How I Treat Myeloma?

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Plasma cell dyscrasias, commonly referred as myeloma are relatively rare type of hematological malignancies[1]. However, in recent years the awareness of these conditions have increased due to, 1. Better understanding of their pathogenesis, 2. Availability of more effective modalities of treatment, leading to improved response and survival and finally, 3. Involvement of high profile NGOs in the field of research and care of these patients.

As a medical oncologist, while working earlier in an academic set up and now in practice, I get to see most of these patients after a fair amount of diagnostic work up. This often eliminates some differential diagnostic conditions. Nevertheless, we should be aware of certain benign as well as malignant disorders while working up a case of suspected myeloma. These could be metabolic bone diseases, parathyroid pathology, osteoporosis, bone tuberculosis, osteomyelitis and metastatic bone disease.

WORK UP OF A MYELOMA PATIENT

For me it is extremely important to spend sufficient time in working up a case of myeloma so as to understand the biology of the disease in a given patient (tables 1 -4). Using evidences from the literature as well as utilizing years of experience in the field, I try to find out which features of the CRAB (table 2) are dominant in the patient.[1-3]

Table 1. International Staging System (ISS) for Multiple Myeloma

Stage	% of patients	Features	Median survival
I	28	b2M <3.5 mg/L Albumin >3.5 G/dl	62 months
II	33	b2M <3.5 mg/L Albumin <3.5 G/dl Or b2M 3.5 – 5.5 mg/L	44 months
III	39	b2M >5.5 mg/L	29 months

b 2 M – Beta 2 microglobulin

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Table 2. Criteria for end-organ damage due to multiple myeloma (CRAB)

Hypercalcemia:
Serum calcium >0.25 mmol/L (1mg/dl) above the upper limits of normal or >2.75 mmol/L (11 mg/dl)
Renal insufficiency
Serum creatinine >173 mmol/L (1.96 mg/dl)
Anemia
Hb 2 g/dl below lower limits of normal or Hb <10 g/dl
Bone lesions
Lytic lesions or osteopenia with compression fractures
Others:
Symptomatic hyperviscosity, amylodosis, recurrent bacterial infections

Table 3. Translocation and Cyclin D (TC) classification of Multiple Myeloma

Group Prevalence ~ %	Primary Ig Trans location		Cyclin D	Hyperdiploid
TC 1	t(11;14) (q13;q32)	D 1	NH	15
	T(6;14) (p21;q32)	D 3	NH	3
TC 2	None	D 1 lo	H	43
TC 3	None	D 2	H=NH	17
TC 4	t(4;14) (p16;q32)	D 2	NH > H	15
TC 5	t(14;16) (q32;q23)	D 2	NH	5
	T(14;20) (q32;q11)	D 2	NH	2

Table 4. Poor Prognostic Factors in Multiple Myeloma

Demographic	Advanced age, >70 years
Tumour Clone	IgA subtype
↑Proliferative activities	Chromosomal abnormalities
	↑ Microvessel density
Surrogate markers	Anemia (Hb <10 G/dl)
	↑serum creatinine
	↑serum LDH
	↑serum CRP
	↑serum b2M
	↓serum albumin

CRAB

C- Hypercalcemia is a manifestation of bone remodeling resulting from deregulated calcium metabolism in myeloma. Not all patients with hypercalcemia are symptomatic. Symptomatic hypercalcemia could be considered as an oncologic emergency.

R- Renal involvement always sets the patient apart from others. The patient needs very careful assessment for renal functions. Associated co-morbid conditions like diabetes mellitus, hypertension or other rare conditions that may affect the kidneys, may complicate the picture further. High-dose chemotherapy with autologous stem cell transplantation, although not an absolute contraindication for these patients, one should be prepared for increased transplant related complications. Presence of raised serum creatinine level calls for adequate hydration for a first few days before definitive therapy for myeloma is initiated.

A – Anemia will indicate me to look at the retic count and red cell indices, so as not to miss deficiency of iron, B12 and folate or hemoglobinopathies. In a country like India, we tend to come across these associated pathologies on regular occasions. Then I concentrate on myeloma related anemia. Immune mediated anemia in myeloma could be frustrating to manage.

B - Bone events at presentation causing significant damage to the weight bearing bones with pathologic fractures alarm me about the future of the patients. The quality of life (QOL) may never be optimum in many patients. Frequent bone events in spite of adequate systemic response of myeloma frustrate patients. I make it a point to warn the patients and the family to be extra cautious.

MYELOMA-INDUCED BONE DISEASE

Malignant plasma cells acquire the property of damaging the bones causing osteolytic lesions through increased osteoclastic resorption and lowered bone formation. Most of these bone destruction activities occur in the vicinity of myeloma mass in the marrow, thus suggesting that the pathology results from local production of an osteoclast activation factor (OAF) by the myeloma and/or stromal cells. In recent years our understanding of this pathology has improved significantly,[4,5] Two OAFs – RANKL/OPG (receptor activation of NFêB ligand and its decoy receptor osteopretogerin) system and the chemokine MIP-1 (macrophage inflammatory protein) have been identified and their roles studied.

Additionally, the prognostic markers/factors like b_2 Microglobulin (b_2M) LDH are important at diagnosis.[6,7] Both markers should be taken as only prognostic markers and never as markers for monitoring the disease activity while on therapy or follow up visit. If done so (monitor MRD/relapse/progression), it could send you on a wild goose chase.

CYTOGENETICS

Karyotyping – I always try to convince the patients to have this done at diagnosis. It is a pity that not many in the country bother to ask for this test. There is enough evidence of its prognostic importance. Presence of t(4;14)(p16;q32) or t (14;16) (q32;q23) identifies a poor prognostic sub group.[8]

FISH – Often conventional karyotyping may miss smaller genetic events. FISH studies with relevant probes should be requested; for example, conventional cytogenetics picks up ~15% patients with 13q abnormality, whereas interphase FISH studies using this probe can detect more number of cases (40-54%).[9]

Cyclin D – Overexpression of one of the cyclin-D[10] genes has been found to be a universal molecular feature of myeloma. Combining this feature with cytogenetic abnormalities, a new classification, called TC (translocation – cyclin) has been developed (table 3). For example, t(11;14)(q13;q32) results in upregulation of cyclin-D1.

Gene Expression Profiling (GEP) – At the present time the technology can not be utilized for prospective treatment planning. It is a very expensive tool too. Nevertheless, it is helping us in identifying the genes involved in the pathogenesis and progression of the disease[11]. In the course of time, it might be possible to develop therapeutic targets against the critical genes involved in the intiation and maintenance of the disease.

Finally, a higher LI is indicative of a poor outcome.[6]

Management of Myeloma

Solitary Plasmacytomas

Once I am sure of a solitary medullary plasmacytoma, I discuss the probabilities of disease progression in future; 50% will develop multiple myeloma in next 5 years and another 25% in next 5 years and the rest 25% will never progress after initial local therapy.[1] The treatment is either a complete resection or local radiotherapy. I do not put them on systemic therapy (any age) but follow closely for progression of the disease. Once it progresses, I ask for complete work up and then proceed with systemic therapy according to the age.

EXTRAMEDULLARY PLASMACYTOMA

These are most commonly seen in the head and neck area and are usually cured with radical dose radiotherapy. However, I follow them up for rare but possible recurrence and long-term radiotherapy complications like hypothyroidism (if neck is radiated) and other oral complications.

Multiple Myeloma

YOUNG MYELOMA PATIENTS

Myeloma remains an incurable disease although there is some evidence that a subset do not experience relapse after allogeneic stem cell transplantation. Given this premise, the discussion certainly veers towards chalking out a long-term treatment plan after taking a close look at the prognostic factors (table 4). This comprises of, initial disease bulk reduction with systemic therapy, followed by high dose chemotherapy with autologous stem cell rescue and necessity of maintenance therapy and treatment of relapsed disease.[12-14] All along this, the importance of supportive care of pain, pathological fracture, hypercalcemia, infections, anemia, hyperviscosity, renal insufficiency, rehabilitation, etc are never forgotten.

Before taking a therapeutic decision, I make sure that patients with indolent/ smouldering myeloma are not offered cytotoxic therapy immediately, but remains on close observation.[1] The tempo of disease progression may vary.

SUPPORTIVE CARE

Pain management – NSAIDS are avoided as much as possible. In most cases, pain abates rapidly after institution of steroid therapy. Local radiotherapy, vertebroplasty and kyphoplasty are reserved for selected cases.

Pathological fractures – A surgical consult becomes necessary in such situations. I often prefer prophylactic surgical interventions if large osteolytic lesions are identified in the long bones. Once a fracture develops, the QOL suffers severely.

Anemia – severely anemics will need packed red cell transfusions. Deficiency anemias could be effectively treated. Erythropoietin given weekly 30,000 to 40,000 units subcuteneously for the duration of 3-4 months helps majority of patients in maintaining an optimal level of hemoglobin level and improved QOL. However, immune mediated (CD 95/Fas ligand mediated) anemia could be extremely difficult to treat.

Hypercalcemia – This could be a presenting feature with symptoms and signs of raised calcium level. With adequate hydration, steroids (dexamathasone) and bisphosphonates (choice of a particular bisphosphonate depends on serum creatinine level), most patients improve rapidly. Calcitonin is rarely used. As bone events are invariably associated with hyercalcemia, a bisphosphonate is continued for a prolonged period (usually at monthly intervals) keeping an eye on serum creatinine, serum calcium and possibilities of developing osteonecrosis of the jaw.

Renal failure – It is a common complication of myeloma and is multifactorial. In many it is reversible with adequate initial support and definitive therapy. Poor response to initial therapy in the first few weeks is a very poor prognostic sign. Patients with raised creatinine are admitted in our hospitals and started on adequate hydration, oral and intra venous. A nephrology consult is sought although renal dialysis is infrequently used. Both the VAD regimen and thalidomide based initial therapy are reasonably safe in presence of renal failure. However, alkylating agents with their delayed

clearance may produce prolonged and severe marrow suppressions. Hence, melphalan is usually avoided or administered in a lower dose. NSAIDS for pain and ionic contrast dyes for diagnostic purposes should be avoided during this period.

Infections – Due to the low levels of normal immunoglobulins, steroid therapy and associated co-morbid conditions, myeloma patients remain prone to develop various infections easily. Prophylactic antimicrobials are usually not practical. Early detection and prompt management is the key.

Hyperviscosity status – Plasmapheresis is an effective emergency therapy. . One hopes that with appropriate control of myeloma, hypervicosity related problems will resolve.

Deep vein thrombosis – The exact mechanism of DVT in myeloma has not been elucidated. It is an infrequent presenting feature, but the incidence rises exponentially with institution of steroids (3-5%), cytotoxic drugs (10-15%) and addition of thalidomide (15-25%).[15] Use of prophylactic antithrombotic agent like low molecular weight heparin (LMWH) may reduce the incidence significantly.[15] However, even with the use of aspirin, an antiplatelet agent used for arterial thrombosis appears to be effective. Although not universally accepted, there could be some reason for aspirin to be effective in this setting. I do prescribe aspirin for most cases, but from scientific view point, would be more comfortable using LMWH, a more expensive drug and requires parenteral route of administration.

Definitive Therapy

VAD REGIMEN OR THALIDOMIDE AS INITIAL THERAPY?

It is a hot debate now. While it is widely accepted that dexamethasone (dexa) is the backbone in myeloma management, the partner drugs could either be chemotherapeutic agents or newer biologicals (immunomodulatory drugs or proteasome inhibitors). Based on earlier results, some have continued to use the cumbersome VAD regimen. However, there is a genuine concern regarding the role of vincristine which is a relatively weak antimyeloma agent and being neurotoxic, compromises future use of newer drugs like thalidomide and bortezomib. Viewing same data from a different critical angle, others have shown that either dexamethasone alone or addition of thalidomide to dexa could produce equivalent or better responses[16,17]. It will take another couple years to resolve this issue. In the meantime, thalidomide has established itself as an effective therapy for a subset of myeloma patients.[18]

I have moved onto using the thalidomide and dexa combination. There are a number of reasons in favor of this regimen – ease of administration, ability to modify dose as per toxicity or response, availability of agents to minimize side effects (for DVT) and relatively less infectious complications. Nevertheless, I am constantly aware of toxicities of both the drugs and keep warning the patients. I try to maintain the dose of thalidomide at 200 mg daily and rarely venture a higher dose. Some of my peers, possibly justifiably (for them more is always better) may not agree with me. This approach has not created any hurdles in collection of sufficient number blood stem cells. I evaluate a response at 10-12 weeks as per EBMT or more recently published international response criteria[19,20] and then proceed with high dose melphalan with autologous stem cell rescue. We have not been practicing double autologous stem cell transplants so far due to a number of issues relevant in our context. However, the approach has its own advantage in a subset of patients as shown by the French study.

I have no experience of using bortezomib as an upfront drug (too expensive), but realize that in coming years it might become a serious contender[21-23].

Consolidation therapy with high dose melphalan and autologous stem cell transplantation (ASCT)

Being involved in the field of stem cell transplantation for almost two and a half decades, it is natural that I would continue to keep my interest alive in the area. However, I have always conscientiously tried not be biased towards high dose chemotherapy. At the present

time, I consider that high dose melphalan has an important role to play in majority of young myeloma patients.[12-14] It offers opportunities to the patient to return to an active life for a significant duration and be prepared for subsequent therapy when the disease progresses. A small subset of patients (~10%) may experience a very long (> 5 years) relapse free period. Of course, in case of a poor response (in ~25% of patients), the effort goes in vain.

High dose melphalan with peripheral blood stem cell rescue is very safe now. Transplant related mortality is <2%. In my own experience with over more than 50 patients, there has been only one early death, apparently due to poor tolerance of melphalan.

MAINTENANCE THERAPY

Whether we use the VAD regimen x 4-6 cycles, thal –dex alone for about 6 months or proceed with a high dose chemotherapy + ASCT, the issue of further therapy (maintenance) is out in the open although the recent French study supports use of thalidomide maintenance.[24] Myeloma being an incurable disease, the patients, families and physicians raise many questions at this point. There is no easy answer at this moment. I tend to follow, 1. In a complete or near complete responder, offer a close observation, 2. If the patient has made up a mind not to accept high dose melphalan at any time of the illness (i.e. lifetime), add oral melphalan to thal-dex and continue therapy for another 6 months to complete one year's therapy, 3. In patients with significant residual disease, offer salvage therapy with whatever is practical, e.g. oral cyclcophosphamide + dexa, possibly VAD (if not used upfront) and bortezomib.

TREATMENT OF RELAPSED DISEASE

The real test comes now. Depending on the time of progression (early progression is always a bad news) and number of cytotoxic drugs exposure in a given patient I discuss about resumption of thalidomide, cyclophosphamide, dexa, bortezomib, etc. Only rarely I discuss about an allogeneic SCT and as a result my experience in this area remains inadequate. We have done reduced intensity transplants with no great achievements. In case of late relapses, ~50% respond favorably to salvage therapy, although the response is maintained for a shorter length. In my own experience, as also noted by other physicians, oral cyclophosphamide is an excellent palliative agent for relatively slow growing relapsed myeloma.[24,25]

Bortezomib, a proteasome inhibitor, has shown to be very effective (about one-third) in this setting.[21-23] If combined with dexa or other effective antimyeloma drugs, the response is usually better. As it happens with other antimyeloma agents, bortezomib also maintains a response for about 12-14 months. The drug causes peripheral neuropathy and rapidly reversible thrombocytopenia.

Till date, I have no personal experience of using revlimid (lenalidomide). As the drug has recently been approved by the US FDA, we should be using it frequently, given its favorable activity on relapsed disease even in some thalidomide non-responders.[26]

TREATMENT OF REFRACTORY MYELOMA AFTER MULTIPLE THERAPEUTIC INTERVENTIONS

The discussion with patient and family does not end up satisfactorily at this junction. We discuss about further palliation with whatever drug is available at a given point for a given patient. We also discuss about newer drugs, clinical trials, etc. More often, it is a corticosteroid along with supportive care, we agree upon. It is not uncommon to see the patient knocking the door of another physician and/or alternative therapy and such things. I do not feel lost out to some other human beings but only to the nature.

ELDERLY MYELOMA PATIENTS

Until recently, the approach was to treat with the age honored MP regimen of oral melphalan and prednisolone for patients above 65 years of age. Melphalan is one of the most potent agents for myeloma. With the advent of thalidomide in myeloma, the Italian and the French investigators pioneered clinical trials combining melphalan, prednisolone and thalidomide (MPT regimen) and have shown response comparable with high dose melphalan + ASCT.[27,28] It will be interesting to see the duration of response in these patients. If proven to be equivalent or better, the option might open

up to the younger patients. In such a case, there is a possibility of ASCT in myeloma going the CML allogeneic SCT way.

I certainly treat all elderly myeloma patients with the MPT regimen for a year and then observe. The tolerance and the response have been satisfactory. However, it appears that most elderly patients tolerate only a lower dose (~100 mg daily) of thalidomide. Availability of revlimid for upfront use may allow optimal dose therapy.

CONCLUSIONS

The management of multiple myeloma is a rapidly changing paradigm due to better understanding of its biology and development of newer molecules. Managing a myeloma patient is a much more challenging at the current time, especially with the availability of diagnostic and prognostic assessment and therapeutic agents. A complete diagnostic and prognostic work up is necessary to plan out a total therapy in a given patient. Current advances have made it possible to effectively manage even the elderly patients of multiple myeloma; however, associated co-morbid conditions remain a hurdle in these patients. High dose chemotherapy with ASCT will remain an important therapeutic approach for some years. While it is crucial to continue to have pivotal clinical trials, in clinical practice, every myeloma patient needs an individualistic care based on available scientific evidence. In this article, I have attempted to discuss the different aspects of myeloma as per evidence-based medicine; nevertheless, in an attempt to be concise in the review, it has not been possible to analyze every issue with detailed discussions. The readers are advised to refer to published studies for in-depth information.

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