Multiple Myeloma: Treatment Options for Newly Diagnosed Patients in Bangladesh Perspective

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Treatment of multiple myeloma, a plasma cell malignancy, has been changed in last decades. The definition, staging and response to treatment have been standardized. Thalidomide, lenalidomide and bortezomib the three new drugs recently available in Bangladesh. These drugs and zoledronic acid should be incorporated into the treatment plan of newly diagnosed or relapsed patients. Economic consideration should be sought before initiation of these new treatments. Complication of myeloma should be treated along with the disease. Lack of bone marrow transplant (BMT) is still the main drawback for the optimum treatment option here in Bangladesh.

Key words: Multiple myeloma, Bangladesh, thalidomide, lenalidomide, bortezomib, zoledronic acid, MP, VAD.

Introduction

Multiple myeloma (MM) is a malignant plasma cell disorder that accounts for approximately 10% of all hematologic cancers.1 In last 15 years there was a revolution in the treatment of multiple myeloma. In the recent past, the treatment option is relatively simple with limited options from melphalan, prednisolone and dexamethason. With invent of new molecules treatment outcome of multiple myeloma become better. Thalidomide, lenolidamide and bortezomib are the three new drugs which bring the changes. These drugs are now used in various combinations along with older drugs. In Bangladesh these drugs are now available though relatively costly. In this article we try to outline the treatment option here in Bangladesh especially with the new class of drugs.

Defining multiple myeloma and related disorders:

Not every multiple myeloma patient undergoes treatment. Only symptomatic multiple myeloma needs treatment. The International Myeloma Working Group has published criteria for the diagnosis of symptomatic myeloma, which include the detection of ≥10% plasma cells in the bone marrow (or tissue biopsy), a monoclonal protein in the serum (>3gm/dl) or urine and the presence of end-organ damage. Hypercalcemia, renal insufficiency, anemia or bone lesions (referred to by the acronym “CRAB”) each fulfill the definition of end-organ injury (Table 1).2 Patients without these features are considered to have asymptomatic myeloma, and are not offered therapy until symptoms supervene.3

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Table II: Definitions of myeloma and related monoclonal gammopathies

<table>
<thead>
<tr>
<th>Standard name</th>
<th>New name</th>
<th>Definition</th>
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<tbody>
<tr>
<td>MGUS (Monoclonal Gammopathy of Undetermined Significance)</td>
<td>MGUS (i.e., No change)</td>
<td>Monoclonal protein present No underlying disease state</td>
</tr>
<tr>
<td>Smoldering or Indolent Myeloma</td>
<td>Asymptomatic myeloma</td>
<td>Higher level of disease than MGUS, but still no symptoms or organ damage</td>
</tr>
<tr>
<td>Myeloma</td>
<td>Symptomatic myeloma</td>
<td>Monoclonal protein present and One or more “CRAB” features of organ damage present*</td>
</tr>
</tbody>
</table>

*Organ damage classified as “CRAB”
- C – calcium elevation (>10 mg/l)
- R – renal dysfunction (creatinine >2 mg/dl)
- A– anemia (hemoglobin <10 g/dl)
- B – bone disease (lytic lesions or osteoporosis)

ONE OR MORE required for diagnosis of SYMPTOMATIC MYELOMA

Risk stratification for treatment
Before starting treatment disease stage must be done to identify the high risk patient. Prognosis in myeloma is determined by both the number and specific properties of myeloma cells in a given patient. In 1975, the Durie/Salmon myeloma staging system was developed. This system brings together the major clinical parameters in correlation with measured myeloma cell mass (the total number of myeloma cells in the body).

International Myeloma Working Group developed an International Prognostic Index based on serum levels of β2-microglobulin and albumin that separates patients into three prognostic groups and is recommended in preference to the Durie/Salmon staging system. Recently cytogenetics based risk stratification was practiced by advanced centers like Mayo clinic. Though the information using for the treatment yet to be standardized.

Table II: International staging system (ISS)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>1</td>
<td>Serum β2 microglobulin &lt; 3.5 mg/dl</td>
</tr>
<tr>
<td></td>
<td>Serum albumin ≥3.5 g/dl</td>
</tr>
<tr>
<td>2</td>
<td>Not 1 or 3*</td>
</tr>
<tr>
<td>3</td>
<td>Serum β2 microglobulin &gt; 5.5 mg/dl</td>
</tr>
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* There are 2 possibilities for stage 2:
- Serum β2 microglobulin < 3.5 mg/dl, but serum albumin <3.5 g/dl or
- Serum β2 microglobulin 3.5 – 5.5 mg/dl

Assessment of response
Before starting the treatment it is important to stage the disease. As response to the treatment is needed to assess the treatment response detailed in table 3.

Treatment options
The aims of treatment in myeloma are to control disease, maximize quality of life and prolong survival. These will be achieved by a combination of specific chemotherapy and supportive care. Treatment should be individualized. Although high-dose therapy is recommended where possible, in Bangladesh the lack of bone marrow transplant facilities majority of patients will not be able to receive such therapy. Also because of age, specific problems or general poor performance status many patients are not eligible to transplantation. It is also important to have a strategy at the start of treatment for the management of relapse when it occurs. The availability of new treatment options in Bangladesh, such as thalidomide, lenalidomide and bortezomib, now gives the haematologist to have much more freedom (and also difficulties to choose!) between treatment plans.
Table III: International Myeloma Working Group uniform response criteria: CR and other response categories

<table>
<thead>
<tr>
<th>Response subcategory</th>
<th>Response criteriaa</th>
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<tbody>
<tr>
<td>sCR</td>
<td>CR as defined below plus Normal FLC ratio and Absence of clonal cells in bone marrowb by immunohistochemistry or immunofluorescence</td>
</tr>
<tr>
<td>CR</td>
<td>Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrowb</td>
</tr>
<tr>
<td>VGPR</td>
<td>Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level to100 mg per 24 h</td>
</tr>
<tr>
<td>PR</td>
<td>≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to &lt;200 mg per 24 h If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required</td>
</tr>
<tr>
<td>SD (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)</td>
<td>Not meeting criteria for CR, VGPR, PR or progressive disease</td>
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</table>

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.

a All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

b Confirmation with repeat bone marrow biopsy not needed.

**Induction therapy in patients eligible for autologous stem-cell transplantation**

Young patient with no co-morbidity should be encouraged for ASCT. But as Bangladesh has no bone marrow transplant center so this option is out of scope of this review.

**Therapy in patients not eligible for transplantation**

Elderly patients and patients with co-morbidity are not fit for ASCT. In Bangladesh all chemotherapy protocol for multiple myeloma are in this group. But if BMT is planned or possible alkalytor based protocol (eg MP) must be avoided.

**For newly diagnosed patients**

**Conventional therapy:**

Melphalan, prednisolone, dexamethason are the main three drugs historically used in the front line treatment. Two protocols are known to medical community. These protocols are suitable for poor patients for Bangladesh.
Alkylating agents:

**MP:**
Melphalan is given at a dose of 8–10 mg/day daily for 7 days along with prednisone 60 mg/day during the same 7 days. Treatment is repeated every 6 weeks. A CBC in 3 weeks to ascertain whether adequate myelosuppression has occurred is used as a guide to adjust the dosage of melphalan for subsequent cycles. Therapy is typically continued until a plateau phase is reached. MP also has fewer side-effects and is administered orally, thus preserving quality of life.\(^5\)

**Corticosteroid:**
Patient with renal failure or with high tumor burden where a rapid response is needed corticosteroid based treatment is given.

**VAD:**
Repeated every 4 weak
Vincristine, 0.4 mg per day IV continuous infusion on days 1 – 4 Doxorubicin, 9 mg/m\(^2\). IV continuous infusion on days 1– 4 Dexamethasone, 40 mg PO on days 1– 4, 9 –12, and 17 –20.\(^6\)

**Pulsed dexamethasone:**
Repeated every 4 –5 weaks Dexamethasone, 40 mg PO on days 1–4, 9–12, and 17–20.\(^7\)

Dexamethason alone is recommended over VAD as response is almost equal with fewer complications and easy administration.

**Novel agents:**
In past decades introduction of novel agents which have curative potential for myeloma patient revolutionized the treatment option for the physician. Among them thalidomide, lenalidomide and bortezomib are available in Bangladesh. Though relatively costly but this drug should give the earliest in myeloma patient.

**Thalidomide:**\(^8\)
Thalidomide was initially used in Europe as a sedative, tranquilizer, and antiemetic for emesis gravidarum. It was withdrawn from the market in 1961 because of reports of congenital defects when taken during early gestation. This product now used singly or in combination with newly diagnosed cases.

Sedation, fatigue, constipation and rash are common adverse effects but usually are responsive to dose reduction. Peripheral neuropathy occurs with long-term use and often necessitates the discontinuation of the therapy or a dose reduction. The incidence of deep-vein thrombosis is only 1 to 3 percent in patients receiving thalidomide alone but increases to 10 to 15 percent in patients receiving the drug in combination with dexamethasone and to about 25 percent in patients receiving the drug in combination with other cytotoxic chemotherapeutic agents, particularly doxorubicin.

**Lenalidomide:**\(^9\)
As a means to overcoming the nonhaematologic toxic effects of thalidomide, including teratogenicity, several active analogues of thalidomide have been developed. Lenalidomide is an amino substituted variant of thalidomide that belongs to a class of analogues known as immunomodulatory drugs. It is more potent and more promising than the thalidomide. Dose adjustment with renal function is needed. Though thrombosis is less than thalidomide but hematological toxicities with cytopenia is relatively common.

**Bortezomb:**\(^10\)
Bortezomib is a new group of drug which is a proteasome inhibitor. Inhibition of the proteasome results in disruption of homeostatic mechanisms within the cell that lead to cell death. This is the only drug that can bring molecular remission which previously only can be achieved by bone marrow transplant.

The most common adverse effects of bortezomib are gastrointestinal symptoms, cytopenia, fatigue, and peripheral neuropathy. A decrease in the platelet count to less than 50,000 per cubic millimeter occurs in almost 30 percent of patients. Peripheral neuropathy, often painful, develops in approximately 30 percent of patients and is more frequent in those who have previously received neurotoxic therapy and those with a preexisting neuropathy.
These new drugs are now incorporated with the old protocols. The common regimens are discussed below.

**Melphalan, prednisone, thalidomide (MPT).** Three recent randomized trials have compared MP with MPT. Significantly higher response and progression-free survival rates were observed with MPT compared with either MP or tandem ASCT groups. More importantly, the trial demonstrated a significant survival advantage with MPT. After numerous attempts to improve on MP over the years with a variety of combination chemotherapy regimens, the results of these 3 randomized trials finally changed the standard of care for elderly patients.

**Melphalan, prednisone, bortezomib (MPV).** The combination of MPV in newly diagnosed myeloma showed a promising response. In Mayo clinic protocol it is recommended for the high risk patient based on cytogenetic study.\(^{11}\)

**Melphalan, prednisone, lenalidomide (MPR).** As a next generation molecule lenalidomide are now tested against thalidomide. An ECOG randomized trial is comparing MPT with MPR.

**Thal-Dex:** Thalidomide combined with high or low dose dexamethason. Response is better than high dose dexamethason alone but inferior than MP in respect of overall survival (OS) especially in elderly patients. Aspirin or antithrombotic drugs should be used due to high percentage of DVT.

Table IV: Treatment plan for multiple myeloma

<table>
<thead>
<tr>
<th>Conventional First line treatment:</th>
<th>New MPT</th>
<th>Td</th>
<th>MPV</th>
<th>MPR</th>
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Table V. Treatment of Complications in Multiple Myeloma

<table>
<thead>
<tr>
<th>Complication</th>
<th>Therapeutic Options</th>
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| Myeloma bone disease | Pamidronate or zoledronic acid in patients with documented bone disease  
Encouragement of activity to prevent osteopenia and deep-vein thrombosis  
Pain control with narcotic analgesics, if needed; avoidance of nonsteroidal antiinflammatory agents  
Radiation to treat painful bony lesions refractory to pain medication or cord compression  
Surgical intervention to prevent or treat pathologic fractures Vertebroplasty or kyphoplasty for selected vertebral lesions, to reduce pain and improve height |
| Anemia | Treatment of reversible causes such as deficiencies of iron, B12, or folate Erythropoietin for symptomatic anemia during chemotherapy  
Transfusions as needed |
| Infections | Vaccination against Streptococcus pneumoniae, Haemophilus influenzae, and influenza  
Consideration of prophylactic broad-spectrum antibiotic therapy when corticosteroids are used  
Consideration of prophylaxis against Pneumocystis carinii when prolonged corticosteroid therapy is used; avoidance of trimethoprim–sulfamethoxazole when thalidomide is used |
| Hypercalcemia | Intravenous fluids and corticosteroids  
Bisphosphonates when hypercalcemia is severe or unresponsive to hydration and corticosteroids |
| Renal failure | Correction of reversible causes such as dehydration, hypercalcemia, and hyperuricemia  
Chemotherapy (e.g., vincristine, doxorubicin, and dexamethasone; dexamethasone alone; or thalidomide–dexamethasone) for rapid control of disease  
Alkaline diuresis for acute renal failure due to cast nephropathy; avoid alkalization in patients with hypercalcemia |
Treatment of complications:
Table 5 summarizes current management strategies for complications observed in patients with myeloma. Important advances include the prevention and treatment of hypercalcemia and bony lesions with the monthly administration of bisphosphonates in patients with myeloma bone disease. Zoledronic acid is the only bisphosphonates working in myeloma bone disease available here.\(^{12}\)

Conclusion:
Treatment of multiple myeloma still not optimum here in Bangladesh due to absence of bone marrow transplant facilities. However, judicious use of novel agents available here can improve the survival and quality of life of the patient.

Practice points:
- Only symptomatic multiple myeloma need treatment.
- MP/MPT should be the initial treatment for elderly patient not eligible for BMT.
- Dexamethason based treatment should use in case of renal impairment or for early response.
- High dose dexamethason is preferable than VAD.
- Thalidomide, lenalidomide or bortezomib should be used from the beginning.
- Bisphosphonates should be used routinely to prevent skeletal complications.

References
3. Durie BGM. Concise Review of the Disease and Treatment Options. International Myeloma Foundation, 2006. 15