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

*Rahman MM,[1] Aziz MA,[2] Islam MM,[3] Zaman AM,[4] Afrose S,[5] Khan MA[6]

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.

[Dinajpur Med Col J 2010 Jan; 3 (1):39-44]

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.[1]

1. *Dr. M. Mizanur Rahman, Dhaka Medical College Hospital, Dhaka, Bangladesh
2. Dr. Md. Abdul Aziz, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
3. Dr. Md Mahabubul Islam, Dinajpur Medical College, Dinajpur, Bangladesh Email- shawon71@yahoo.com,
4. A.K. M Mostofa Zaman, Dinajpur Medical College, Dinajpur, Bangladesh
5. Dr. Salma Afrose, Dhaka Medical College Hospital, Dhaka, Bangladesh
6. Dr. M.A. Khan, Dhaka Medical College Hospital, Dhaka, Bangladesh

*For correspondence

Table II: Definitions of myeloma and related monoclonal gammopathies[3]

Standard name	New name	Definition
MGUS (Monoclonal Gammopahty of Undetermined Significance)	MGUS (i.e., No change)	Monoclonal protein present No underlying disease state
Smoldering or Indolent Myeloma	Asymptomatic myeloma	Higher level of disease than MGUS, but still no symptoms or organ damage
Myeloma	Symptomatic myeloma	Monoclonal protein present and One or more "CRAB" features of organ damage present*

*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.[3]

Table II: International staging system (ISS)

Stage	Criteria
1	Serum □2 microglobulin < 3.5 mg/dl Serum albumin ≥3.5g/l
2	Not 1 or 3*
3	Serum □2 microglobulin > 5.5 mg/dl

* 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 asses the treatment response detailed in table 3.[4]

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

Response subcategory	Response criteria[a]
sCR	CR as defined below plus Normal FLC ratio and Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence
CR	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrow[b]
VGPR	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
PR	≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <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
SD (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)	Not meeting criteria for CR, VGPR, PR or progressive disease

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.

Bortezomib:[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

Conventional	First line treatment: MP VAD/HiDex
New	MPT Td MPV MPR

Abbreviation: HiDex- Hi dose dexamethasone, MP – Melphalan, prednisolon, MPR- Melphelan, prednisolon, lenalidomide MPT- Melphalan, prednisolon, thalidomide, MPV- Melphalan, prednisolon, bortezomib, Td- Thalidomide, low dose dexamethasone, VAD- Vincristin, adriamycin, dexamethason.

Table V. Treatment of Complications in Multiple Myeloma

Complication	Therapeutic Options
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 alkalinization 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

1. Kyle RA, Rajkumar SV. Multiple myeloma. N Engl J Med. 2004; 351:1860-1873.
2. International Myeloma Working Group.Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group.Br J Haematol.2003;121:749-757.
3. Durie BGM. Concise Review of the Disease and Treatment Options. International Myeloma Foundation, 2006. 15
4. Durie BGM, Harousseau JL, Miguel JS, et al. on behalf of the International Myeloma Working Group. International uniform response criteria for multiple myeloma. Leukemia 2006; V-20, No-10.
5. Myeloma Trialists'Collaborative Group. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials.J Clin Oncol 1998;16:3832-42.
6. Alexanian R, Barlogie B, Tucker S. VAD-based regimens as primary treatment for multiple myeloma. Am J Hematol 1990;33:86-9.
7. Alexanian R, Dimopoulos MA, Delasalle K, Barlogie B. Primary dexamethasone treatment of multiple myeloma.Blood. 1992;80:887-90.
8. Palumbo A, Facon T, Sonneveld P, et al. Thalidomide for treatment of multiple myeloma: 10 years later. Blood. 2008; 111: 3968-3977.
9. Barlogie B, Shaughnessy J, Tricot G, et al. Treatment of multiple myeloma. Blood, 2004; 103, 20-32.
10. Richardson PG, Mitsiades C, Hideshima T, Anderson KC. Bortezomib: Proteasome Inhibition as an effective anticancer therarpy. Annu. Rev. Med. 2006. 57:33–47
11. Dispenzieri A, Vincent S, Rajkumar SV. Treatment of Newly Diagnosed Multiple Myeloma Based on Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART): Consensus Statement. Mayo Clin Proc. 2007;82:323-341
12. Berenson JR, Rosen LS, Howell A, et al. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases.Cancer 2001;91:1191-200.[Erratum,Cancer 2001;91:1956.]