

# 37 Novel Therapies for Multiple Myeloma

**Abstract:** Current standard of management for newly diagnosed multiple myeloma are continuously evolving due to the advent of a number of novel agents with different mechanisms of action. The immunomodulatory drugs thalidomide and its recently developed analogue lenalidomide, and the proteasome inhibitor bortezomib, have been investigated extensively, alone or in combinations with known anti-myeloma drugs like corticosteroids (prednisone or dexamethasone) and cytotoxic chemotherapy agents (doxorubicin – conventional or liposomal, cyclophosphamide, melphalan, etc) for relapsed/refractory disease and now being incorporated in front-line care. These therapies along with much improved supportive care with bisphosphonates (pamidronate, zoledronic acid and ebandronate), minimal access surgery for vertebral repair, VDT prophylaxis have not only improved initial responses but also prolonged duration of response and vastly improved quality of life. Additionally, availability of multiple effective agents has given options to the clinicians to individualise therapy for elderly patients with co-morbid conditions without compromising efficacy. For example, patients with pre-existent diabetic neuropathy may avoid agents like thalidomide or bortezomib, but may receive equally effective lenalidomide which is non-neurotoxic. There is emerging interest in developing regimens that might obviate the need for high-dose chemotherapy and autologous stem cell transplantation for majority of patients. Nevertheless, high-dose chemotherapy with autologous stem cell transplantation currently remains an integral part of management of younger myeloma (< 65 yrs of age) patients.

It is becoming increasingly evident that for survival and progression of myeloma cells the marrow microenvironment also plays an important role; efforts are on to develop agents to target these tissues and their products. As myeloma remains an incurable disease, it is hoped that these approaches will keep the disease in an indolent chronic state requiring long but effective therapy.

## INTRODUCTION

Multiple myeloma is a disease of the elderly with a median age of 55-60 yrs in Western world and apparently a few years younger in Indians. However, the disease develops in people in 30-40 s. Being an incurable disease, it is crucial to do maximum for each patient, so as to reduce the tumor load to minimum level, maintain such a status for a prolonged period and design appropriate therapeutic strategies for relapsed disease. As a result of intense research in the field, current therapeutic strategies have produced a median overall survival in excess of 5 years and a subset living beyond 10 years. Nevertheless, myeloma is a biologically heterogeneous disease; therefore, it is important to understand its clinical-pathological nature in each individual at diagnosis and at relapse.<sup>1</sup>

## DIAGNOSTIC WORK UP

In a clinically suspected case of myeloma, following investigations should be completed:

- Complete blood count
- ESR
- Blood biochemistry for LFT, RFT, uric acid, calcium, phosphorus, CRP, beta 2-microglobulin ( $\beta_2M$ ), LDH
- Serum protein electrophoresis including immunofixation

- Urine protein electrophoresis including immunofixation
- Free light chain (kappa and lambda) protein ratio in selected cases
- Skeletal survey with X-rays
- MRI spine
- Bone marrow aspirate and biopsy for
  - Morphology
  - Cytogenetics by karyotyping and FISH
  - Molecular studies, whenever possible
  - Labeling index.

## **PROGNOSTIC FACTORS**

Durie-Salmon staging system conventionally determines the tumor load by dividing the disease into stages I, II, III and subdividing to A and B based on renal involvement. However, the staging system has no prognostic value for many patients. Currently, an International Staging System (ISS) is in use to prognosticate the patients at diagnosis.<sup>2</sup> This system takes into account two simple objective findings, serum albumin and beta2 microglobulin and groups the patients into 3 prognostic categories (Table 1).

## **STANDARD MANAGEMENT OF MYELOMA**

All myeloma patients may not require treatment immediately at diagnosis. Some myeloma patients may have indolent biology and can wait for quite a long period before a beneficial therapeutic intervention is indicated. One should evaluate for fulfilment of the CRAB (C-hypercalcemia, R-renal involvement, A-anemia, B-bone involvement that may be functionally critical) criteria; any one criterion should be present to justify myeloma directed therapy.

## **OLD STANDARD OF THERAPY**

Corticosteroids, either prednisolone or high-dose dexamethasone with melphalan was the backbone of myeloma therapy for many years. This approach could produce only about 3 years of median survival. Subsequent advent of combination chemotherapy of VAD or C-VAMP regimens produced better initial responses, but without impacting overall survival. However, this regimen provided the platform for adequate blood stem cell collection for an autologous stem transplantation.

## **NEW AGENTS IN MANAGEMENT OF MYELOMA**

While a corticosteroid remains the backbone of myeloma therapy, a number of new agents have become an integral part of myeloma management, both at diagnosis and at relapse. These agents appear not only to target the myeloma clone, but also the microenvironment that supports myeloma cell proliferation and survival.

### **Thalidomide**

It is not a new drug but has found its place in myeloma therapy in the last decade. An old agent, developed in 1950s as a sedative, had to be banned due to birth of malformed babies in mothers who received this drug during the first half pregnancy for morning sickness. Its powerful antiangiogenic property was probably responsible for this effect. This activity, along with multiple other biological properties brought thalidomide into the frontline of myeloma therapy. The exact mechanism(s) of the agent has not been understood yet, but inhibition of tumor necrosis factor alpha, prevention of free-radical-mediated DNA damage, suppression of

angiogenesis, an increase in cell-mediated cytotoxic effects, and the altered expression of adhesion molecules, have been proposed as possible ones.

The first phase I study from the university of Arkansas had shown 25% overall response in a previously heavily treated and relapsed patient cohort.<sup>3</sup> Once its efficacy was proven in relapsed/refractory cases, prednisolone + thalidomide became a frontline therapy for many patients. This regimen was found to be more effective than the VAD combination chemotherapy. It also does not impede stem cell collection. However, thalidomide has many unpalatable side-effects like constipation, abdominal discomfort, skin rash, drowsiness, and peripheral neuropathy. A significant number of patients can not tolerate higher than 100 mg daily dose although the standard dose was found to be 200 mg.

### **Bortezomib**

Bortezomib is a specific inhibitor of 26S proteasome, a large intracellular ATP-dependent protease responsible for protein catabolism in all eukaryotic cells. Ubiquitinated proteins are identified and degraded in the central portion of the proteasome, a pathway critical for normal cellular events to occur. Inhibition of this pathway leads to arrest of cell cycle and apoptosis. In myeloma, it probably causes direct cytotoxicity and also affects the marrow microenvironment. Proteasome inhibition leads to accumulation of I $\kappa$ B, an inhibitor of the major transcription factor NF- $\kappa$ B, which consequently leads to decrease in the expression of adhesion molecules and various growth, survival, and angiogenic factors. There could be other mechanisms responsible for anti-myeloma effect. Preliminary data show that the agent has ability to overcome del(13) abnormality that confers poor prognosis in patients treated with chemotherapy drugs.

The starting dose is 1.3 mg mg/m<sup>2</sup> intravenous bolus on days 1, 4, 8, 11 of each 21 day cycle.<sup>4</sup> If significant side-effects occur, the dose could be reduced to 0.7 mg to 1 mg/m<sup>2</sup>. Usually 6-8 cycles are administered. A phase II study in heavily pre-treated patients has produced 27% partial response with 4% complete responses. The median duration of response was 12 months. The responses occur very rapidly, usually following 2-3 cycles. The common side effects are peripheral neuropathy, gastro-intestinal, fatigue, and variable degree of thrombocytopenia that reverts to normal level in majority before the next cycle. Combination regimens with dexamethasone, liposomal doxorubicin, melphalan, cyclophosphamide and even thalidomide or lenalidomide are being developed to use this agent in first line therapy of myeloma.

### **Lenalidomide**

Intense research in the field led to the development of a thalidomide analogue, lenalidomide, an agent as efficacious as its original compound but devoid of neurotoxicity.<sup>5</sup> It is oral agent. However, it has a side effect profile that causes cytopenia and DVT in high-risk patients. Further studies have shown that its efficacy is non-cross resistant with that of thalidomide; a significant number of patients refractory to thalidomide have responded to lenalidomide.

### **Phase III Trials of Lenalidomide + High-dose Dexamethasone**

Two phase III randomized, placebo-controlled trials – MM-009 and MM-010 have demonstrated that combination of these two effective agents relapsed/refractory MM, compared with dexamethasone alone resulted in significantly higher overall response (ORR) (MM-009, 54.4% vs 21.2%; MM-010, 15% vs 3.4%) ( $p < 0.001$  for all). The time to progression (TTP) in MM-009, 11.1 months; MM-010, 11.3 months vs 4.7 months also has been significantly better.

Follow-up analysis have shown the following events,

1. The combination is significantly more effective in patients with first relapse in terms of ORR (64% vs 27%;  $p < 0.001$ ), TTP (16.5 months vs 4.7 months;  $p < 0.0001$ ) and OS (29.6 months vs 25 months;  $p = 0.011$ ).
2. Non-cross resistance between thalidomide and lenalidomide ORR 50% vs 21%,  $p = 0.04$ ; TTP 7.2 months vs 3.7 months,  $p = 0.007$ .
3. Efficacy in patients with prior AASCT - ORR 63% vs 24%, CR 13% vs 3%, TTP 44.1 months vs 20.1 months ( $p < 0.001$ ).
4. Efficacy in elderly patients (< 65 yrs, 65-70 yrs, >75 yrs) - ORR (58.4%-63.9%) and TTP (48.1-57 weeks), compared with dexamethasone alone ( $p < 0.001$ ).
5. Efficacy in patients with renal impairment, although the trial were designed to include patients serum creatinine < 2.5 mg/dl. Table 2 shows recommended dose adjustment at the start of lenalidomide therapy in patients with impaired renal function.

A phase II study of lenalidomide plus dexamethasone in patients with del(13) or t(4;14) shown that this combination can overcome the poor prognosis associated with other conventional therapy including ASCT. While Table 3 shows nonhematological adverse events. Table 4 shows the recommendations for management of hematologic adverse events associated with lenalidomide treatment.

## RECENT MAJOR IMPROVEMENT IN LONG-TERM SURVIVAL

Two major studies published recently have shown significantly better survival. The SEER database studied in patients diagnosed with myeloma from 1990-1992 and 2002-2004 showed 5 yrs survival improvement from 28.8 to 34.7% and 10 yrs survival from 11.1 to 17.4%.<sup>6</sup> In younger patients, the average relative survival increased from 4 years after diagnosis in 1990-1992 to almost 7 years after diagnosis in 2002-2004. Stem cell transplantation, newer drugs and improved supportive care were the factors in offering this benefit.

The second study from the Mayo Clinic analysing patients from the time of diagnosis and one from the time of relapse found dramatic improvement in survival among recently diagnosed patients, both from the time of diagnosis and from relapse after stem cell transplantation.<sup>7</sup> The overall survival improvement has been 50% in patients diagnosed in the last decade. As noted in the SEER data, in this study also the benefit of newer therapeutic approaches that included stem cell transplantation was evident in younger patients (< 65 yrs) and in females.

## Management of Young Myeloma Patients

Currently, patients < 65 years old are considered young enough to receive aggressive anti-myeloma therapy that includes high-dose chemotherapy with autologous stem cell transplantation (ASCT).<sup>8</sup> After assessing the disease stage, prognostic factors, co-morbid conditions and associated complications arising from myeloma, the total therapy is planned. This includes:

1. Supportive care for hypercalcemia, renal failure, infection, bone fractures, DVT prophylaxis, and anemia (if any or more of these are present).
2. Initial therapy with anti-myeloma agents using any of the following combinations for 2-3 months (any of these producing an overall response of 65-90%, newer ones with increased responses),
  - a. Thalidomide plus dexamethasone
  - b. Bortezomib plus dexamethasone
  - c. Bortezomib plus dexamethasone plus liposomal doxorubicin
  - d. Lenalidomide plus dexamethasone
  - e. Bortezomib plus dexamethasone plus cyclophosphamide
  - f. Bortezomib plus dexamethasone plus lenalidomide
  - g. Chemotherapy regimens like the conventional VAD (vincristine, doxorubicin and dexamethasone) or dVD (liposomal doxorubicin, vincristine and dexamethasone).

3. Eligible candidates, usually the responders of initial therapy proceed to high-dose chemotherapy (intravenous melphalan 200 mg/m<sup>2</sup>) and autologous stem cell transplantation. Partial responders may be benefited with double autologous transplants.
4. Maintenance therapy with thalidomide. However, this remains an open area for further studies.
5. As most of the patients will relapse after a variable period (median 12-18 months), will require salvage therapy with other anti-myeloma agents.
6. Allogeneic stem transplant is usually reserved for selected cases, as tandem autologous followed by reduced-intensity allogeneic SCT, or in very young people as an elective procedure without a prior autologous transplant.

The role of tandem autologous followed by matched donor allogeneic transplantation remains an investigational approach for younger patients.

### Management of Elderly Patients

Many of these patients are usually frail and have co-morbid conditions; therefore, unable to tolerate aggressive therapy. Only a few with biologically young age, may proceed to high-dose chemotherapy with stem cell transplants. The ways to manage them (after full evaluation) are:

1. Supportive care as in young patients.
2. Anti-myeloma therapy with any of the following:
  - a. Oral melphalan plus prednisone (MP). This is not the best option at present due to an inferior outcome. However, some would be eligible only for this.
  - b. Oral melphalan plus prednisone plus thalidomide (MPT regimen). Currently, this has become the standard of care.<sup>9</sup>
  - c. Lenalidomide plus dexamethasone.
  - d. Bortezomib plus dexamethasone.
3. The duration of therapy is for about a year in responders or until a plateau phase is achieved.
4. At relapse, use anti-myeloma agents that have not been used earlier, could be used.

### CONCLUSION

It is clearly evident now that improved understanding of biology of myeloma development and progression along with emergence of newer therapeutic agents have changed the natural history of the disease to a great extent in many patients with multiple myeloma. Clinicians now have a number of options to individualise therapy according to the patient's prognostic factors and associated co-morbid conditions. There is definite hope that in near future further improvement will continue to occur.

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multiple choice questions

1. **In International Staging System (ISS) of myeloma what factors are taken into account?**
  - A. Serum albumin
  - B. Serum beta 2 microglobulin level
  - C. None of the above
  - D. Both of them
2. **What is the starting dose of bortezomib in myeloma?**
  - A. 1 mg/m<sup>2</sup> IV
  - B. 0.7 mg/m<sup>2</sup> IV
  - C. 1.3 mg/m<sup>2</sup> IV
  - D. 2.0 mg/m<sup>2</sup> IV
3. **Thalidomide is:**
  - A. Directly cytotoxic to myeloma cells
  - B. Active through an immunomodulatory mechanism
  - C. Antiangiogenic
  - D. All of the above
4. **Lenalidomide is toxic to *except*:**
  - A. Myelotoxic
  - B. Nephrotoxic
  - C. Neurotoxic
  - D. Hepatotoxic
5. **Autologous Stem Cell Transplantation in myeloma is:**
  - A. A curative therapy
  - B. Improves response rate and duration
  - C. An ineffective therapy
  - D. Offered to patients of all ages
6. **Deep vein thrombosis (DVT) in myeloma is caused by:**
  - A. Thalidomide
  - B. Lenalidomide
  - C. Dexamethasone
  - D. All of the above

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**1. A, B 2. C 3. D 4. C 5. C 6. D**