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Scientific Article

The Safety Profile of Concurrent Therapy for Multiple Myeloma in the Modern Era

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Abstract

Purpose: The management of multiple myeloma has evolved in the modern era, partially owing to the increasing number of biologic therapeutics. Nonetheless, radiation remains an important treatment in the management of painful lytic lesions from multiple myeloma. The goal of this study is to evaluate the side effect profile of radiation therapy (RT) while patients are concurrently treated with biologic agents.

Methods and Materials: We conducted a retrospective study based on data collected from patients receiving RT at our institute from 2007 to 2017. A total of 130 patients (279 treatment sites) were included in this study with a median follow-up time of 14 months. Patients were required to be receiving a biological agent at least within 1 month before starting and up to 1 month after RT. Generalized estimating equations with a log link function and binomial distribution were used to estimate the prevalence ratio (PR) and corresponding 95% confidence interval (CI) and compare the side effects between patients with RT alone and RT + biologic agent.

Results: The median age of all patients in our cohort was 64 years, with 53 men (58.9%) and 37 women (41.1%). The mean Karnofsky performance status score of all cohorts was 80. No significant difference in incidence of acute (PR: 1.33; 95% CI, 0.80-2.22; $P = .2660$) or subacute (PR: 0.90; 95% CI, 0.49-1.67; $P = .7464$) toxicities was found between patients with or without biologic agents who were treated concurrently with RT. No significant difference was found in reduction in laboratory values between patients with or without biologic agents treated concurrently with RT for white blood cells ($P = .6916$), platelets ($P = .7779$), or hematocrit ($P = .0858$).

Conclusions: Our study did not detect any significant toxicity rates from palliative radiation while patients were concurrently treated with biologic agents.

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Introduction

Multiple myeloma (MM) is caused by the proliferation of a single clone of plasma cells that produce a monoclonal immunoglobulin. In turn, these plasma cell clones can cause extensive skeletal destruction with osteolytic lesions, osteopenia, or pathologic fractures. Additional disease-related complications include hypercalcemia, renal insufficiency, anemia, and infections. Some of the most common symptoms include fatigue, bone pain, and recurrent infections.[1,2]

The mechanism through which MM causes bone damage is thought to be due to a host of different changes to the bone marrow microenvironment, including induction of angiogenesis, the suppression of cell-mediated immunity, and the development of paracrine signaling loops involving cytokines such as interleukin 6 and vascular endothelial growth factor.[3] Discoveries such as these have led to the development of multiple targeted agents,[4] including new applications of thalidomide and usage of bortezomib.[5]

There have been a number of new biologic agents introduced during the past decade that have improved the outcomes of this disease, including notably daratumumab, a monoclonal antibody to CD38, which myeloma cells have been shown to overexpress. Several studies have shown its efficacy as a monotherapy as well as in combination with pomalidomide and dexamethasone, which show overall survival (OS) rates of 18 months and progression-free survival (PFS) rates of 12 months, while maintaining a tolerable side effect profile.[6-9]

As patients live longer, the development of pain metastatic lesions from MM becomes ever more prevalent. Radiation therapy (RT) has long been used for the management of painful bone lesions in patients with MM, with excellent response rates (as high as 89.6% complete or partial pain resolution in modern cohorts). Currently, RT remains a major therapeutic component for the management patients with MM because it provides pain relief but does not interfere with a potential stem cell transplant.[10-12] Palliation of the lytic myeloma lesions can be accomplished using 20 Gy to 30 Gy in 5 to 10 fractions, and higher doses are often reserved for solitary plasmacytomas.[13] In addition, different fractionation schemes have been employed with great success, including the utilization of a single 8-Gy fraction.[14]

Currently, lytic lesions that lead to bone pain are seen in as many as 60% of patients at the time of diagnosis, and as many as 40% of patients require RT to control the disease at some point during its course.[15] Radiation in this setting is entirely palliative and therefore should ideally not interrupt ongoing systemic therapy.

The addition of daratumumab to other biologic agents, such as borterzomib, has shown a significant improvement in PFS compared with bortezomib and dexamethasone alone, for example. However, higher rates of thrombocytopenia, neutropenia, and infusion reactions were seen when daratumumab was added to bortezomib and dexamethasone.[16] These increased rates of hematological toxicities were also seen when adding daratumumab to lenalidomide.[17]

In addition, a second-generation proteasome inhibitor, carfilzomib, has also been introduced for the management of refractory MM and has shown an improvement in PFS of as much as 26.3 months versus 17.6 months when added to dexamethasone and lenalidomide, with a safe toxicity profile.[18,19] This drug has also demonstrated an improvement of 8 months when added to dexamethasone and lenalidomide in median OS versus regimens without.[20]

In the modern era, patients often receive these biologic agents, but whether they should continue or end treatment while undergoing palliative RT owing to toxicity concerns by combining both treatments remains unclear. There are isolated reports of toxicity associated with concurrent RT, but there is a lack of systematic review of such toxicities.[21] The current guidelines by the International Lymphoma Radiation Oncology Group raised the concern for lack of evidence pertaining to the safety of combining RT and chemotherapy agents, "specifically in terms of sensitization of normal tissue toxicity or depletion of the bone marrow reserve."[22] A retrospective review showed no differences in terms of hematologic toxicity between patients treated with RT alone and those receiving RT with concurrent, novel, agent-based chemotherapy.[23]

Given the important roles of both new biologic agents and RT in the management of MM, a presentation of a large modern series indicating the safety of the concurrent use of these 2 interventions was necessary, considering that many patients will require both at one point. Herein, we report on the largest modern, retrospective series to evaluate the safety and toxicity of concurrent biologic therapies including carfilzomib, bortezomib, and daratumumab.

Methods and Materials

We conducted a retrospective study on the basis of data collected from patients receiving RT at our institute between 2007 and 2017, for which institutional review board approval was obtained. Patients were required to be

Table 1 Patient demographics (upper half of table) and by lesions treated (lower half of table)

(Per patient)	Overall N = 130
Age at time of first RT, years Median (range)	64 (28-85)
Sex	
Male	81 (62%)
Female	49 (38%)
Ethnicity	
White	50 (40%)
African American	37 (30%)
Hispanic/Latino	19 (15%)
Asian/other	18 (15%)
ISS stage	26 missing data
1	64 (62%)
2	14 (13%)
3	26 (25%)
Karnofsky performance status score (first on record) Median (range)	80 (30-100)
Treatment sites per patient Median (range)	1 (1-6)
Courses of RT per patient Median (range)	2 (1-13)
Prior chemotherapy/cytotoxic agents (before first RT)	
Yes	116 (89%)
No	14 (11%)

(Per lesion)	Overall RT N = 279	RT + BA N = 172	RT All N = 107
Radiation dose group			
≤20 Gy	171 (61%)	98 (57%)	73 (68%)
20-30 Gy	35 (13%)	25 (15%)	10 (9%)
≥30 Gy	73 (26%)	49 (28%)	24 (22%)
Dose (Median, range)	20 (2-40)	20 (8-40)	20 (2-40)
Radiation fractions (Median, range)	10 (1-20)	10 (1-20)	10 (1-20)
Radiation technique			
3-dimensional	134 (48%)	85 (49%)	49 (46%)
2-dimensional	102 (37%)	61 (35%)	41 (38%)
Intensity modulated RT	21 (8%)	13 (8%)	8 (7%)
Stereotactic radiation surgery/ Stereotactic RT/ Stereotactic body RT	17 (6%)	8 (5%)	9 (8%)
En face/Electrons/ Electron boost	5 (2%)	5 (3%)	0 (0%)
Common sites (top 6 sites)			
Spine	104 (37%)	65 (38%)	39 (36%)
Pelvis	38 (14%)	27 (16%)	11 (10%)
Skull	32 (11%)	23 (13%)	9 (8%)
Shoulder	25 (9%)	10 (6%)	15 (14%)
Leg	20 (7%)	10 (6%)	10 (9%)
Arm	19 (7%)	8 (5%)	11 (10%)
Biologic agents			
Bortezomib	/	72 (42%)	/
Carfilzomib		39 (23%)	
Daratumumab		25 (15%)	
Other		36 (20%)	

Abbreviations: BA = biologic agent; RT = radiation therapy.

receiving a biologic agent at least within 1 month before starting and up to 1 month after RT. The medical oncologists did not withhold therapy for these patients, and dosing was based on standard parameters as opposed to RT. A total of 130 patients and 279 treatment sites were included in this study with a median follow-up time of 14 months. A total of 91 patients received concurrent RT with at least 1 of the aforementioned biologic agents to 172 different sites. The remaining 39 patients received RT alone to 107 different sites. Toxicities were rated according to Common Terminology Criteria for Adverse Events, version 5.0. We reviewed the last complete blood count before starting RT and the first complete blood count after completion.

Continuous variables were summarized by the median and range, and categorical variables were summarized by number and percentage. Demographic information and general treatment variables were described per patient, and radiation characteristics were summarized by RT. Generalized estimating equations with a log-link function and binomial distribution were used to estimate the prevalence ratio (PR) and corresponding 95% confidence interval (CI) and to compare the risk of onset of acute side effects (within 4 weeks of treatment), subacute side effects (during 4 weeks and 6 months of treatment), and hematological events (grade ≥3 anemia, need for platelet transfusion, and need for neupogen) between patients with RT alone and RT + biologic agents.

A compound symmetrical covariance structure was assumed to control for intrasubject correlation. A mixed model analysis of covariance was used to estimate the changes in blood counts (white blood cells, platelets, and hematocrit) before and after treatment while adjusting for pretreatment values. All hypothesis testing was 2-sided, and conducted at the 5% level of significance. Statistical analyses were performed with the SAS, version 9.4 (SAS Institute Inc, Cary, NC) software package.

Results

The median age of all patients in our cohort was 64 years (range, 28-85 years). A total of 91 patients received

Table 2 Toxicity frequency data (Number of events of each toxicity noted, by lesion treated in the upper half and by patients in the lower half of the table).

Type	Event	RT + BA N of Tx = 172	RT alone N of Tx = 107	Total RT N of Tx = 279
Acute	Fatigue	29	13	42
Acute	Erythema	8	0	8
Acute	Constipation	3	1	4
Acute	Cough	3	2	5
Acute	Insomnia	3	1	4
Acute	Numbness	3	0	3
Subacute	Fatigue	7	7	14
Subacute	Pain	9	1	10
Subacute	Constipation	4	0	4
Subacute	Appetite loss	1	2	3

Type	Event	RT + BA	RT al1	Number of Patients
Acute	Fatigue	17	12	25*
Acute	Erythema	4	0	4
Acute	Constipation	2	1	3
Acute	Cough	1	2	3
Acute	Numbness	3	0	3
Acute	Insomnia	2	1	3
Subacute	Fatigue	5	5	10
Subacute	Pain	4	1	5
Subacute	Appetite loss	1	2	3

Abbreviations: BA = biologic agent; RT = radiation therapy; Tx = toxicity.

* Two patients who experienced fatigue had RT both with and without BA.

Toxicities <3 times in the database were not included in the table by lesion treated for simplification purposes. No Grade 3 toxicities noted in the cohort, only grades 1 and 2 reported

at least 1 biologic agent. Among the entire cohort, there were 81 men (62%) and 49 women (38%). Most patients had International Staging System for MM, stage 1 with 64 patients or 62% of the cohort. Fourteen patients (13%) and 26 patients (25%) were disease stage 2 and 3, respectively, and the remainder did not have staging information available. The median number of treatment sites per patient was 1 (range, 1-6 sites), and the median number of treatment courses per patient was 2 to different treatment sites. The mean Karnofsky performance status score of all cohorts was 80. By far, the most commonly treated site was the spine. Two hundred and seventy nine lesions were treated in total. The median dose was 20 Gy (range, 2-40 Gy). The median number of fractions was 10 (range, 1-20; Table 1).

No grade ≥3 toxicity was noted in the entire cohort. The most common acute toxicity that was documented in our entire cohort was fatigue, as reported by patients (42 events; 15.05%), followed by erythema (8 events, 2.86%), and cough (5 events, 1.79%). The most common subacute toxicities were fatigue (14 events; 5.01%), pain (10 events; 3.58%), and constipation (4 events; 1.43%; Table 2). Biologic agents had similar numbers of acute and subacute toxicities (Table 3; Fig 1).

No significant difference in incidence of acute (PR: 1.33; 95% CI, 0.80-2.22; $P = .2660$) or subacute (PR: 0.90; 95% CI, 0.49-1.67, $P = .7464$) toxicities was found between patients with or without biologic agents concurrently with RT. Furthermore, no significant difference in anemia was observed. Similarly, neupogen requirements or rates of platelets transfusion were not different between the 2 groups (Table 4). No significant difference was found in reduction in laboratory values between patients with or without biologic agents concurrently with RT for white blood cells ($P = .6916$), platelets ($P = .7779$), or hematocrit ($P = .0858$). Therefore, receiving the biologic agents concurrently with RT did not predispose these patients to lower white blood cell, hematocrit, or platelet counts compared with patients receiving RT alone (Table 5).

Discussion

Our data suggest that the concurrent use of biologic agents for the treatment of MM together with palliative RT does not portend upon these patients worse acute or subacute side effects compared with RT alone. In addition, these patients are not at a higher risk of having lower blood cell counts when receiving RT concurrently with the biologic drugs. As previously noted, daratumumab

Table 3 Toxicities by drug combination (by lesion treated in the upper half of the table, and by patients in the lower half)

Type	RT + bortezomib	RT + carfizomib	RT + daratumumab	RT + other	RT only	Total RT
Acute	13	17	14	8	20	72
Subacute	4	1	6	12	14	37

Type	RT + bortezomib	RT + carfizomib	RT + daratumumab	RT + other	RT al1
N (Patient)*	48	24	18	23	69
Acute	8 (17%)	10 (42%)	9 (50%)	5 (22%)	19
Subacute	3 (6%)	1 (4%)	4 (22%)	6 (26%)	11

Abbreviation: RT = radiation therapy.

* Total number of patient who received that particular type of treatment combination.

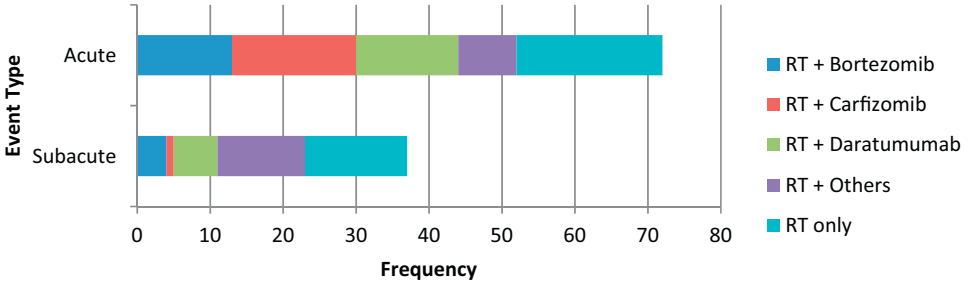

Figure 1 Acuity of Toxicities vs. Toxicity Frequency with Different Drugs.

can increase risk of neutropenia, anemia, thrombocytopenia, and leukopenia in these patients, with as many as 50% of patient experiencing some degree of anemia from the drug.[6,17,24] We noted, however, that combining this drug with RT did not increase the risk of hematological complications.

Complications from RT, including risk of fractures, have always been a source of concern for patients.[25] Historically, radiation has not been shown to worsen risk of fractures in patients with bony metastases and is a safe treatment for these patients.[26,27] In addition, in our study, patients were not at risk for further gastrointestinal or skin toxicities.

The toxicities of these biologic agents are well known, and current studies include gastrointestinal toxicities, upper airway/respiratory symptoms, and hematological toxicities.[17,28] Given that our studies show minimal amounts of these side effects (except for coughing in 1.79% of the cohort, no respiratory toxicities were noted), differences in toxicity between the different classes of biologic agents while undergoing RT are unlikely.

Our study has some limitations, primarily its retrospective nature. In addition, the study is not randomized, which would be optimal when attempting to compare 2 groups (eg, patients who receive biologic agents vs those who do not). Nonetheless, based on the results of our large retrospective series, we can conclude that palliative RT can be safely administered concurrently with biologic agents without concern for major adverse effects. As these patients live longer the likelihood of RT being used in their care becomes more common; thus, this finding has important clinical implications for this patient population.

Conclusions

Treatment with biologic agents does not need be held before, during, or after RT. Currently there are a number of new drugs being studied for MM, such as oral deacetylase inhibitor and panobinostat (not included in our

Table 4 Prevalence ratios for side effects and hematological events

	Toxicity event by RT	Prevalence ratios (95% CI)	*P*-value
Acute side effects (N = 157)			
RT alone	20/52	Ref	
RT + BA	52/105	1.33 (0.80-2.22)	.2660
Subacute side effects (N = 121)			
RT alone	14/42	Ref	
RT + BA	23/79	0.90 (0.49-1.67)	.7464
Anemia (N = 226)			
RT alone	3/73	Ref	
RT + BA	14/153	2.49 (0.66-9.33)	.1772
Platelet transfusion (N = 227)			
RT alone	11/73	Ref	
RT + BA	38/154	1.35 (0.67-2.71)	.3978
Neupogen needed (N = 226)			
RT alone	8/73	Ref	
RT + BA	35/153	1.58 (0.54-4.64)	.4008

Abbreviations: BA = biologic agent; CI = confidence interval; RT = radiation therapy.

Table 5 Estimated means of reduction in laboratory values (white blood cells/platelets/hematocrit pre- and post-RT)

	Estimates (95% CI)	Difference (RT + BA-RT alone)	*P*-value
White blood cells*			
RT alone	1.12 (0.54-1.69)	0.13 (−0.52, 0.78)	.6916
RT + BA	1.25 (0.79-1.71)		
Platelets*			
RT alone	21.27 (6.10-36.44)	2.63 (−15.81, 21.07)	.7779
RT + BA	23.90 (12.77-35.03)		
Hematocrit*			
RT alone	−0.12 (−1.05 to 0.82)	0.94 (−0.13, 2.01)	.0858
RT + BA	0.82 (0.08-1.55)		

Abbreviations: BA = biologic agent; CI = confidence interval; RT = radiation therapy.

* Adjusted for baseline laboratory values.

study) for which the safety with concurrent RT should be studied in the future before widespread concurrent utilization.[29-31] Maintenance systemic therapy and control is key to the management of MM, and we have shown that maintenance systemic therapy does not need to be stopped to treat MM.

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