International Journal of Research in Medical Sciences
Anand AS et al. Int J Res Med Sci. 2016 Dec;4(12):5093-5098
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20164155

Original Research Article

Transplant ineligible multiple myeloma patients presenting as paraplegia/paraparesis a prospective single institution study

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Received: 08 November 2016
Revised: 10 November 2016
Accepted: 12 November 2016

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ABSTRACT

Background: Multiple myeloma a plasma cell neoplasm characterized by heterogeneous myriad of presentation with paraparesis or paraplegia in 20% cases due to spinal cord compression by vertebral collapse, compression or fracture.
Methods: This is a prospective observational study of thirty transplant ineligible multiple myeloma patients with paraplegia/paraparesis. Pretreatment evaluation done as per standard protocol including MRI whole spine. Involved spine XRT 8Gy single fraction followed by BLD (Bortezomib 1.3mg/m^2 weekly once, Lenalidomide 10mg/m^2 for 21 days, oral dexamethasone 40 mg weekly once). Neurological parameters, time to neurological and tumor response at 6 months assessed. Patients in very good partial response or complete response were maintained on Lenalidomide and bisphosphonate therapy for a period of two years. The duration of symptoms and time to response were analyzed with Mann Whitney Cox test.
Results: 15 patients were grade 0 power and others grade 1 or 2. Median time to any neurological response was 2.97 weeks. 63.3% of patients achieved power of grade 5, 30% grade 4 and 6.7% grade 3 powers. 23.3% patients received complete response while 63.3% patient's very good partial response.
Conclusions: Bedridden myeloma patients had an excellent improvement in quality of life and tumor control with this treatment schedule.

Keywords: Bortezomib, Multiple myeloma, Paraplegia, Radiation

INTRODUCTION

Multiple myeloma (MM) is a clonal B-cell disorder characterized by proliferation and accumulation of B-lymphocytes and plasma cells in the bone marrow and, more rarely, at extra medullary sites.[1] Spine is the bone site that is most frequently affected by MM-related lesions.[2] Vertebral lesions can result in pain, permanent deformity, kyphosis, walking impairment, permanent disability, or paralysis. In almost 20% of the cases, spinal cord compression (SCC) may occur; diagnosis and treatment must be carried out rapidly in order to avoid a permanent sensitive or motor defect.[3]

It can be estimated that over 60% of bone lesions occurring in MM patients involve the spine, as compared with 90% in metastatic prostate cancer, 75% in breast cancer, and 45% in lung cancer.[4]

Displacement and compression of the spinal cord can be caused by either epidural invasion by neoplastic tissue or by osseous fragments protruding from a fractured vertebral body. Pain is the first and most common presenting symptom.[5,6] The reason for the pain could be either, mechanical which becomes more intense in case of cough/exercise or radicular pain caused by nerve-root compression. Motor weakness is the second most

frequent neurological symptom of SCC. Patients complain about weakness of lower limbs, which can range from difficulty while walking or climbing up the stairs to frank paraparesis/paraplegia. Sensory symptoms such as paresthesias, tingling, or numbness can occur simultaneously or following motor dysfunction; but they usually precede autonomic-sphincteric symptoms with bladder dysfunction the common presentation.[5,6] Early recognition of these symptoms is of paramount importance as it may invariably proceed to paraplegia if not intervened early and otherwise results are dismal.[7]

The gold standard diagnostic investigation to evaluate SCC is spinal magnetic resonance imaging (MRI), which allows a clear identification of bone lesions, tumor masses, and neural alterations like cord edema.[8] Decompressive laminectomy was frequently performed in the past but it is now not that propagated due to the residual instability of the vertebral column, possible delay in the initiation of anti-myeloma therapy after surgery and, above all, because of the excellent response of neoplastic cells to steroids and radiotherapy.[9]

High-dose steroids, such as dexamethasone at doses of 40 mg/day for 4 days are started immediately at the advent of signs and symptoms suggestive of SCC, to reduce spinal cord edema. Radiotherapy, either 30 Gy in 10 fractions or shorter courses is also administered at the earliest, for an optimal local control of the disease and symptom relief.

It has been frequently observed in our clinical practice that patients with long standing paraplegia are not treated radically with the aim of complete ambulation especially in hospitals with no oncological expertise. But we have realized from our clinical experience that even these subset of bedridden patients with longstanding paraplegia tend to improve to better motor power if treated with radical intent. Taking this observation into consideration we have conducted this prospective observational study.

Primary objective was to assess the neurological improvement of paraplegia/paraparesis multiple myeloma patients after single local radiation of 8 Gy to the affected area of the spine followed by combination chemotherapy with Bortezomib, Lenalidomide & Dexamethasone (BLD) and secondary objective was to evaluate the treatment response to BLD schedule

METHODS

A total of thirty multiple myeloma patients who satisfied the inclusion and exclusion criteria were enrolled for the study from 2012 to 2014.

Inclusion criteria

- Newly diagnosed as multiple myeloma according to international myeloma working group diagnostic criteria
- Transplant ineligible patients
- Patients with motor grade power - 0, 1 or 2
- ISS stage 2 or 3

Exclusion criteria

- Platelet count <1 lakh/mm^3
- Patients with severe peripheral neuropathy
- Uncontrolled diabetes mellitus

Methodology

Patients satisfying the selection criteria are recruited for the study. A detailed neurological evaluation done. Motor and sensory power assessed. A whole spine MRI screening done for all patients. The extent of spinal cord compression assessed, vertebral and soft tissue involvement recorded. Local XRT 8 Gy single radiation given to involved spine and soft tissue as early as possible. Patient was started on BLD chemotherapy (Bortezomib 2mg s/c weekly once, Lenalidomide 10mg HS d1- d21 , Dexamethasone 40mg weekly once) within 1 week if hematological parameters were normal or were started on Dexamethasone initially followed by BLD once parameters were suitable for the same. Thereafter all patients were started on Inj. Zoledronic acid (Z.A) 4mg monthly if renal parameters were within normal limits. Patients had a dental evaluation prior to the start of Z.A.

If renal parameters were deranged then they were started with BD schedule. Lenalidomide and Z.A added once renal function improved. First response evaluation was done 6 months after initiation of therapy, which included serum and urine immunofixation studies and free light chain assay. If these investigations were within normal limits, then bone marrow aspiration was done, to assess whether they have gone in for complete response (<5% plasma cells). Patients were classified based on response criteria by international myeloma working group.[16] If complete response achieved, those patients started on maintenance therapy with Lenalidomide 10mg D1 to D21 of 28 day cycle. If very good partial response (VGPR), partial response (PR) continue BLD X 2-4 cycles till CR and then maintenance with lenalidomide. For stable and progressive disease individualized alternate regimen given. Neurological assessment of the patient was made weekly when the patient reported for weekly bortezomib and recorded systematically. Statistical analysis was carried out using SPSS version 18.0 Software.

Ethical approval

The study was approved by the institutional human ethics committee and institutional review board. All procedures performed in the study were in accordance with the ethical standards of the institutional ethics committee and with the1964 Helsinki declaration and comparable ethical standards.

RESULTS

A total of 30 patients diagnosed as multiple myelomas as per the standard protocols with paraparesis or paraplegia at presentation was, included in this study. The baseline characteristics of the patients are depicted in Table 1.

Table 1: Baseline characteristics of the patients.

Variable	Frequency
Sex	
Male	20 (66.67 %)
Female	10 (33.33 %)
Median age (years)	56 (39 -78)
Median duration of symptoms at the time of presentation (days) 20.50	
Neurological status at time of admission	
Paraplegia	15 (50%)
Paraparesis	15 (50%)
With sensory symptoms (other than pain)	11 (36.7%)
Bowel/bladder symptoms	4 (14.3%)
MRI spine – involved area	
Thoracic vertebra	N=15 (50%)
Lumbosacral vertebra	N=10 (33.33%)
Thoracic and lumbosacral	N=5 (16.67%)
Motor grade of power at the time of presentation	
Grade 0	15 (50%)
Grade 1	9 (30%)
Grade 2	6 (20%)
International staging system	
ISS 2	17 (56.7 %)
ISS 3	13 (43.3 %)
Median beta2 microglobulin level (mg/dl)	6.3
Median serum LDH level (IU/L)	342

Median age of patients at presentation was 56 years. The median follow up period of the study was 27 months. The median duration of neurological deficit at the time of presentation was 20.5days. 50% of patients were having grade zero power at the time of admission and 30% were having either grade 1 and 20% grade 2 motor power. When the duration of symptoms were less than 30 days at the time of presentation, the mean time to any response was 2.30 weeks, time to best motor grade was 4.17 weeks, compared to 5.14 and 7.14 weeks respectively, when the duration of symptoms were more than 30 days. Mann Whitney Test compared its statistical significance with p=0.01 and p=0.019 respectively, both favoring the less than 30 days subset.

Thoracic vertebra was the most common site of spinal compression, seen in 50% of the patients followed by lumbosacral in 33.3% and multiple sites in remaining patients. ISS stage 2 and 3 were only included in this study. 56.7% was ISS stage 2 and the remaining 43.3% stage 3. The median beta 2 microglobulin level was 6.3mg/dl and LDH level 342 IU/L. After the planned treatment the median time for any neurological response was 2.97 weeks and the median time for best motor response was 4.87 weeks. More than 70% of patients the first neurological parameter improved were motor function followed by sensory function. Surprisingly 63.3% of patients achieved Grade5 motor powers, 30% grade 4 powers and the remaining Grade 3 power. With regard to pain control 96.6% of patients had pain control without any analgesics.

Table 2: Post treatment response of patients.

Variables	Result
Median time to any neurological Response (in weeks) (N=30)	2.97
Paraparesis (in weeks) (N=15)	3.33
Paraplegia (in weeks) (N=15)	2.67
Time to best motor response (in weeks) (N=30)	4.87
Paraparesis (in weeks) (N=15)	5.47
Paraplegia (in weeks) (N=15)	4.27
First neurological parameter to improve	
Motor	N=21 (70%)
Sensory	N=6 (20%)
Bowel/Bladder	N=3 (10%)
Best motor grade achieved	
Grade 3	N=2 (6.7%)
Grade 4	N=9 (30%)
Grade 5	N=19 (63.3%)
Pain control	
Complete Pain Relief	N=12 (40%)
Partial Pain Relief	N=17 (56.6%)
Response rate to BLD regimen	
CR	N=7 (23.3%)
VGPR	N=19 (63.3%)
PR	N=4 (13.3%)
Median follow up (in months)	27 (17-38)
Mean progression free survival (in months)	34.2

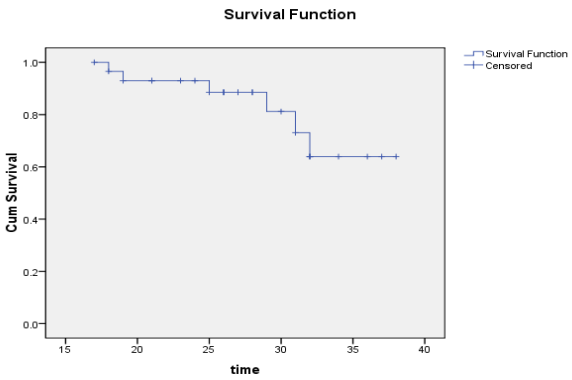

Figure 1: Kaplan Meier estimates for mean Progression free survival in the study population.

In present study population of high risk myeloma BLD regimen is a good regimen, as 23.3% achieved complete response, 63.3% very good partial response followed by partial response in 13.3% of patients. Two out of the three patients who had expired had good neurological improvement, but were on long term dialysis and had only partial response to the therapy. The third patient had congestive cardiac failure not attributable to the myeloma. The mean Progression Free Survival (PFS) estimated using Kaplan Meier survival estimate analysis.

DISCUSSION

Metastatic spinal cord compression (MSCC) is a common bothersome problem affecting the quality of life of cancer patients. It affects 5% to14% of all patients with cancer.[10,12] Multiple myeloma presents as spinal cord compression in nearly 20% patients. The study population in present study is unique in that all these patients were either paraplegic or presenting with paraparesis and thus bed ridden. These patients were initially evaluated in the peripheral hospitals and referred to the oncology department without any scope for improvement as all of them had sustained neurological weakness of several days. At the same time, these patients were high risk patients as they were either ISS stage 2 or 3 and elevated S. LDH levels. They generally tend to have a poor general condition in view of the longer duration of symptoms, prolonged hospital stay and delay in initiating anti myeloma therapy. We aimed at providing the best possible oncological and supportive care rather than residing to only pain and palliative management. Our results were extremely encouraging as most of the subjects gained a reasonably good gain of motor function and better quality of life.

As per the literature there are various palliative XRT schedules for patients who had spinal cord compression. The studies to date addressing the issue of spinal cord compression in malignancy have all incorporated radiosensitive and non -sensitive tumors. The most commonly used fractionation schedule in these metastatic spinal cord compressions is 30Gy as 10 fractions. To our knowledge there is no prospective study in the literature till date solely incorporating multiple myeloma. Hence our study is the first one of this kind. In present study 100% of the patient became ambulatory with more than 93% with normal or near normal motor function. A study by Patchell et al which included all types of metastatic spinal cord compression showed a motor response rate of 70% with a protracted radiation of 10 fractions. But in their study, the definition of motor response was stability and improvement. When the strict definition of attaining the motor function as in our study is taken into consideration the response rate in study by Patchell et al is still lower by another 29 %. Our study has proved beyond doubt that single XRT of 8Gy can bring the best possible motor function in a radiosensitive tumor like myeloma. This suggests the fact that fractionated RT as in other metastatic bone disease may not be necessary in multiple myeloma as the biology of the bony pathology is different.

The postulated pathology behind bone destruction in myeloma has been an imbalance in the osteoclast and osteoblast activity, where there is an increase in osteoclast activity and decrease in osteoblast activity. The bone marrow milieu in myeloma cell rich environment results in an increase in osteoclast activation factors like IL-1β, TNF-β (lymphotoxin), IL-6, and MIP-1α. The receptor activator of nuclear factor kappa B ligand (RANKL) plays an important role in osteoclast differentiation and osteoprotegerin acts as a decoy receptor for RANKL, and has been implicated in the pathogenesis of lytic bone lesions in myeloma.[19] We have also observed that none of present patients experienced an in- field progression of disease in the follow up period.

Several authors have advocated the use of surgical decompression and stabilization after or before radiation. One of the studies shifting the emphasis from surgery to RT was a retrospective review of 235 patients by Gilbert et al.[14] In this study analysis was based on the radio sensitivity of the tumor and preoperative functional status. The overall rate of postoperative ambulation in the laminectomy and RT versus RT alone was 46% and 49%, respectively. Patients with radiosensitive tumors had better functional neurologic outcome compared to less radiosensitive tumors, regardless of the treatment.

Those patients ambulatory at the outset of treatment also had better outcomes compared to those paraparetic (nonambulatory) or paraplegic. It may be stressed that in our study all these multiple myeloma patients achieved the best motor response without any surgical intervention, even in patients who were bedridden for a long period of time. This is in contrary to the study by Patchell et al where the overall ambulatory rates were poor in radiation alone arm compared to radiation and surgical intervention combined arm.[15] This because they have incorporated both radiosensitive and radio resistant tumors in their study and also the response received by further continuum of treatment by cytotoxic therapy varies between different tumor types. In this scenario it may be pointed out that the BLD chemotherapy which is continued after the initial emergency radiation brings out excellent tumor response with an overall response rate of 86.6%, i.e. complete and very good partial response combined. These results are similar to the already published phase 2 and phase 3 trials from the western world.[17,20] Bortezomib is a proteasome inhibitor with blockade of NFκB activation and related paracrine IL-6 production by bone marrow stromal cells. Bortezomib has also been demonstrated to act directly on MM cells to induce caspase 8 and 9 activated apoptosis and potentiates the anti tumour effects of Lenalidomide and Dexamethasone. Therefore it's critical that Bortezomib based regimens should be initiated at the earliest in poor prognostic patients to maximize the benefits of treatment.[18]

The mean Progression Free Survival (PFS) estimated using Kaplan Meier statistical tool, was 34.2 months (Figure 1), which is at par with the western results for BLD regimen, confirming the effectiveness of the three drug protocol in this poor prognostic subset of patients.[17]

Present study results challenge the need for a protracted radiation treatment or a combined surgical decompression and radiation treatment for this set of radio and chemo sensitive tumor like multiple myeloma. The current general concept with regard to radiation fractionation is that short course hypofractionated schedules are selected for poor prognosis metastatic spinal cord compression and long course small fraction radiation treatment for good prognosis patients expecting good survival. But we wish to add a note to this generalization, which we have proved from our study that the tumor biology of the patient is very important in decision making. As there is paucity of high level of evidence in the management of metastatic spinal cord compression the information achieved from studies like ours may be of clinical significance in decision making.

As per the currently available literature early initiation of local treatment either decompression or radiation to the affected area is of paramount importance to achieve maximal results with regard to neurological improvement, our study has revealed that this set of radiosensitive tumors must not be left untreated even when several days have elapsed after sustaining paraplegia. In our study the median duration of neurological deficit was more than 20 days but still patients have achieved the best motor response. Lenalidomide and Zoledronic acid maintenance therapy were well tolerated by almost all patients and definitely it has provided good progression free survival.

CONCLUSION

Multiple myeloma patients who present even with paraparesis and poor performance status can be offered reasonable quality of life and disease free survival with planned oncological treatment. This set of patients who are usually put purely on non-oncological palliative treatment must be provided individualized oncological treatment. From our study we conclude that bedridden myeloma patients achieve excellent improvement in quality of life and disease control with single 8 Gy local spine XRT and BLD induction followed by Lenalidomide maintenance, along with bisphosphonate therapy. It is further observed that this combined modality treatment is well tolerated and maintenance with Lenalidomide 10mg is a feasible option. Henceforth these patients should be treated with a radical intent.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Anand AS, Kuriakose VG, Resmi KP, Sabarinath PS. Transplant ineligible multiple myeloma patients presenting as paraplegia/paraparesis a prospective single institution study. Int J Res Med Sci 2016;4:5093-8.