Original Study

Feasibility and Efficacy of Local Radiotherapy With Concurrent Novel Agents in Patients With Multiple Myeloma

Samuel M. Shin,[1] Robert J. Chouake,[1] Nicholas J. Sanfilippo,[1] Timothy B. Rapp,[3] Perry Cook,[2] Silvia C. Formenti,[1] Amitabha Mazumder,[2] Joshua S. Silverman[1]

Abstract

Treatment of multiple myeloma with radiotherapy concurrent with novel agents, cytotoxic therapy, or both was safe, effective, and well tolerated in the majority of patients, with no dose adjustment or significant treatment-related toxicity.

Introduction: This study evaluated the safety and efficacy of radiotherapy (RT) with concurrent novel agents (NAs), cytotoxic therapy (CTx), or both in the management of osteolytic bone lesions in multiple myeloma (MM). **Patients and Methods:** A total of 39 patients with MM received RT to 64 different bone sites during the 2007-2012 period, with a dose of 8 to 37.5 Gy (mean, 26.8 Gy) delivered in 1 to 15 fractions (median, 10 fractions). Of these patients, 21 also received concurrent NAs or CTx. Pain response, M protein and κ light chain response, and adverse events were evaluated. **Results:** RT was completed in 35 of 39 patients (89.7%) in this study. Pain relief was observed in 30 of 31 patients (96.7%). Hematologic toxicity (grade 3 or 4 by the Radiation Therapy Oncology Group system) was seen in 43.2% of treated patients, and NA therapy was stopped in 2 patients owing to grade 4 toxicity. RT adverse effects resolved at 4 to 6 weeks posttreatment. Changes in pre- and posttreatment levels of M protein trended toward significance in patients treated with RT + systemic therapy (ST) versus. RT alone ($\Delta M\ Protein_{RT+ST} = 5.6$ g/L; $\Delta M\ Protein_{RT} = 0$ g/L; $P = .089$). **Conclusion:** Treating MM with RT concurrently with CTx including NAs was safe and well tolerated in the majority of patients (14 of 16 [87.5%] for those taking NAs and 19 of 21 [90.5%] for all patients). Excellent clinical pain response (> 95%) was also seen in patients regardless if they were treated with RT + ST or RT alone.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 14, No. 6, 480-4
Keywords: Multiple myeloma, Novel agents, Radiation, Safety, Toxicity

Introduction

Multiple myeloma (MM) is a malignant neoplasm of plasma cells that accumulates in the bone marrow, leading to bone destruction and marrow failure. Owing to increased activation of osteoclasts by tumor necrosis factor β, interleukin-1, and interleukin-6, there are resulting osteolytic bone lesions leading to bone pain and fractures that occur spontaneously or after minor trauma.[1] Bisphosphonates can be used to decrease the incidence of skeletal complications with decreased bone pain, formation of osteolytic lesions, hypercalcemia, and bone fractures.[2-4] In addition, other types of systemic therapy (ST), such as cytotoxic chemotherapy (CTx) and novel agents (NAs), can further delay progression of myelomatosis.

The use of NAs in patients with MM has resulted in increased clinical complete response, translating to delayed time to progression, improved progression-free survival, and improved overall survival.[5,6] NAs include proteasome inhibitors and immunomodulatory drugs such as thalidomide, bortezomib, carfilzomib, and lenalidomide.[7-12] Cytotoxic drugs such as melphalan and cyclophosphamide have also proven to be effective in the treatment of MM.[13-15]

In addition to ST, myeloablative therapy with allogeneic or autologous stem cell transplant has also been used in the overall management of MM, with the possibility of cure due to graft-versus-myeloma effect.[16] After treatment response, patients may receive maintenance therapy to prolong duration of remission.[17]

However, MM remains incurable,[18,19] and local therapies are frequently used to treat MM-induced lesions in the palliative setting

[1]Department of Radiation Oncology
[2]Department of Medical Oncology
[3]Department of Orthopaedic Surgery
New York University School of Medicine and Langone Medical Center, New York, NY

Submitted: Apr 8, 2014; Revised: Jul 17, 2014; Accepted: Jul 29, 2014; Epub: Aug 1, 2014

Address for correspondence: Joshua S. Silverman, MD, PhD, Department of Radiation Oncology, New York University Langone Medical Center, 160 E 34th St, LL1, New York, NY 10016
E-mail contact: joshua.s.silverman@nyumc.org

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2014.07.010

and solitary osseous or extraosseous plasmacytomas in the definitive setting.[20,21] Surgery may be indicated in the management of plasmacytomas to repair fractures, to stabilize bone at risk of pathologic fracture, or to relieve spinal cord compression.[22,23] Radiotherapy (RT) is used to treat bone pain, to manage areas at risk for pathologic fracture, and to sterilize residual disease after surgery.[24] MM is highly responsive to RT owing to its radiosensitivity, with clinical response rates as high as 97%.[25,26]

Literature is lacking regarding the safety and efficacy of treating patients with MM using local RT concurrently with CTx, NAs, or both. However, there are small, retrospective studies that have found safety of RT concurrently with CTx. A German study reviewed 77 patients with MM who were treated with RT.[27] The response rate was 80% in patients treated with RT concurrently with melphalan and prednisone and was 39.6% in patients treated with RT alone. In addition, the duration of local remission and pain relief was 31.8 ± 3.6 months versus 24.8 ± 17.9 months in patients receiving RT with and without chemotherapy, respectively. Their analysis determined that combined treatment with RT and melphalan resulted in higher response rates and a longer local remission compared with treatment with RT alone. However, there is little known regarding the use of concurrent RT with NAs.

This retrospective analysis evaluates patients with a diagnosis of MM who have been treated with local RT with and without concurrent ST in a single institutional setting from 2007 to 2012. The goal of this retrospective analysis is to evaluate the safety and efficacy of RT concurrently with ST, including NAs, in the management of MM.

Patients and Methods

For the 2007-2012 period, 39 consecutive patients with MM treated with or without ST and RT were analyzed (Table 1). The median ages at diagnosis and treatment were 60.5 years (range, 29-78) and 63 years (range, 29-85), respectively; 20 men and 19 women were treated. The majority of patients treated were either white (n = 15), Hispanic (n = 8), or African American (n = 12). All 39 patients were diagnosed with MM of stage I to stage III by the International Staging System. Although 3 patients had had no prior chemotherapy, most (31) had received prior chemotherapy; 10 patients had undergone prior autologous bone marrow transplant.

The prescribed RT dose ranged from 8 to 37.5 Gy (mean, 26.8) and was delivered in 1 to 15 fractions (median, 10). A total of 66 different sites were treated; 24 of 39 patients (61.5%) received radiation to lesions within the vertebral column, and 21 of 39 patients (53.8%) received radiation to 25 different sites with ST concurrently. The ST included the use of NAs (bortezomib, carfilzomib, thalidomide, or lenalidomide) in 17 patients and CTx (cyclophosphamide or bendamustine) in 4 patients.

Treatment efficacy was evaluated through clinical and hematologic response after RT. Subjective treatment response was evaluated through pain response, and objective treatment response was evaluated through comparison of pre- and posttreatment myeloma protein (M protein) (n = 9) and kappa light chain (κ) in patients whose data included those levels (n = 12). Adverse effects from ST and RT were evaluated to investigate whether or not concurrent ST and RT significantly increased toxicity. This study was approved by the institutional review board. A paired-samples *t* test was performed to determine the difference in treatment effect on M protein and κ light chain response, and a 2-tailed value of $P < .05$ was considered statistically significant. All patients were included for intent-to-treat analysis. All authors had access to patient data.

Table 1 Patient and Tumor Characteristics

Variable	Value
No. of Patients	39
Age (years) at Treatment, Median (Range)	63 (29-85)
Sex	
Male	20
Female	19
Ethnicity	
White	15
African American	12
Hispanic	8
Asian	3
Other	1
Tumor Type	
Multiple myeloma	39
Stage (International Staging System)	
I	1
II	5
III	22
Not recorded	11
Previous Bone Marrow Transplants	
Yes	10
No	8
Not recorded	21
Prior Chemotherapy	
Yes	31
No	3
Not recorded	5
M Protein	
No. of Patients	9
Pretreatment in g/L, mean (range)	1.21 (0-4)
Light Chain Kappa	
No. of Patients	12
Pretreatment in mg/L, mean (range)	49.2 (.18-199)
Radiation	
Dose (Gy), mean (range)	27.1 (8-46)
Fractions, mean (range)	10.1 (1-23)
Number of radiation treatment courses	53
Sites treated	64
Chemotherapy (Concurrent)	
Yes	21
No	18
Novel agents	16
Cytotoxic ± novel	5

Results

A total of 39 patients were included in the final analysis; however, 4 patients were unable to conclude their course of RT. One patient