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Research Letter

Impact of the Number of Administered Systemic Treatment Lines on Local Response to Radiation Therapy for Multiple Myeloma

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Purpose: Multiple myeloma (MM) tends to develop resistance to systemic therapy through multiple mechanisms that might as well induce radioresistance, as suggested by preclinical studies. The aim of the present analysis was to elucidate whether the number of systemic treatment lines received prior to radiation therapy (RT) might confer radioresistance and influence local response.

Methods and Materials: This single-center retrospective study enrolled patients who received RT for MM at our institution between January 1, 2005, and January 31, 2023. Information regarding RT, systemic therapy, and characteristics of the patients and disease were retrieved from medical records. The primary outcome for this analysis was radiologic local response at 6 months after RT, according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) or PERCIST 1.0 (Positron Emission Tomography Response Criteria in Solid Tumors) criteria. The secondary outcome was toxicity reported during the RT course.

Results: Data from 665 MM lesions from 366 patients were analyzed. Data regarding local response at 6 months were available for 217 lesions, reporting 29 complete responses (13.4%), 141 partial responses (65%), 42 stable diseases (19.4%), and only 5 disease progressions (2.3%). The number of previous systemic treatment lines had no impact on radiologic response at 6 months ($p = .721$). RT BED_{10} (Biologically Effective Dose) had a significant impact on response at 6 months ($p = .007$). The toxicity profile was optimal, as grade > 2 events during RT were reported only in 0.9% of cases.

Conclusions: In this large retrospective cohort of MM patients, the number of systemic treatment lines administered before RT had no impact on the local response, confuting concerns of cross-resistance raised by multiple preclinical studies. Disease control after RT was optimal, and instances of severe toxicities during treatment were rare.

Introduction

Multiple myeloma (MM) represents a significant therapeutic challenge because of its tendency to develop

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resistance to therapy. While systemic agents constitute the cornerstone of MM treatment,[1] the role of radiation therapy (RT) is increasingly being recognized, providing an essential component of its multimodal management.[2,3]

Indeed, MM cells are particularly radiosensitive, allowing high response rates and optimal local disease control after irradiation, even with relatively low doses.[4] In recent years, the landscape of MM therapy has been overhauled by the introduction of several novel agents targeting specific pathways.[5] Nonetheless, despite the expanded therapeutic armamentarium, disease progression almost invariably occurs because of the selection of resistant cell clones.[6,7]

Resistance tends to increase with the number of therapeutic lines, and the surviving clones often present cross-resistance to multiple agents. Since many mechanisms responsible for chemoresistance could also induce radioresistance,[8,9] it may be intuitive to assume that MM clones surviving despite the administration of systemic agents could be less prone to radiation response.

Several previous publications suggest that exposure to chemotherapy and other systemic agents might confer cross-resistance to RT in solid tumors[10-12] and MM cell lines.[13]

Understanding the interplay between systemic therapy and RT is crucial for optimizing treatment sequencing and maximizing therapeutic gains. Currently, no clinical experience has evaluated the impact of previous systemic treatment on the response of MM to RT. The aim of the present analysis was to elucidate whether the number of systemic treatment lines received prior to RT might confer radioresistance and influence local response.

Methods and Materials

The present study retrospectively enrolled patients who received RT for MM at our institution between January 1, 2005, and January 31, 2023. Information regarding RT, eventual systemic therapy, and characteristics of the patients and disease were retrieved from medical records. Patients were grouped based on the number of systemic treatment lines before RT start and by biologically effective dose assuming an α/β ratio of 10 (BED_{10}) of RT into 3 subgroups: <15 Gy, 15 to 38 Gy, and >38 Gy. The primary outcome for this analysis was radiologic local response at 6 months after RT, according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) or PERCIST 1.0 (Positron Emission Tomography Response Criteria in Solid Tumors) criteria. The secondary outcome was toxicity, likely because of RT, which was reported during the RT course and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. This protocol was approved by the Ethics Committee of our hospital.

Pain assessment was mostly performed according to the Numeric Rating Scale (NRS-11), in which the patient is required to assign a number from 0 (no pain) to 10 (worst pain imaginable). Nonetheless, given the retrospective nature of the study, for a relevant fraction of the patients, the precise number was not reported. Therefore, pain control was classified into 3 groups: complete if the patient reported no pain (corresponding to a value of 0 in NRS-11), partial if the patient still experienced pain but with reduced intensity compared with the symptom before RT, and no control if there was no pain reduction after RT.

Statistical analysis was performed using IBM-SPSS software version 27.0.1 (IBM SPSS, Inc). The normality of the distributions was assessed using the Kolmogorov-Smirnov test. Continuous variables were compared using the Mann-Whitney U test and the Kruskal-Wallis test. Categorical variables were presented as frequencies or percentages and compared with the use of the χ^2 test and Fisher's exact test, as appropriate; associations of the cross-tabulations were verified using standardized adjusted residuals. A 2-sided α level of .05 was used for all tests.

Results

The current analysis included 366 patients who received RT to 665 MM lesions. Characteristics of patients, lesions, and RT are summarized in Table 1.

RT was administered before systemic treatment started for 127 lesions (19.2%), after 1 to 2 previous lines of systemic therapy for 323 lesions (48.8%), and after more than 2 lines for 212 lesions (32%). The number of systemic treatment lines received before RT is shown in Table 1. About a third of patients received 3 or more lines of systemic treatment, and 8.2% received 6 or more cycles, which would be considered a heavily pretreated population.

Considering BED_{10}, 69 lesions (10.4%) were treated with a $BED_{10} < 15$ Gy, 220 lesions (33.1%) with a BED_{10} of 15 to 38 Gy, and 376 lesions (56.5%) with a $BED_{10} >$ 38 Gy. The prescribed total dose and number of fractions for all the lesions are summarized in Table 1.

Complete data regarding toxicity during RT were available for 662 lesions. In total, 338 instances of side effects likely because of RT were identified (summarized in Table 2). Considering the maximum grade for all side effects during treatment, no toxicity probably related to RT was reported in 63.1% of cases, grade 1 toxicity in 33.4% of cases, grade 2 in 2.6% of cases, grade 3 in 0.6% of cases, and grade 4 in 0.3% of cases. RT suspension secondary to toxicity was definitive for 10 lesions (1.5%) and temporary for 9 lesions (1.4%).

Data regarding local response at 6 months were available for 217 lesions, reporting 29 complete responses

Table 1 Main characteristics of treated patients, systemic treatment, and radiation therapy

Age mean (considering 474 accesses)			
Mean (years)		68.6	
Median (years)		70.1	
Sex, n (%)			
Male		185 (50.5)	
Female		181 (49.5)	
Concurrent treatment, n (%)			
No systemic treatment		235 (35.5)	
Lenalidomide-based treatment		90 (13.2)	
Bortezomib + dexamethasone		72 (10.9)	
VTD, VMP, or PAD		129 (19.5)	
Monoclonal antibodies		52 (7.9)	
Chemotherapy		79 (11.9)	
No. of previous lines, n (%)			
No previous sysmetic treatment		127 (19.2)	
One		246 (37.2	
Two		80 (12.1)	
Three		73 (11)	
Four		41 (6.2)	
Five		41 (6.2)	
Six or more		54 (8.2)	
Site treated with RT, n (%)			
Vertebrae		399 (60)	
Extremities		127 (19.1)	
Skull		15 (2.3)	
Ribs/sternum		44 (6.6)	
Pelvic bones		64 (9.6)	
Other		16 (2.4)	
RT dose			
Total dose, n (%)		**Dose per fraction, n (%)**	
8 Gy	63 (9.5)	8 Gy	57 (8.6)
20 Gy	217 (32.6)	4 Gy	188 (28.3)
30 Gy	366 (55)	5 Gy	34 (5.1)
40 Gy	6 (0.9)	3 Gy	372 (55.9)
Other	13 (2)	2 Gy	11 (1.7)
		Other	3 (0.5)
RT technique, n (%)			
3D-CRT		474 (71.3)	
IMRT		9 (1.4)	
VMAT		43 (6.5)	
Tomotherapy		13 (2)	
2D-RT		117 (17.6)	
Cyberknife		2 (0.3)	

Abbreviations: 2D-RT = 2-dimensional radiation therapy; 3D-CRT = 3-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy; PAD = bortezomib, doxorubicin, and dexamethasone; RT = radiation therapy; VMAT = volumetric modulated arc therapy; VMP = bortezomib, melphalan, and prednisone; VTD = bortezomib, thalidomide, and dexamethasone.

(13.4%), 141 partial responses (65%), 42 stable diseases (19.4%), and only 5 disease progressions (2.3%).

The number of previous systemic treatment lines had no impact on the radiologic response, either by considering the absolute number of previous lines ($p = .721$) or by dividing patients into subgroups that received 0, 1 to 2, and >2 systemic treatment lines before RT ($p = .623$).

RT BED_{10} had a significant impact on response at 6 months ($p = .007$), with an association between complete or partial response for $BED_{10} > 38$ Gy.

The RT technique had no impact on radiologic response at 6 months ($p = .924$).

Because of the limited number of in-field disease progression, no risk factors associated with local relapse could be identified.

Response at 6 months after RT was assessed by magnetic resonance imaging for 75.9% of lesions, positron emission tomography-computed tomography (CT) for 7.4% of lesions, and CT scan for 16.7% of lesions.

Radiologic assessment performed with magnetic resonance imaging was significantly associated with higher rates of partial response and lower rates of stable disease compared with CT scan ($p = .001$), likely because of the superior image quality for bone and soft tissue and the ability to perform functional evaluation. No significant differences were detected between positron emission tomography-CT and other imaging modalities.

Data regarding systemic treatment administered between RT and radiologic assessment at 6 months were available for 189 lesions; ongoing therapy was continued in 41.8% of cases, while in 9.5% of cases, no therapy was administered. For the remaining 92 lesions (48.7%), a further line of treatment was administered: autologous stem cell transplant for 78.2% of lesions, bortezomib-based therapy for 6.5%, lenalidomide-based or carfilzomib-based treatment for 4.3%, and daratumumab-based or other chemotherapy for 3.3%. Administration of a new line of treatment was significantly associated with higher radiologic partial response rates at 6 months, while continuation of ongoing treatment was associated with higher rates of stable disease ($p = .01$). No significant differences in complete response and disease progression were detected among these groups.

Data regarding pain control at 1 month, 3 months, and 6 months after RT are reported in Table 3. Uncontrolled pain in treated sites was reported for only 2.9%, 2.88%, and 5.57% of lesions at 1, 3, and 6 months after RT, respectively. The number of previous systemic treatment lines (no systemic treatment vs 1-2 lines vs >2 lines) had no impact on pain control at 1 month ($p = .134$), 3 months ($p = .763$), and 6 months ($p = .375$) after RT.

Among the 217 lesions with available data for radiologic control at 6 months after RT, information regarding pain control was retrieved for 75.1% at 1 month, 77.9% at 3 months, and 77% at 6 months after RT. No concordance was identified among pain control at 1 month, 3 months,

Table 2 Number and rate of most common toxicity likely because of radiation therapy reported during the treatment course

Grade	Pain increase, n (%)	Pharyngodynia, n (%)	Esophagitis, n (%)	Dermatitis, n (%)	GI, n (%)	Fatigue, n (%)	Mucositis, n (%)
1	47 (7.1)	30 (4.5)	66 (10)	14 (2.1)	86 (13)	19 (2.9)	14 (2.1)
2	0	0	4 (0.6)	0	13 (2)	2 (0.3)	2 (0.3)
3	0	0	1 (0.2)	0	0	0	0
4	0	0	0	0	0	0	0

Abbreviations: GI = gastrointestinal toxicity.

Table 3 Pain control at 1 month, 3 months, and 6 months after radiation therapy

Pain control	1 mo after RT, n (%)	3 mo after RT, n (%)	6 mo after RT, n (%)
Total lesions, N	379	382	377
Complete control	256 (67.55)	287 (75.13)	296 (78.51)
Partial control	112 (29.55)	84 (21.99)	60 (15.92)
No control	11 (2.90)	11 (2.88)	21 (5.57)

Abbreviations: RT = radiation therapy.

and 6 months after RT and radiologic response at 6 months after RT.

Discussion

As the number of drugs approved for MM has remarkably increased in recent years, with a consequent prognostic improvement,[14] a large and growing proportion of patients who are candidates for RT have been heavily pretreated with several lines of therapy.

Although MM is known to be a radiosensitive neoplasm, preclinical data suggest that exposure to systemic therapy might select refractory clones that could develop cross-resistance to RT.[13]

This may raise relevant clinical concerns, as RT is often used for symptomatic or palliative purposes to treat lesions that relapsed after 1 or more treatment lines.[2]

To the best of our knowledge, this is the study with the largest sample assessing the radiologic response of MM to RT and the first evaluating the impact of the number of treatment lines on local disease control.

In contrast with preclinical data suggesting the induction of radioresistance because of clonal selection after administration of systemic therapy in multiple solid tumors and MM,[10-13] in our cohort, the number of treatment lines before RT had no effect on local radiologic response at 6 months.

Administration of RT resulted in optimal rates of pain control, with uncontrolled pain reported for 2.9%, 2.88%, and 5.57% of treated lesions at 1, 3, and 6 months, respectively, and no impact on the number of previous systemic treatment lines.

Consistent with previous series,[15,16] RT allowed optimal disease control, with only 2.3% of in-field progressions. As reported in other publications,[15,16] schedules with higher BED_{10} improved local control rates. Nonetheless, local progression at 6 months was uncommon for all BED_{10} groups, reaching a maximum of 4.8% in the case of $BED_{10} < 15$ Gy.

The toxicity profile of RT in our cohort was optimal, with only 0.9% of patients experiencing grade > 2 side effects attributable to RT. This result is also in line with the current literature.[15,17]

The main limitation of this study is its retrospective nature. This could explain the relatively low proportion of patients for whom radiologic response data were available. In fact, patients with MM lesions generally undergo RT in a palliative setting and subsequently return to hematologists for follow-up. Periodic imaging for MM is not routinely performed at our institution to assess response to RT if systemic disease is controlled and in the absence of symptoms, and this limits the sample for local control assessment. Moreover, a new systemic therapy administered between RT and radiologic assessment and the imaging modality adopted both had an impact on disease response definition. On the other hand, it must be noted that because of the limited sample of analyzed subgroups (more than 40%, including less than 5 cases), these associations were weak, although significant. Similarly, the limited number of local progressions could restrict the robustness of the statistical analysis. Another limitation of the analysis is the heterogeneous pain assessment, as NRS-11 was the most used scale

but was not reported for all the patients. This highlights the need for a more standardized pain assessment, such as adopting measures like the Brief Pain Inventory. Indeed, the adoption of specific scales might reduce the risk of underestimation by the physician and improve symptom monitoring. Moreover, in our study, the correspondence between radiologic response and pain response was low. This could be because of the multifactorial etiology of cancer bone pain, which is not limited to structural instability but involves a complex interplay of inflammatory signals that stimulate the nociceptors.[18] Considering that RT is mostly delivered as a symptomatic treatment for MM, pain should, therefore, be considered as a primary and independent endpoint to assess response to RT.

Conclusions

In this large retrospective cohort of MM patients, the number of systemic treatment lines administered before RT had no impact on the local response, confuting concerns of cross-resistance raised by multiple preclinical studies. Disease control after RT was optimal, and instances of severe toxicities during treatment were rare.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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