>At least 30% decrease in proteinuria or drop below 0.5 g/24 h, in the absence of renal progression defined as a &gt;25% decrease in eGFR</td>
</tr>
<tr>
<td><strong>Hepatic response</strong></td>
<td>50% decrease in alkaline phosphatase</td>
</tr>
<tr>
<td></td>
<td>Reduction in liver size by 2cm radiographically</td>
</tr>
</tbody>
</table>

dFLC – Difference between involved and uninvolved free light chains.

**Supportive care in Amyloidosis [44]**

In a patient with primary systemic amyloidosis in addition to the definitive care, organ and symptom specific supportive care is also required as follows:

1. Salt restriction
2. Diuretics (Be cautious as aggressive diuresis can lead to intravascular fluid depletion and this can worsen cardiac function as cardiac function is preload dependent).
3. Patients at high risk of venous thromboembolism should be considered for prophylactic heparin and low risk for Ecospirin.

4. Patients with gastrointestinal symptoms should receive nutritional support.

**Treatment of Relapsed Amyloidosis**

The choice of treatment depends on the agents used in upfront therapy, response to the initial therapy and the clinical presentation. An attempt to restore response with the regimen used frontline can be made if first remission was prolonged (> 1 year).

Bortezomib combination is an option in patients who have no neuropathy and who are naïve to Bortezomib.

Lenalidomide based regimen (Lenalidomide – Dexamethasone) is an option for patients who are already exposed to Bortezomib and the response was <2 years.

Patients who relapse/progress within 1 year of upfront therapy or autologous stem cell transplantation should be given long term Melphalan- Dexamethasone. The prognosis and outcomes are extremely poor in this subset of patients.
WALDENSTROM MACROGLOBULINEMIA (WM)

Waldenstrom macroglobulinemia (WM) is a lymphoplasmacytic lymphoma with immunoglobulin M (IgM) monoclonal protein. Clinical features include anemia, thrombocytopenia, hepatosplenomegaly, lymphadenopathy, and rarely hyperviscosity [45].

**Diagnosis of WM:** Presence of IgM monoclonal protein associated with >10% clonal lymphoplasmacytic cells in bone marrow confirms the diagnosis.

**Investigations at diagnosis**

1. Complete blood counts.
2. Liver and renal function tests, serum electrolytes including Ca, Ph, Uric acid, LDH, beta 2 microglobulin.
3. Lymph node biopsy
4. Bone marrow – Aspiration, Trephine biopsy, & karyotyping
5. [Del 6q, del 11q, trisomy 4 are adverse prognostic factors].
6. MYD 88 mutation
7. Serum electrophoresis with immunofixation, immunoglobulin levels
8. Imaging of the abdomen for lymph nodes
9. Direct and indirect Coomb’s test
10. PT and aPTT (as the monoclonal protein can coat the coagulation factors and platelets and can cause coagulopathy). If there is significant bleeding despite a normal PT, aPTT and platelet counts, a platelet function test is also required.
Risk stratification - IPSS for WM [46]

<table>
<thead>
<tr>
<th>Factors</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;65yrs.</td>
</tr>
<tr>
<td>Hb</td>
<td>≤11.5gm%</td>
</tr>
<tr>
<td>Platelet count</td>
<td>≤100,000/cu.mm</td>
</tr>
<tr>
<td>Beta 2 microglobulin</td>
<td>&gt;3mg/L</td>
</tr>
<tr>
<td>Monoclonal IgM</td>
<td>&gt;7gm/dL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Score</th>
<th>Median survival (mon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-1 except age</td>
<td>142.5</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2 or age &gt;65</td>
<td>98.6</td>
</tr>
<tr>
<td>High</td>
<td>&gt;2</td>
<td>43.5</td>
</tr>
</tbody>
</table>

The IPSS for WM should be used only for patients who require treatment. It should not be used to determine if a patient requires treatment. The decision to treat continues to be based on clinical scenario. Serial monitoring of beta 2 microglobulin is not indicated.

Treatment of WM [47-49]

Not all patients with WM need therapy. The indications to initiate therapy are as follows:

1. Symptoms related to infiltration of bone marrow by tumour cells
   a. Peripheral blood cytopenia (Hb <10gm% or platelet <100,000cu.mm)
2. Constitutional symptoms – fever, night sweats, significant weight loss
3. Extramedullary disease, symptomatic organomegaly
4. Bulky lymphadenopathy - >5 cm in maximum diameter
5. Symptoms related to hyperviscosity – Headache, visual blurring
6. Moderate to severe immune haemolytic anemia or thrombocytopenia
7. Peripheral neuropathy
8. Symptoms related to cryoglobulinemia – Raynaud’s phenomenon, skin ulcers and necrosis, urticaria.
9. Altered coagulation parameters.
10. Nephropathy secondary to WM
11. Amyloidosis secondary to WM.
12. Relative indication: IgM >6000mg/dL even if asymptomatic*

Close observation is recommended for patients who do not fulfil the criteria for WM, and for whom laboratory evidence may be the only indicator of development of progressive disease (eg. a minor decrease in haemoglobin level with asymptomatic anemia or mild increases in IgM) or mild increase of lymphadenopathy or splenomegaly without discomfort for the patient. Treatment can be delayed in an asymptomatic patient with high serum IgM levels. *However, if the IgM is >6000mg/dL, empirical therapy may be considered even if asymptomatic to prevent hyperviscosity related tissue injury [50].

**Approach to WM [47] [51]**

<table>
<thead>
<tr>
<th>Indication to treat</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;60 yrs</td>
<td>Bortezomib-Dexa-Rituximab x 4 every 21 days followed by maintenance BDR once in 3 months for 4 cycles (1yr)</td>
</tr>
<tr>
<td>Potential auto transplant candidate</td>
<td>Bendamustine-Rituximab x 4 followed by maintenance rituximab every 3 months for 2 years</td>
</tr>
<tr>
<td>Age &gt;60 yrs</td>
<td></td>
</tr>
<tr>
<td>Relapsed WM</td>
<td></td>
</tr>
</tbody>
</table>

**Initial response > 24 months** - Repeat initial therapy
Initial response > 24 months - Alternate Rituximab containing regimen* f/b autologus stem cell transplant
* Bendamustine-Rituximab
* Fludarabine-Rituximab
* Dexamethasone-Cyclophosphamide-Rituximab
Relaps after autograft - Salvage followed by Allogeneic stem cell transplant
Response assessment in WM [52]

| CR (Complete response) | Absence of serum monoclonal IgM protein by immunofixation  
Normal serum IgM level  
Complete resolution of extramedullary disease, i.e., lymphadenopathy and splenomegaly if present at baseline  
Morphologically normal bone marrow aspirate and trephine biopsy |
|------------------------|---------------------------------------------------------------------------------------------------------------|
| VGPR (Very good partial response) | Monoclonal IgM protein is detectable  
≥90% reduction in serum IgM level from baseline  
Complete resolution of extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline  
No new signs or symptoms of active disease |
| PR (Partial response) | Monoclonal IgM protein is detectable,  
≥50% but <90% reduction in serum IgM level from baseline  
Reduction in extramedullary disease, i.e., lymphadenopathy/ splenomegaly if present at baseline  
No new signs or symptoms of active disease |
| MR (Minor response) | Monoclonal IgM protein is detectable  
≥25% but<50% reduction in serum IgM level from baseline  
No new signs or symptoms of active disease |
| SD (Stable disease) | Monoclonal IgM protein is detectable  
<25% reduction and <25% increase in serum IgM level from baseline  
No progression in extramedullary disease, i.e., lymphadenopathy/ splenomegaly  
No new signs or symptoms of active disease |
| PD (Progressive disease) | ≥25% increase in serum IgM level from lowest nadir (requires confirmation)  
and/or progression in clinical features attributable the disease |
POEMS SYNDROME

POEMS syndrome is a paraneoplastic syndrome secondary to an underlying plasma cell neoplasm. The acronym refers to several, but not all, of the features of the syndrome: polyradiculoneuropathy, organomegaly, endocrinopathy, monoclonal PCD, and skin changes.

There are three important points that relate to this memorable acronym:

1. Not all of the features within the acronym are required to make the diagnosis;
2. There are other important features not included in the POEMS acronym, including papilledema, extravascular volume overload, sclerotic bone lesions, thrombocytosis/erythrocytosis, elevated VEGF levels, a predisposition towards thrombosis, and abnormal pulmonary function tests;
3. There is a Castleman disease variant of POEMS syndrome may be associated with a clonal PCD.

Diagnosis of POEMS syndrome [53]

Any patient who presents with neuropathy and any of the following should elicit an in depth search for the diagnosis of POEMS syndrome – monoclonal protein (almost always λ), anasarca, thrombocytosis or papilledema.

The diagnosis of POEMS syndrome is based on a composite of clinical and laboratory criteria as given below. A diagnosis of POEM syndrome is confirmed when both of the mandatory criteria, one of the three major criteria, and one of the six minor criteria are present.
### Mandatory (Both needed)
1. Polyneuropathy (Typically demyelinating) – seen in all patients (peripheral, ascending, symmetrical, and affecting both sensation and motor function should be elicited)
2. Monoclonal plasma cell proliferative disorder (almost always λ)

### Major (1/3 needed)
1. Castleman disease *a*
2. Sclerotic bone disease
3. Elevated VEGF levels*

### Minor (1/6 needed)
1. Organomegaly (Hepatomegaly, Splenomegaly, lymphadenopathy)
2. Extravascular fluid overload (edema, pleural effusion, ascites)
3. Endocrinopathy *b* (adrenal, thyroid, pituitary, gonadal, parathyroid, and pancreatic)
4. Skin changes (Hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, and white nails)
5. Papilledema (seen in 1/3 of patients)
6. Thrombocytosis/polycythaemia

*VEGF levels are not available in CMC.

*a* There is a Castleman disease variant of POEMS syndrome that occurs without evidence of a clonal PCD that is not accounted for in this table. This entity should be considered separately.

*b* Because of the high prevalence of diabetes mellitus and thyroid abnormalities, this diagnosis alone is not sufficient to meet this minor criterion.

### Approach to treatment

The treatment algorithm in POEMS syndrome is based on the extent of the plasma cell infiltration. The following algorithm summarizes approach to therapy [53]
Management of POEMS syndrome with disseminated bone marrow involvement/ >2 bone lesions

Once there is disseminated bone marrow involvement or > 2 bony lesions, albeit even with a low plasma cell percentage, radiation is not expected to be curative. There are no randomized trials available that compares one line of therapy to the other in POEMS syndrome. The treatment armamentarium is borrowed from other plasma cell disorders most notably multiple myeloma and light chain amyloidosis. Myelotoxic agents like melphalan and prolonged use of lenalidomide should be avoided for upfront therapy in young and fit patients who are prospective candidates for an autologous stem cell transplantation later. Upfront autologous stem cell transplantation is an option in young and fit patients without major organ dysfunction.

Response Assessment in Poems Syndrome

The goals of treatment are twofold: to stabilize or reverse organ dysfunction and to eliminate or inactivate clonal plasma cells.
Universal response criteria have not been published. The ideal response criteria would evaluate organ response and hematologic response. Other clinicians have used serum free light chain assays to assess hematologic response. The most widely used criteria is modified from the uniform response criteria used for multiple myeloma.

Serum paraprotein levels are monitored monthly while on therapy. A full response assessment is usually performed three to six months after initiating therapy. Response to treatment is determined using a whole body fluorodeoxyglucose positron emission tomography (FDG-PET) scan, complete blood count, vascular endothelial growth factor (VEGF) level, serum protein electrophoresis with immunofixation, and 24-hour urine protein electrophoresis with immunofixation. Markers of endocrinopathy should only be tracked if they were abnormal at baseline. Either serum or plasma VEGF level can be used, but when comparing VEGF values over time, the method of VEGF measurement used for both values must be the same.

**Hematologic response**

- Complete response (CR\textsubscript{H}) – Negative bone marrow and negative immunofixation of the serum and urine. Patients are not required to have a repeat bone marrow aspirate if the baseline bone marrow was negative.

- Very good partial response (VGPR\textsubscript{H}) – A 90 percent reduction in the M-protein or immunofixation positive only as long as M-protein was at least 0.5 g/dL at baseline.

- Partial response (PR\textsubscript{H}) – A 50 percent reduction in M-protein or immunofixation positive as long as baseline M-protein was at least 1.0 g/dL.

- No response – Less than a PR\textsubscript{H}. 
VEGF response

- Complete response (CRV) – Normalization of VEGF (<87 pg/mL).
- Partial response (PRV) – Decrease of ≥50 percent (baseline must be ≥200 pg/mL).
- No response (NRV) – Less than a PRV.

Radiologic response by FDG-PET

- Complete radiologic response (CRR) – Initial FDG avidity on a baseline PET scan that disappears.
- Partial radiologic response (PRR) – Initial FDG avidity that was 50 percent improved.
- No radiologic response – Not meeting CRR or PRR.

Clinical response

A clinical response assessment incorporates information regarding peripheral neuropathy, organomegaly, papilledema, erythrocytosis, thrombocytosis, endocrinopathy, extravascular fluid overload (ascites, effusions, edema), and abnormal pulmonary function tests. There are four clinical response categories, which include clinical improvement (I_C), clinical progression (P_C), mixed clinical response (M_C), and clinical stability (S_C).
REFERENCES


31. Palumbo, A., et al., Prevention of thalidomide- and lenalidomide-


ANNEXURES
Multiple Myeloma

Name:   Age:   Gender:   MRDNumber:

FISH - del 17p, t (14; 16), t (4; 14) –

Diagnosis with subtype:

ISS:   ECOG:

Other comorbidities: DM/HTN/IHD/Other…………………………

**Tick the diagnostic criteria**

1. Clonal plasma cells ≥10% in BM or biopsy proven bony or extra medullary plasmacytoma.  
   and
2. Any one or more of the following myeloma defining events.
   a. Hypercalcemia:
   b. Renal insufficiency:
   c. Anaemia:
   d. Bone lesions:
   e. Clonal bone marrow plasma cell percentage ≥ 60%
   f. FLC ratio > 100 (involved free light chain level must be > 100 mg/L)
   g. >1 focal lesions on magnetic resonance imaging (MRI) studies (at least 5 mm in size)

**TREATMENT PLAN & STRATIFICATION. (TICK)**

1. Group 1: Transplant Eligible – No del17p
   CyBorD (4-6) -> Auto SCT -> Lenalidomide Maintenance

2. Group 2: Transplant Eligible with del17p
   CyBorD (4-6) -> Tandem auto-auto SCT -> Bortezomib + Lenalidomide Maintenance

   CTD (4-6) -> Auto SCT -> Thalidomide Maintenance

4. Group 4: Transplant Ineligible
   CyBorD (4-6) -> Bortezomib + Dexamethasone Maintenance

5. Group 5: Transplant Ineligible – with resource constraints.
   CTD (6-9) -> Thalidomide maintenance

Registrar……………………             Consultant……………………..
# MULTIPLE MYELOMA – PROGRESS SHEET

<table>
<thead>
<tr>
<th>Name:</th>
<th>Age/Sex:</th>
<th>Performance status:</th>
<th>Hosp. No.</th>
<th>Beta 2 microglobulin</th>
<th>ISS stage</th>
<th>End organ damage (at diagnosis)</th>
<th>Hb</th>
<th>Bone lesions</th>
<th>Creatinine</th>
<th>Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final diagnosis with Subtype and Staging</td>
<td>FISH panel: del 17p/TP53</td>
<td>t(14;16)</td>
<td>t(4;14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Date (MM/YYYY)
- Haemoglobin
- WBC
- Platelets
- Creatinine
- Calcium
- Albumin
- Globulin
- Ig level
- IgG
- IgA
- IgM
- SPEP (M band)
- 24 hr. urine protein
- Urine BJP
- Immunofixation electrophoresis
- BM aspiration (% plasma cells)
- BM trephine
- FISH
- Beta 2 microglobulin
- Skeletal survey
- FLC (K/L)
- ISS
- LDH
- Treatment Regimen
- Radiation (site & dose)
- Stabilization procedure
- Bisphosphonate
- Status of disease
  - (sCR/CR/VGPR/PR/Relapse)
- Auto PBSCT
- Allo PBSCT
- Infective episodes /6 m
- Total months of treatment completed
- Significant side effects
Cyclophosphamide-Bortezomib-Dexamethasone
(CyBorD Regimen)

INDICATION
A. Initial therapy for young patients with myeloma

TREATMENT PLAN
Tab. Cyclophosphamide 300mg/ m²/day orally days 1, 8, 15, 22,
Inj. Bortezomib* 1.5 mg/ m²/day s/c days 1, 8, 15, 22,
Tab. Dexamethasone 40 mg (p/o or IV)
   a) For Cycles 1 and 2: Day 1 – 4, Day 9-12 and Day 17 to 20
   b) For cycle 3 and 4: 40mg po once a week.
Repeat each cycle of CyBorD once every 4 weekly intervals for 4 cycles.
*Bortezomib 1.3 mg/ m²/day - Subcutaneously on days 1, 4, 8, 11 in the first cycle in case of renal failure, large plasmacytoma causing compressive symptoms.

PROPHYLAXIS
Tab Seprtan DS 1 BD 2/7 for Cycles 1 and 2 (Patient on High dose Dexamethasone)
Tab Acyclovir 400 mg BD* during and upto 6 months after last dose of Bortezomib.
(*Full dose if CrCl >25, 200mg BD if CrCl 10-25, 200mg OD if CrCl <10, 200mg BD with dose after dialysis if on dialysis)

SUPPORTIVE CARE
Zoledronic acid 4mg* in 100ml NS over 20 minutes once a month for first year, then once in 3 months during the 2nd year. (*4mg if CrCl >60, 3.5mg if CrCl 50-60, 3.3mg if CrCl 40-49, 3mg if CrCl 30-39, contraindicated if CrCl <30)

REFERENCE
DEPARTMENT OF HAEMATOLOGY
Christian Medical College, Vellore, India

Bortezomib-Lenalidomide-Dexamethasone
(VLD Regimen)

INDICATION
A. Initial therapy for young patients with myeloma

TREATMENT PLAN
1. Tab. Lenalidomide 10-25 mg Oral Days 1-14
2. Inj. Bortezomib 1.3 mg/m²/day s/c Days 1, 4, 8, 11
3. Tab. Dexamethasone 40 mg Oral Days 1, 8, 15
Repeat each cycle of VLD once every 3 weekly intervals for 4 cycles.

SUPPORTIVE CARE
Inj. Zoledronate 4mg IV once a month for one year, then once in 3 monthly during second year (If not contraindicated)

Dose modification for Lenalidomide based on renal failure

<table>
<thead>
<tr>
<th>Cr Cl &gt;60</th>
<th>30-59</th>
<th>15-29</th>
<th>&lt;15 / on dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>15mg OD</td>
<td>10mg OD</td>
<td>15mg on alt. days</td>
<td>5mg OD</td>
</tr>
</tbody>
</table>

PROPHYLAXIS
Tab Acyclovir 400 mg BD during and upto 6 months after completions of the 4 cycles

REFERENCE
Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood 2012, 119: 4375-4382
DEPARTMENT OF HAEMATOLOGY  
Christian Medical College, Vellore, India

Bortezomib-Thalidomide Dexamethasone  
(VTD Regimen)

INDICATION  
A. Initial therapy for young patients with myeloma  
B. Therapy for refractory and relapsed myeloma

TREATMENT PLAN  
1. Cap. Thalidomide 100mg/day orally Days 1-21  
2. Inj. Bortezomib 1.3 mg/m^2/day s/c Days 1, 4, 8, 11  
3. Tab. Dexamethasone 40 mg orally Day 1 – 4, Day 9-12  
Repeat each cycle of VTD once every 3 weekly intervals for 4 cycles.

PROPHYLAXIS  
Tab Septran DS 1 BD 2/7  
Tab Acyclovir 400 mg BD during and upto 6 months after completions of the 4 cycles

SUPPORTIVE CARE  
Zoledronic acid 4mg* in 100ml NS over 20 minutes once a month for first year, then once in 3 months during the 2nd year. (*4mg if CrCl >60, 3.5mg if CrCl 50-60, 3.3mg if CrCl 40-49, 3mg if CrCl 30-39, contraindicated if CrCl <30)

REFERENCE  
VTD (Velcade, Thalidomide, Dexamethasone) as Primary Therapy for Newly-Diagnosed Multiple Myeloma. Blood 2004 104:210
DEPARTMENT OF HAEMATOLOGY
Christian Medical College, Vellore, India

CTD Regimen
Induction regimen for MM in resource poor settings

REGIMEN
1. Cyclophosphamide 300mg/m² Oral Days 1,8,15,22
2. Dexamethasone 40mg Oral Days 1,8,15,22
3. Thalidomide 100mg Oral Day 1-28

4-6 cycles at an interval of 28 days.

SUPPORTIVE CARE
1. Zoledronic acid 4mg in 100ml NS over 20 minutes once a month for first year, then once in 3 months during the 2nd year.
   (*4mg if CrCl >60, 3.5mg if CrCl 50-60, 3.3mg if CrCl 40-49, 3mg if CrCl 30-39, contraindicated if CrCl <30)
2. Ecospirin 75mg once a day
   - Dexamethasone dose to be reduced to 20 mg in presence of uncontrolled blood sugar / blood pressure / infections.
   - Cyclophosphamide dose to be reduced by 25%
     a. In presence of ANC < 1 x 10⁹ /L
     b. Neutropenic infection >/= grade 3
   - Thalidomide dose to be started with 50 mg/day and subsequently increased by 50 mg/ week to a maximum of 300 mg/ day.

Neurotoxicity of Grade 2 requires dose reduction and if it persists after dose reduction, then to stop Thalidomide and continue only CD.

REFERENCE
Charalampia Kyriakou et al, British Journal of Haematology; 129; 2005; 763-770
### MPT Regimen

**REGIMEN**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melphalan</td>
<td>4mg/m²</td>
<td>Oral</td>
<td>Days 1-7</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>40mg/m²</td>
<td>Oral</td>
<td>Days 1-7</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>100mg</td>
<td>Oral</td>
<td>Day 1-28</td>
</tr>
</tbody>
</table>

6 cycles at an interval of 28 days
Followed by Thalidomide Maintenance

**SUPPORTIVE CARE**

**Zoledronic acid** 4mg in 100ml NS over 20 minutes once a month for first year, then once in 3 months during the 2nd year.

(*)4mg if CrCl >60, 3.5mg if CrCl 50-60, 3.3mg if CrCl 40-49, 3mg if CrCl 30-39, contraindicated if CrCl <30

**Ecospirin** 75mg once a day

- Thalidomide dose to be started with 50 mg/day and subsequently increased to 100mg

Neurotoxicity of Grade 2 requires dose reduction by 50% and if it persists after dose reduction, then to stop Thalidomide and continue only MP

**REFERENCE**

Oral Melphalan and prednisone chemotherapy plus thalidomide compared with Melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Palumbo et al, Lancet 2006, 367; 825-831
DEPARTMENT OF HAEMATOLOGY  
Christian Medical College, Vellore, India

Lenalidomide-Dexamethasone  
(Rd Regimen)

TREATMENT PLAN
1. Tab. Lenalidomide  10-15mg  Oral  Days 1-21  
2. Tab. Dexamethasone  40 mg  Oral  Days 1-4, 9-12, 17-20
Repeat each cycle of RD once every 4 weekly intervals for 4 cycles.

SUPPORTIVE CARE
Inj. Zoledronate 4mg IV once a month for one year, then once in 3 monthly during second year
(If not contraindicated) (*4mg if CrCl >60, 3.5mg if CrCl 50-60, 3.3mg if CrCl 40-49, 3mg if CrCl 30-39, contraindicated if CrCl <30)

Dose modification for Lenalidomide based on renal failure

<table>
<thead>
<tr>
<th>Cr Cl</th>
<th>30-59</th>
<th>15-29</th>
<th>&lt;15 / on dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>15mg OD</td>
<td>10mg OD</td>
<td>5mg OD</td>
</tr>
<tr>
<td>15-29</td>
<td>10mg OD</td>
<td>15mg on alt. days</td>
<td>5mg OD</td>
</tr>
</tbody>
</table>

REFERENCE

Lenalidomide plus Dexamethasone for Relapsed or Refractory Multiple Myeloma.  
Dimopoulos M et al NEJM 2007; 357: 2123-32
Pomalidomide-Dexamethasone
(PomDex Regimen)

INDICATIONS
1. Myeloma refractory to Lenalidomide and Bortezomib
2. Myeloma relapsed <1 year after autologous SCT.

TREATMENT PLAN
1. Tab. Pomalidomide 4mg Oral Days 1-21/28
2. Tab. Dexamethasone 40 mg* Oral Days 1, 8, 15, 22
   *20mg if >75 years of age
Repeat each cycle of Pom-Dex once every 4 weekly till progression of disease.
All patients to be on Ecospirin 75 mg as thromboprophylaxis.

SUPPORTIVE CARE
Inj. Zoledronate 4mg IV once a month for one year, then once in 3 monthly
during second year
(If not contraindicated) (*4mg if CrCl >60, 3.5mg if CrCl 50-60, 3.3mg if CrCl
40-49, 3mg if CrCl 30-39, contraindicated if CrCl <30)

No dose modification is required for Pomalidomide in renal and hepatic
failure. However if hepatic dysfunction develops/worsens while on Pomalidomide, therapy has to be temporarily withheld and restarted at low doses once LFT normalizes. In patients who are on haemodialysis, Pomalidomide has to be administered after completion of that respective day’s dialysis.

REFERENCE
INDICATIONS
1. Myeloma refractory to Lenalidomide and Bortezomib
2. Myeloma relapsed <1 year after autologous SCT.

TREATMENT PLAN
1. Tab. Pomalidomide 4mg Oral Days 1-21/28
2. Inj. Bortezomib** 1.3 mg/ m2 /d s/c Days 1, 4,8,11
3. Tab. Dexamethasone 40 mg* Oral Days 1, 8, 15, 22
   *20mg if >75 years of age
Repeat each cycle of PVD once every 4 weekly for 8 weeks, then to continue Pomalidomide till progression.
All patients to be on Ecospirin 75 mg as thromboprophylaxis.

SUPPORTIVE CARE
Inj. Zoledronate 4mg IV once a month for one year, then once in 3 monthly during second year
(If not contraindicated) (*4mg if CrCl >60, 3.5mg if CrCl 50-60, 3.3mg if CrCl 40-49, 3mg if CrCl 30-39, contraindicated if CrCl <30)

No dose modification is required for Pomalidomide in renal and hepatic failure.
However if hepatic dysfunction develops/worsens while on Pomalidomide, therapy has to be temporarily withheld and restarted at low doses once LFT normalizes. In patients who are on haemodialysis, Pomalidomide has to be administered after completion of that respective day’s dialysis.

REFERENCE
1. Pomalidomide, Bortezomib, Dexamethasone (PVD) for patients with relapsed Lenalidomide refractory multiple myeloma. ASH abstract Blood 2014, 124:304
DEPARTMENT OF HAEMATOLOGY
Christian Medical College, Vellore, India

Carfilzomib- Lenalidomide- Dexamethasone
(KRd Regimen)

INDICATIONS
Myeloma relapsed after 2-3 prior lines of therapy if
1. There was no progression while on bortezomib therapy
2. There was no adverse effects/ progression during first 3 months while on Lenalidomide.

TREATMENT PLAN
1. Inj. Carfilzomib 27mg/m² IV (10 mnts infusion) Days 1, 2, 8, 9, 15, 16 (Cycles 1-12)
   (*20mg/m² for day 1, 2 of cycle 1) Days 1, 2, 15, 16 (Cycles 13-18)
2. Tab. Lenalidomide (10-25mg) orally Days 1-21 in 1 28 day cycle.
3. Tab. Dexamethasone 40 mg* orally Days 1, 8, 15, 22
   *20mg if >75 years of age

Repeat each cycle of KRd once every 4 weeks.
Carfilzomib is stopped after 18 cycles, Lenalidomide and Dexamethasone to be continued till progression/tolerated.
All patients to be on Ecospirin 75 mg as thromboprophylaxis and on Acyclovir as antiviral prophylaxis.

CARFILZOMIB INFUSION PROTOCOL
Carfilzomib in Cycle 1 will be initiated at 20 mg/m² on Days 1 and 2 and escalated to 27 mg/m² for Days 8, 9, 15, and 16 of Cycle 1 and for the rest of the treatment.

Carfilzomib for Injection is supplied as a lyophilized parenteral product in single-use vials of 60mg strength. The lyophilized product is reconstituted with water for Injection to a final carfilzomib concentration of 2.0 mg/mL prior to administration. Reconstituted carfilzomib can be stored at 2-8 degree Celsius for 24 hrs.

Carfilzomib will be given as an IV infusion over approximately 10 minutes.

The dose will be calculated using the subject’s actual BSA at baseline. Subjects with a BSA > 2.2 m² will receive a dose based upon a 2.2 m² BSA. Dose adjustments do not need to be made for weight gains/losses of ≤ 20%.
HYDRATION

**Oral hydration:** To be started 48 hrs prior to starting Carfilzomib

At least 48 hours before Cycle 1 Day 1, oral hydration should be given as follows: 30 mL/kg/day (approximately 6 to 8 cups of liquid per day) continuing up to the time of treatment. Subject compliance must be assessed before initiating treatment, which is to be delayed if oral hydration is not adequate. Oral hydration may be continued in Cycle 2 and beyond at the physician’s discretion.

**IV hydration**

IV hydration will be given immediately prior to carfilzomib during Cycle 1, and at the physician’s discretion in Cycle 2. This will consist of 250 to 500 mL normal saline or other appropriate IV fluid. The goal of the hydration program is to maintain urine output ≥ 2 L/day). Subjects should be monitored periodically during this period for evidence of fluid overload. Post dose IV hydration (between 250 mL and 500 mL normal saline or other appropriate IV fluid formulation) should be given.

**DOSE MODIFICATIONS IN CASE OF ADVERSE EVENTS**

**Cytopenia**

<table>
<thead>
<tr>
<th>Platelet counts</th>
<th>Lenalidomide</th>
<th>Carfilzomib</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30,000</td>
<td>Hold dose till more than 30,000, start at lower dose and then escalate</td>
<td>10000-30000 without bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;10,000 or bleeding</td>
</tr>
</tbody>
</table>

**Neutrophil count**

<table>
<thead>
<tr>
<th>Neutrophil count</th>
<th>Lenalidomide</th>
<th>Carfilzomib</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000</td>
<td>Hold dose, start G-CSF and start full dose once ANC &gt;1000.</td>
<td>500-1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;500</td>
</tr>
</tbody>
</table>

If there is persistent cytopenia, dose has to be reduced by 1 level as given below.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting dose</th>
<th>Level-1</th>
<th>Level-2</th>
<th>Level-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide</td>
<td>25mg</td>
<td>15mg</td>
<td>10mg</td>
<td>5mg</td>
</tr>
</tbody>
</table>
### Renal failure

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Carfilzomib</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl 15-29</td>
<td>Full dose</td>
</tr>
<tr>
<td>CrCl &lt;15</td>
<td>Hold dose and restart at full dose once CrCl &gt;15. <em>In case patient is on dialysis, the maximum dose should be 20mg mg/m² and has to be given after dialysis.</em></td>
</tr>
</tbody>
</table>

Renal dose modification of Lenalidomide, please refer main text.

**REFERENCE**

DEPARTMENT OF HAEMATOLOGY
Christian Medical College, Vellore, India

Carfilzomib - Dexamethasone
(Kd – Regimen)

INDICATIONS
Relapsed & Refractory Myeloma after 2-3 prior lines of therapy

TREATMENT PLAN
1. Inj. Carfilzomib  20mg/m2 IV (30 mnts infusion)  Days 1, 2 of cycle 1,
                   56mg/m2 IV (30 mnts infusion)  Days 8, 9, 15, 16, of cycle 1.
                   56 mg/m2IV (30 mnts infusion) Days 1, 2, 8, 9, 15, 16
                      from cycle 2
2. Tab. Dexamethasone  20 mg* Oral/IV  Days 1, 2, 8, 9, 15, 16,
                          22, 23

Repeat each cycle of Kd once every 4 weeks.
All patients to be on Ecospirin 75 mg as thromboprophylaxis and on Acyclovir as antiviral prophylaxis. In case of previous VTE, LMWH to be given as prophylaxis.

REFERENCE
Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): randomised, phase 3, open-label, multicentre study.
Lancet Oncol 2016; 17: 27–38
Panobinostat – Bortezomib- Dexamethasone (IBD – Regimen)

INDICATIONS
Relapsed & Refractory Myeloma after at least 2 prior lines of therapy

TREATMENT PLAN:
Cycles 1-8
1. Cap. Panobinostat 20 mg Days 1, 3, 5, 8, 10 and 12
2. Inj. Bortezomib 1.3mg/m2 s.c Days 1, 4, 8, 11
3. Tab. Dexamethasone 20 mg Days 1, 2, 4, 5, 8, 9, 11, 12

Cycles 9 onwards
1. Cap. Panobinostat 20 mg Days 1, 3, 5, 8, 10 and 12
2. Inj. Bortezomib 1.3mg/m2 s.c Days 1, 8
3. Tab. Dexamethasone 20 mg Days 1, 2, 8, 9

Repeat each cycle of IBD once every 3 weeks.
All patients to be on Ecospirin 75 mg as thromboprophylaxis and on Acyclovir as antiviral prophylaxis. In case of previous VTE, LMWH to be given as prophylaxis.

PRECAUTIONS:
1. ANC to be >1000, PC to be >100000 before starting Panobinostat
2. ECG - QTc to be <480 msec to start Panobinostat, monitor for QTc prolongation
   The dose should be omitted, if QTc is ≥ 480 msec or above 60 msec from baseline.
   If QT prolongation is resolved within 7 days, resume treatment at prior dose for initial occurrence or at reduced dose if QT prolongation is recurrent.
   If QT prolongation is unresolved within 7 days, treatment should be discontinued.
   If any QTc is >500 msec, therapy should be permanently discontinued
3. Reduce dose of Panobinostat by 5mg if persistent cytopenia
4. Grade IV diarrhoea despite on antidiarrheal medications – To stop Panobinostat
5. No dose adjustment for Panobinostat in renal failure
6. In liver dysfunction – no data on dose modifications, to monitor for side effects more closely
7. Close monitoring in >65 yr. old & start at low dose (10mg) if >75 yr. old

REFERENCE:
Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial (PANORAMA 1).

Lancet Oncol 2014;15: 1195–206
Daratumumab Monotherapy

INDICATIONS
Heavily pre-treated relapsed or refractory myeloma

TREATMENT PLAN
Inj. Daratumumab 16mg/kg IV weekly for 8 weeks, then
once every 2 weeks for 16 weeks, then
once every 4 weeks thereafter.
Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week after starting Daratumumab and continue for 3 months following treatment.
Ecospirin or low molecular weight heparin to be given as anti-thrombotic prophylaxis to all patients.
Blood pressure to be monitored before and after all Daratumumab infusions.
Daratumumab should be held if there is any grade IV haematological toxicity or grade III thrombocytopenia with bleeding.
For details and guidelines for Daratumumab infusion, please refer to the document “Daratumumab infusion protocol”

REFERENCE
Daratumumab-Lenalidomide-Dexamethasone

INDICATIONS
1. Relapsed and refractory myeloma.
2. There was no adverse effects/progression while on Lenalidomide.

TREATMENT PLAN
1. **Inj. Daratumumab 16mg/kg IV Days 1, 8, 15, 22 (weekly) in Cycles 1-2**
   - Days 1 & 15 (once in 2 weeks) in Cycle 3-6
   - Days 1 of each cycle from cycle 7.
2. **Tab. Lenalidomide (10-25mg) orally Days 1-21 in 1 28 day cycle.**
3. **Tab. Dexamethasone 40 mg* orally Days 1, 8, 15, 22**
   - *20mg if >75 years of age or if BMI <18.5

If the Dexamethasone administration falls on the day of Daratumumab infusion, 50% of dose (i.e. 20mg) is given as IV as a premedication to Daratumumab before the infusion and the rest will be given orally on the next day. In all other days, Dexamethasone will be administered as a single oral dose.

Repeat each cycle once every 4 weeks till progression or tolerated.

Initiate **antiviral prophylaxis** to prevent herpes zoster reactivation within 1 week after starting Daratumumab and continue for 3 months following treatment

**Ecospirin or low molecular weight heparin** to be given as anti-thrombotic prophylaxis to all patients.

Blood pressure to be monitored before and after all Daratumumab infusions.

On daratumumab infusion days, lenalidomide will be administered at the same time as the premeditations. The daratumumab infusion should begin approximately 1 hour after the lenalidomide administration.

Daratumumab should be held if there is any grade IV haematological toxicity or grade III thrombocytopenia with bleeding.

*For details and guidelines for Daratumumab infusion, please refer to the document “Daratumumab infusion protocol”*

REFERENCE
DEPARTMENT OF HAEMATOLOGY
Christian Medical College, Vellore, India

Daratumumab-Bortezomib-Dexamethasone
(DVd Regimen)

INDICATIONS
1. Relapsed and refractory myeloma.
2. There was no adverse effects/progression while on Bortezomib

TREATMENT PLAN
(Cycles 1-8 are 21 day cycles, Cycles 9 and onwards are 28 day cycles).
1. **Inj. Daratumumab 16mg/kg IV Weekly in cycles 1-3**
   - Day 1 in each cycle from cycle 4-9
   - Every 4 weeks thereafter.
2. **Inj. Bortezomib 1.3mg.m\(^2\) s/c Days 1, 4, 8, 11**
3. **Tab. Dexamethasone 40 mg* orally Days 1, 2, 4, 5, 8, 9, 11, 12**
   - *20mg if >75 years of age or if BMI <18.5

If the Dexamethasone administration falls on the day of Daratumumab infusion, 50% of dose (i.e. 20mg) is given as IV as a premedication to Daratumumab before the infusion and the rest will be given orally on the next day. In all other days, Dexamethasone will be administered as a single oral dose.

Initiate **antiviral prophylaxis** to prevent herpes zoster reactivation within 1 week after starting Daratumumab and continue for 3 months following treatment

**Ecospirin or low molecular weight heparin** to be given as anti-thrombotic prophylaxis to all patients.

Blood pressure to be monitored before and after all Daratumumab infusions.

On daratumumab infusion days, lenalidomide will be administered at the same time as the premeditations. The daratumumab infusion should begin approximately 1 hour after the lenalidomide administration.

Daratumumab should be held if there is any grade IV haematological toxicity or grade III thrombocytopenia with bleeding.

For details and guidelines for Daratumumab infusion, please refer to the document “Daratumumab infusion protocol”

REFERENCE
DEPARTMENT OF HAEMATOLOGY
Christian Medical College, Vellore, India

DARATUMUMAB INFUSION PROTOCOL.

DOSE
Recommended dose is 16 mg/kg

INFUSION PROTOCOL.

Premeditations
1. Inj. Methylprednisolone 100mg/Inj. Dexamethasone 20mg IV with first
dose. (In case of subsequent infusions MP can be reduced to 60mg / dexamethasone can be given orally).
2. Inj. Paracetamol 650-1000mg IV Stat

Daratumumab infusion

<table>
<thead>
<tr>
<th></th>
<th>Dilution volume</th>
<th>Initial rate (1st hr.)</th>
<th>Rate increment</th>
<th>Maximum rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>First infusion</td>
<td>1000ml</td>
<td>50ml/hr.</td>
<td>50ml/hr. every hr.</td>
<td>200ml/hr.</td>
</tr>
<tr>
<td>Second infusion</td>
<td>500ml</td>
<td>50ml/hr.</td>
<td>50ml/hr. every hr.</td>
<td>200ml/hr.</td>
</tr>
<tr>
<td>Subsequent infusions</td>
<td>500ml</td>
<td>100ml/hr.</td>
<td>50ml/hr. every hr.</td>
<td>200ml/hr.</td>
</tr>
</tbody>
</table>

POST-INFUSION MEDICATION

Monotherapy
Oral corticosteroid (20 mg methylprednisolone or equivalent dose of an intermediate acting or long-acting corticosteroid in accordance with local standards) on each of the 2 days following all Daratumumab infusions (beginning the day after the infusion).

Combination therapy
Low-dose oral methylprednisolone (≤ 20 mg) or equivalent, the day after the Daratumumab infusion. However, if a background regimen-specific corticosteroid (e.g. dexamethasone) is administered the day after the Daratumumab infusion, additional post-infusion medications may not be needed.

In addition, for any patients with a history of chronic obstructive pulmonary disease, consider prescribing post-infusion medications such as short and long-acting bronchodilators, and inhaled corticosteroids. Following the first
four infusions, if the patient experiences no major infusion reactions, these additional inhaled post-infusion medications may be discontinued.

**Prophylaxis for Herpes Zoster Reactivation**

Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week after starting Daratumumab and continue for 3 months following treatment.

**ADMINISTRATION**

**Available vial strength**

100 mg/5 mL solution in a single-dose vial or 400 mg/20 mL solution in a single-dose vial.

**Preparation**

Calculate the dose (mg), total volume (mL) of DARATUMUMAB solution required and the number of DARATUMUMAB vials needed based on patient actual body weight.

- Check that the DARATUMUMAB solution is colourless to pale yellow. Do not use if opaque particles, discoloration or other foreign particles are present.

- Remove a volume of 0.9% Sodium Chloride Injection, USP from the infusion bag/container that is equal to the required volume of DARATUMUMAB solution.

- Withdraw the necessary amount of DARATUMUMAB solution and dilute to the appropriate volume by adding to the infusion bag/container containing 0.9% Sodium Chloride Injection. Infusion bags/containers must be made of either polyvinylchlordie (PVC), polypropylene (PP), polyethylene (PE) or polyolefin blend (PP+PE). Dilute under appropriate aseptic conditions. Discard any unused portion left in the vial.

- Gently invert the bag/container to mix the solution. Do not shake.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. **The diluted solution may develop very small, translucent to white proteinaceous particles, as daratumumab is a protein.** Do not use if visibly opaque particles, discoloration or foreign particles are observed.

- Since DARATUMUMAB does not contain a preservative, administer the diluted solution immediately at room temperature 15°C–25°C (59°F–77°F) and in room light.

Diluted solution may be kept at room temperature for a maximum of 15 hours (including infusion time) or up to 24 hours at refrigerated conditions 2°C – 8°C (36°F–46°F) and protected from light. Do not freeze.

**REFERENCE**
INDICATIONS
1. Relapsed/refractory multiple myeloma

CHEMOTHERAPY PROTOCOL
3. Tab. Dexamethasone 40mg once a day orally (D1-D4)
4. Tab. Thalidomide 100mg once a day orally daily
5. Inj. Cisplatin 10mg/m2/day continuous infusion IV (D1-D4)
6. Inj. Etoposide 40mg/m2/day continuous infusion IV (D1-D4)
7. Inj. Cyclophosphamide 400mg/m2/day continuous infusion IV (D1-D4)
8. Inj. Doxorubicin 10mg/m2/day continuous infusion IV (D1-D4)
9. Inj. Bortezomib 1mg/m2 s/c Day 1, 4, 8, 11.

(Daily dose of Cisplatin, cyclophosphamide and Etoposide to be combined in a 1litre 0.9% NS bag and infused over 24 hours, Doxorubicin in 100ml of 0.9% NS and infused over 24 hours)

*Cycle Frequency: every 4 to 6 weeks. 2 to 6 cycles in total.
*Delay subsequent cycles until neutrophils >1 x 10⁹ /L & platelets >100 x 10⁹ /L.

REFERENCE
VDTPACE as Salvage therapy for heavily pre-treated MM patients, November 15, 2013; Blood: 122 (21)
DEPARTMENT OF HAEMATOLOGY
Christian Medical College, Vellore, India

DCEP Regimen

INDICATIONS
Relapsed/refractory multiple myeloma

CHEMOTHERAPY PROTOCOL.
1. Tab. Dexamethasone 40mg once a day orally (D1-D4)
2. Inj. Cisplatin 15mg/m2/day continuous infusion IV (D1-D4)
3. Inj. Etoposide 40mg/m2/day continuous infusion IV (D1-D4)
4. Inj. Cyclophosphamide 400mg/m2/day continuous infusion IV (D1-D4)

(Daily dose of Cisplatin, cyclophosphamide and Etoposide to be combined in a 1 litre 0.9% NS bag and infused over 24 hours)

*Cycle Frequency: every 4 weeks. 2 to 6 cycles in total.
*Delay subsequent cycles until neutrophils >1 x 10^9/L & platelets >100 x 10^9/L.

REFERENCE
DCEP for relapsed or refractory multiple myeloma after therapy with novel agents, Ann Hematol. 2014 Jan; 93 (1):99-105
DEPARTMENT OF HAEMATOLOGY
Christian Medical College, Vellore, India

PEG-LIPO-DOXO + LENALIDOMIDE Regimen

INDICATIONS
Relapsed/refractory multiple myeloma

CHEMOTHERAPY PROTOCOL.
1. Inj. Pegylated liposomal Doxorubicin 40 mg/m²  IV  Day 1
2. Inj. Vincristine 2mg  IV  Day 1
3. Tab. Lenalidomide 10 mg daily*  PO  Days 1-21
4. Tab. Dexamethasone 40 mg daily  PO  Days 1 - 4

Repeat each cycle at 28 day intervals x 4 cycles

*increase by 5 mg at each cycle to a maximum of 25 mg /day as per the tolerance and WBC count.

REFERENCE
Lenalidomide and pegylated liposomal doxorubicin based chemotherapy for relapsed or refractory multiple myeloma: safety and efficacy. Annals of Oncology 17: 1766–1771, 2006
DEPARTMENT OF HAEMATOLOGY
Christian Medical College, Vellore, India

Bendamustine-Bortezomib- Dexamethasone
(BBD Regimen)

INDICATIONS
Relapsed/refractory multiple myeloma

CHEMOTHERAPY PROTOCOL.
1. **Inj. Bendamustine** 70 mg/m² IV Day 1 & 4
2. **Inj. Bortezomib** 1.3 mg/m² s/c Days 1, 4, 8, 11
3. **Tab. Dexamethasone** 20 mg daily PO Days 1, 4, 8, 11

Full dose of Bendamustine can be given if creatinine clearance is >10ml/min. However there is no data available on the dose if it is <10ml/min.

Repeat each cycle at 28 day intervals upto 8 cycles

REFERENCES
*Bendamustine-Bortezomib-Dexamethasone is an active and well tolerated regimen in patients with relapsed or refractory multiple myeloma. Blood-2013-08-521468*
# CHEMO MOBILISATION OF PERIPHERAL BLOOD STEM CELLS

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Ht</th>
<th>Sex</th>
<th>Wt</th>
<th>Hosp No</th>
<th>BSA</th>
<th>Diagnosis</th>
</tr>
</thead>
</table>

**Day 1:**
- **Inj.** Cyclophosphamide 4 grams/m² in 500ml Normal saline over 90 minutes
- **Dose:**
  - Hydration 3L/m² with NS/DNS to start two hours prior to Cyclophosphamide
  - To check electrolyte twice daily during hydration
- **Inj.** Mesna 4 grams/m² in 4 divided doses over 24 hrs starting with Cyclophosphamide
- **Dose:**

**Day 4:**
- **Inj.** G-CSF 10 mcg/Kg in divided doses

**Day 11:**
- Check peripheral blood CD34 count and decide on PBSC harvest

To check blood counts daily after initiation of G-CSF.

Alternate peripheral blood CD34 to be done on alternate days once ANC >1000.

Do apheresis once P.B CD34 >10-20%.

# REFERENCE


Registrar: -------------------------------
Consultant: -------------------------------
# AUTOLOGOUS PBSCT SCHEDULE FOR MULTIPLE MYELOMA

<table>
<thead>
<tr>
<th>Name</th>
<th>Hospital number</th>
<th>Blood group:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age/Gender</th>
<th>Weight:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Creat. clearance</th>
<th>Height:</th>
<th>BSA:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Conditioning regimen*

<table>
<thead>
<tr>
<th>Date</th>
<th>Time:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Melphalan**: 200 mg/m²

**DOSE**: ______mg

### PRE-HYDRATION:

NS 2L in 2 hours prior to Melphalan. Give Furosemide to maintain adequate urine output.

## Autologous PBSC INFUSION

<table>
<thead>
<tr>
<th>Date :</th>
<th>Time*** : to________</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Volume**: _____ml

**CD34**: _____x10⁹/kg

### For cryopreserved stem cells

**Total No. of bags**

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Bags</th>
<th>Day 2</th>
<th>Bags</th>
<th>Day 3</th>
<th>Bags</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Melphalan dose modifications:

- Creat clearance >60ml/min : 200 mg/m²
- Creat clearance <60ml/min : 140 mg/m²
- On dialysis : 70 mg/m² IV on day -2, day -1

### Stem cell infusion:

- 12 hrs after IV Melphalan if CrCl >60ml/min
- 24 hrs after IV Melphalan if CrCl <60ml/min
- In patients on dialysis stem cell infusion should be preceded by dialysis 24-36 hours after the melphalan administration.

* During the infusion of melphalan, it is mandatory that patient chews/sucks ice chips that can act as local cryotherapy which helps in reducing the severity of mucositis. This has to be started 5 minutes before melphalan administration and has to be continued for 15 minutes after the end of melphalan administration.

Supportive therapy: **G-CSF 5mcg/kg** s/c once a day from day +7 till ANC
>1500.
Prophylactic antimicrobials: **Acyclovir 400mg twice a day** from day +1 to day+ 180 (upto day +100 in patients who did not get Bortezomib), **Fluconazole 6mg/kg once a day** from day +1 till engraftment.

**REFERENCES**
1. Moreau et al, IFM 9502 trial, Blood 2002 99:731-735

Registrar: Dr.

Consultant: Dr.
**DEPARTMENT OF HAEMATOLOGY**
Christian Medical College, Vellore, India

**Bortezomib-Dexamethasone-Rituximab**
(BDR Regimen)

**INDICATION**
Initial therapy for young patients with Waldenstrom’s macroglobulinemia.

**TREATMENT PLAN**
1. **Inj. Bortezomib** 1.3 mg/m²/day s/c Days 1, 4, 8, 11
2. **Tab. Dexamethasone** 40 mg (p/o or IV) Days 1, 4, 8, 11
3. **Inj. Rituximab** 375mg/m² IV Day 11

**INDUCTION**
Repeat each cycle of BDR once every 3 weekly intervals for 4 cycles.

**MAINTENANCE**
After 12 months of completion of induction therapy, maintenance therapy to be given with BDR repeated for 4 cycles at 12 weeks interval.

**PROPHYLAXIS**
Tab **Septran DS** 1 BD 2/7 for Cycles 1 and 2 (Patient on High dose Dexamethasone)

Tab **Acyclovir 400 mg BD** during and upto 6 months after last dose of Bortezomib.

(*Full dose if CrCl >25, 200mg BD if CrCl 10-25, 200mg OD if CrCl <10, 200mg BD with dose after dialysis if on dialysis)

**REFERENCES**
1. Long-Term Outcome of a Prospective Study of Bortezomib, Dexamethasone and Rituximab (BDR) in Previously Untreated, Symptomatic Patients with Waldenstrom’s Macroglobulinemia. Blood 2015 126:1833
INDICATION
Initial therapy for elderly patients with Waldenstrom’s macroglobulinemia.

TREATMENT PLAN
1. **Inj. Bendamustine 90/ m² IV over 30 minutes Days 1 & 2**
2. **Inj. Rituximab 375mg/m² IV Day 1**

INDUCTION
Repeat each cycle of BR once every 4 weekly intervals for 4 cycles.

MAINTENANCE
Rituximab 375mg/m² IV once in 3 months for 2 years (8 doses)

PROPHYLAXIS
Tab *Acyclovir 400 mg BD* during and upto 6 months after last dose of Bortezomib.

(*Full dose if CrCl >25, 200mg BD if CrCl 10-25, 200mg OD if CrCl <10, 200mg BD with dose after dialysis if on dialysis)

REFERENCE
DEPARTMENT OF HAEMATOLOGY
Christian Medical College, Vellore, India

Dexamethasone- Rituximab – Cyclophosphamide
(DRC Regimen)

INDICATION
Salvage regimen in Waldenstrom’s macroglobulinemia.

TREATMENT PLAN
1. **Inj. Dexamethasone** 20mg IV Day 1
2. **Inj. Rituximab** 375mg/m² IV Day 1
3. **Tab. Cyclophosphamide** 100 mg/m² PO BD Days 1-5

INDUCTION
Repeat each cycle of DRC once every 3 weekly intervals for 6 cycles.

REFERENCE
DEPARTMENT OF HAEMATOLOGY
Christian Medical College, Vellore, India

Fludarabine- Rituximab
(FR Regimen)

INDICATION
Salvage regimen in Waldenstrom’s macroglobulinemia.

TREATMENT PLAN
1. **Inj. Rituximab** 375mg/m² IV on first day of weeks 1, 2, 3, 4, 17, 18, 30, 31 (8 doses)
2. **Inj. Fludarabine** 25 mg/m² IV for 5 days of weeks 5, 9, 13, 19, 23, 27. (6 cycles)

REFERENCE
Long term outcomes to fludarabine and rituximab in Waldenstrom’s macroglobulinemia. Blood 113(16), 3673-3678.