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The impact of one fraction of 8 Gy radiotherapy in palliative treatment of multiple myeloma patients with painful bone destructions

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Background/aim: Radiotherapy is required to overcome pain and to promote recalcification in multiple myeloma (MM) patients. The aim of our prospective study was to evaluate the impact of one fraction of 8 Gy regimen in palliative treatment of MM.

Materials and methods: Forty-six patients with MM and painful bone destructions were treated by 8 Gy single fraction regimen. The visual analog scale was used for evaluation of pain. Analgesic use was measured prior to and after radiotherapy (4, 12, and 24 weeks). Recalcification was evaluated with radiographs before and after radiotherapy at 1 and 3 months. Quality of life questionnaires were completed before and 4 weeks after treatment.

Results: Decrease of pain was observed in 78.3% cases: according to the international consensus on palliative radiotherapy criteria, 43.5% were found to be completely and 34.8% partially responsive. Reduction of analgesic use was present in 68.4% and complete cessation in 31.6%. Recalcification was present in 55%: a complete response was observed in 35% and a partial response in 20%. The side effects after treatment were of the first grade and reversible.

Conclusion: One fraction of 8 Gy regimen is effective in palliative treatment of MM patients with painful bone destructions.

Key words: Multiple myeloma, pain relief, radiotherapy, recalcification

1. Introduction

Multiple myeloma (MM) is a malignancy of plasma cells that accounts for approximately 10% of all onco-hematological disorders (1). The most common clinical features of MM are diffuse osteopenia, osteolytic bone destructions, pathologic fractures, hypercalcemia, and bone pain (2). The skeletal-related events may progress even when patients respond to chemotherapy. In order to overcome pain and to promote recalcification, MM patients require radiotherapy, surgery, and analgesics. Approximately 70% of all MM patients receive 1 or more radiotherapies in the course of their illness (3). Pain relief is obtained in 75%–100% (3–10). Recalcification is achieved in 40%–50% of the irradiated bone destructions (3,8,11–13).

Multiple randomized trials showed the same effect of single fraction (SF) and multiple fraction (MF) regimens regarding pain relief and recalcification for patients with painful bone metastases from solid tumors (14–21). The role of different palliative radiotherapeutic regimens for MM is not well established due to a lack of clinical trials. There are only a few studies in the literature regarding dose-response relationship with analgesia and recalcification (3–12,22,23). Our prospective study analyzed the effect of a SF regimen in the treatment of MM on pain relief, analgesic consumption, and recalcification.

2. Materials and methods

2.1. Study population

From 2011 to 2013, 46 patients (27 women and 19 men; median age: 69 years, range: 51–88 years) with MM and painful bone destructions were involved in the study, which was conducted at the Department of Oncology and Hematology of the Hospital of the Lithuanian University of Health Sciences. Seven patients (16%) had stage II MM and 39 (84%) patients had stage III MM, as defined by the Durie and Salmon staging system (24). Thirty-two (70%) patients had IgG-type M protein, 8 (17%) patients had IgA-type, 4 (9%) patients had light chain-type, and 2 (4%) had nonsecretory MM. Inclusion criteria: patients diagnosed

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with symptomatic MM, as proven by histological data, electrophoresis, and immunofixation of serum and urine; patients with bone destruction or impending fracture as verified by bone X-ray and computed tomography and resulting in pain as judged by the patient; and a Karnofsky Index score above 40. Exclusion criteria: patients with bone metastases from solid tumors, patients with solitary plasmacytoma, patients who had received previous irradiation to the present painful destruction site, patients who were incapable of completing the quality of life questionnaires, and those with poor health status. Patients were treated with 8 Gy in a SF regimen with a 24-week follow-up. Patient's characteristics are shown in Table 1.

2.2. Study design

The indication for radiotherapy was pain for 42 patients (91%) and impending pathologic fracture in the site of the destruction for 4 patients (9%). Nineteen (41%) irradiated sites were in the spine, 12 (26%) in the pelvic bone, and 15 (33%) in the extremities. Thirty-nine patients (85%) were treated with concurrent chemotherapy.

Pain was evaluated according to a visual analog scale (VAS) with scale endpoints of 0 (no pain at all) and 10 (worst imaginable pain) (25). A pain score of ≤4 was classified as mild, 5–7 as moderate, and ≥8 as severe (26). Pain score and analgesic usage were measured before initiation of treatment and at 4, 12, and 24 weeks after radiotherapy. The medication was classified into 2 groups: nonopioids and opioids. Opioid analgesics were converted to the mean morphine-equivalent dose (mg/day) (27). Recalcification was measured by radiologists with radiographs before radiotherapy and after radiotherapy at 1 and 3 months. Patients completed quality of life questionnaires including the European Organization for Research and Treatment of Cancer (EORTC) QLQ - C30 version 3.0 (28) and the EORTC QLQ - MY20 (29) before treatment and after 4 weeks. The EORTC QLQ - C30 consists of 30 items on 5 functional scales, 9 symptom scales, and a scale of global quality of life. The EORTC QLQ - MY20 consists of 20 items on 2 functional scales and 2 symptoms scales. The patients' responses of single items were linearly transformed from 0 to 100 scores according to the EORTC scoring rules (30). High scores on the functional scales indicated a good functional status of the patient and high scores on global health status indicated a high quality of life, while high scores on the symptoms scale indicated poor health condition. Acute side effects were evaluated in the first 4 weeks after radiotherapy on a 5-point scale from 0 (not at all) to 4 (very much) according to the toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the EORTC (31).

The response rate was defined according to the international consensus on palliative radiotherapy criteria (32). Complete response was defined as no pain at the

Table 1. Patients' characteristics.

Characteristics	N = 46	%
Sex		
Male	19	41
Female	27	59
Age (years)		
Range	51–88	
Median (mean ± SE)	69 (69.26 ± 1.23)	
Clinical stage (Durie and Salmon)		
II	7	16
III	39	84
Karnofsky Index (%)	50–80	
Median (mean ± SE)	60 (64.13 ± 1.23)	
Paraprotein		
IgG	32	70
IgA	8	17
Light chain	4	9
Nonsecretory	2	4
Irradiated sites		
Spinal vertebrae	19	41
Pelvic bone	12	26
Extremities	15	33
Surgery		
Yes	17	37
No	29	63
Concurrent chemotherapy		
Yes	39	85
No	7	15
Pain score at admission		
0–4	4	9
5–7	15	32
8–10	27	59
Pain medication		
None	2	4
Nonopioids	6	13
Opioids	38	83
Opioid dose (mg/day)		
Mean	48	
Range	10–190	

SE: Standard error of mean.

treated site without increased analgesic intake. Partial response was defined if pain was lowered by 2 or more points at the irradiated site on the 0–10 scale without increasing analgesic intake or an analgesic reduction of 25% or more from the baseline without an increase in pain.

The response terms of recalcification were as follows: complete response was defined as full reossification of the treated osteolysis lesion or reconstruction of the normal bone structures in the case of a fracture. Partial response was defined as marginal osteosclerosis of the osteolysis lesion, stable disease was defined as no changes of radiological signs, and progressive disease was defined as increase the osteolysis lesion. Pathological fracture was determined as a fracture in the irradiated field confirmed by X-ray.

The study protocol was prepared in accordance with the Helsinki Declaration and was approved by the Lithuanian Regional Research Ethics Committee and State Data Protection Inspectorate. The participants provided informed consent.

2.3. Statistical analysis

Statistical data analysis was performed using IBM SPSS Statistics 21.0 for Windows (SPSS Inc., USA). The chi-square test and Fisher's exact test for small expected frequencies were used to compare pain reduction proportions among groups created by sociodemographic and clinical characteristics. Quantitative data are presented as mean ± standard error of the mean (SE) and quantitative data, which were not normally distributed (Kolmogorov–Smirnov test, $P < 0.05$), are presented as the median (mean ± SE). The Mann–Whitney U test was used for the evaluation of the difference of quality of life scores between 2 independent groups and the Kruskal–Wallis test was used for the evaluation of the difference of quality of life scores among 3 or more independent groups. Differences between compared characteristics were taken as statistically significant if $P < 0.05$.

3. Results

3.1. Pain relief

All our patients before radiotherapy complained of painful bone destructions. The pain was mild in 4 patients (9%), moderate in 15 patients (32%), and severe in 27 patients (59%). Patients in all groups before treatment reported a median VAS of 7.4 (range: 2–10), after 4 weeks after radiotherapy patients reported a median VAS score of 4 (range: 0–10), after 12 weeks the median VAS score was 3.4 (range: 0–9), and after 24 weeks the median VAS was 3.3 (range: 0–9). A decrease of pain was observed in 36/46 patients (78.3%): 20 patients (43.5%) were found to be completely and 16 patients (34.8%) partially responsive. Six patients (13%) were using nonopioid drugs prior to radiotherapy and all of them ceased analgesic intake for 6 months after termination of treatment. Thirty-eight patients (83%) used opioid drugs. The use of opioid analgesics was reduced in 26/38 patients (68.4%), while a complete cessation of opioid analgesics was observed in 12/38 patients. The mean opioid dose at admission was 60 mg/day. At 4 weeks after radiotherapy the mean dose was 40 mg/day; after 12 and 24 weeks the mean dose remained at about 25 mg/day. The plots of pain scores and analgesic intake before and after radiotherapy are shown in Figure 1. Pain relief is clearly shown in the first 12 weeks after treatment. Figure 2 shows the response time of all patients. Median time to response was 6.97 weeks. Significant parameters in pain relief were age of <65 years ($P = 0.034$) and IgG-type paraprotein ($P = 0.037$) (Table 2).

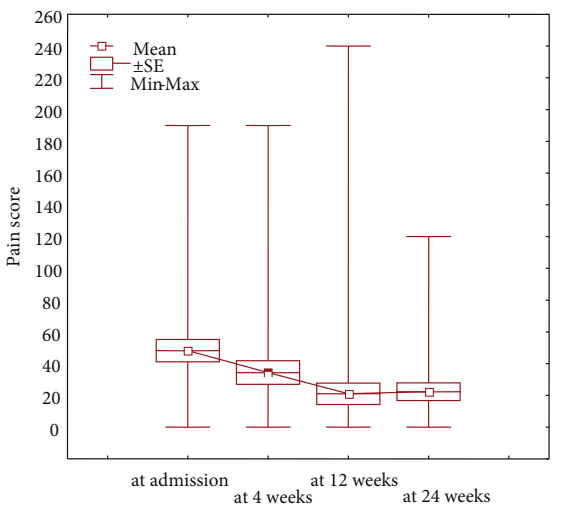

Figure 1a. The pain score within 24 weeks. SE: Standard error of mean.

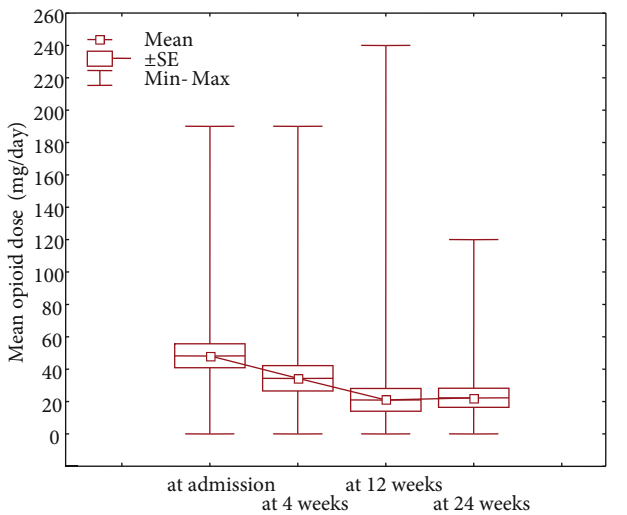

Figure 1b. The analgesic intake within 24 weeks. SE: Standard error of mean.

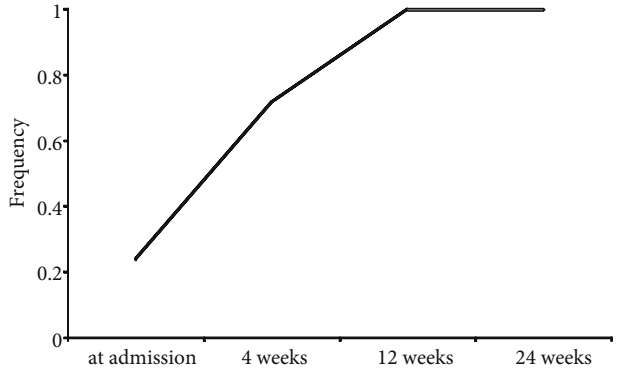

Figure 2. Response time for radiotherapy in all patients.

Table 2. Analysis of pain relief after radiotherapy of painful bone destructions (significant parameters are in bold).

Parameter		Pain reduction (%)	P-value (chi-square test)
Sex	Male vs. female	78.9 vs. 77.8	0.925
Age (years)	**<65 vs. ≥65**	**100% vs. 70.6%**	**0.034**
Karnofsky Index (%)	<60 vs. >60	60% vs. 80.5%	0.295*
Clinical stage (Durie and Salmon)	II vs. III	100% vs. 74.4%	0.13
Paraprotein	**IgA vs. IgG**	**50% vs. 84.4%**	**0.037**
	LC vs. IgG	100% vs. 84.4%	0.618*
	Nonsecretory vs. IgG	50% vs. 84.4%	0.326*
Hemoglobin (g/L)	≤82 vs. >82	85.7% vs. 76.9%	0.604
Concurrent chemotherapy	Yes vs. no	74.4% vs. 100%	0.13
Surgery	Yes vs. no	82.4% vs. 75.9%	0.606
		100% vs. 73.3%	0.530*
Pain score at admission	Mild vs. severe	100% vs. 77.8%	0.561*
	Moderate vs. severe	73.3% vs. 77.8%	0.746

LC: Light chain multiple myeloma. *: P-value of Fisher's exact test.

3.2. Recalcification

Forty patients of the 46 were evaluable. X-ray radiographs of 6 patients were not evaluable due to premature death. Recalcification was observed in 22 patients (55%): a complete response was observed in 14 patients (35%) and a partial response in 8 patients (20%). Disease stability was determined in 12 patients (30%), while progressive bone disease was present in 6 patients (15%) (Table 3). Pathological fractures in the irradiated field occurred in 6 patients.

A significant parameter in recalcification was age of <65 years (P = 0.022). Other investigated parameters were insignificant.

3.3. Quality of life

Table 4 presents the median QLQ scores for global health status and functional and symptom scales of MM patients before radiotherapy, classified by clinical criteria. We analyzed the influence of clinical criteria on QLQ scores before and after radiotherapy. Better functional scores (P = 0.017) and lower symptoms (P = 0.042) scores were observed in men than in women. Significantly higher symptoms scale scores were observed in patients with bone destruction in the spinal column (P = 0.038 and P = 0.028). Better global health status and functional scale scores were found in patients with mild pain scores at admission (P = 0.023 and P = 0.031). There was no

Table 3. Recalcification.

Response to radiotherapy	N = 40	%
Complete response	14	35
Partial response	8	20
Stable disease	12	30
Progressive disease	6	15

Table 4. Numerical characteristics of QLQ scores of multiple myeloma patients before radiotherapy, classified by demographic and clinical criteria. Significant parameters are in bold. Mean and SE are shown only for significant parameters.

Dependent variable	N	Global health status QLQ - C30, median (mean ± SE)	Functional scales QLQ - C30, median (mean ± SE)	Symptom scales QLQ - C30, median (mean ± SE)	Symptom scales QLQ - MY20, median (mean ± SE)
Sex					
Male	19	50	**53 (53.42 ± 4.54)**	**41 (41.74 ± 3.81)**	42
Female	27	33	**38 (38.30 ± 3.32)**	**53 (52.52 ± 2.93)**	54
P-value		0.132	**0.017**	**0.042**	0.072
Irradiated sites					
Spinal cord	19	25	38	**54 (55.53 ± 2.55)****	**58 (55.42 ± 4.16)****
Pelvic bone	12	37	45	**39 (40.92 ± 5.06)****	**35 (38.25 ± 4.56)****
Extremities	15	42	53	**42 (44.33 ± 4.78)**	**43 (44 ± 2.88)**
P-value		0.238	0.290	**0.035* (0.038**)**	**0.024* (0.028**)**
Pain score at admission					
0–4	4	**58 (54 ± 7.31)**	**54.5 (54.50 ± 4.17)**	38	38
5–7	15	**42 (40.47 ± 6.08)**	**48 (54.13 ± 5.68)**	50	38
8–10	27	**25 (25.93 ± 4.45)**	**38 (37.74 ± 3.24)**	52	48
P-value		**0.023***	**0.031***	0.159	0.082

SE: Standard error of mean. *: P-value of Kruskal–Wallis test. **: P-value of post hoc Kruskal–Wallis test.

significant difference between QLQ scores before and at 4 weeks after radiotherapy.

3.4. Side effects

Hematological and nonhematological toxicity was evaluated on a 5-point scale in the first 4 weeks after radiotherapy. The side effects after treatment were different depending upon the irradiated site and were uncommon, low grade, and reversible (Table 5).

4. Discussion

4.1. Pain relief

The bone disease in MM differs from other bone cancers' metastasis as reactive new bone formation at the site of bone destruction is absent in MM (33). Even in patients who respond to chemotherapy, the bone disease may still progress (2). The main mechanism of analgesic effects from radiotherapy is the damage of myeloma cells and inhibition of pain mediators. Radiotherapy destroys radiosensitive inflammatory cells in the bone metastases site and inhibits the discharge of pain mediators, interrupting the inflammatory cytokine cascade (34). The damage caused to myeloma cells results in the regeneration of osteoblastic cells and thus the recalcification process. This is maintained by the fact that concurrent chemotherapy sustains this process (3,8).

The randomized studies of palliative radiotherapy of bone metastases from solid tumors did not report a particular superior radiotherapy regimen in terms of pain relief and recalcification (14–21). In metaanalyses by Sze et al. (35) and Wu et al. (36), no significant difference in overall and complete response in pain reduction between SF and MF palliative radiotherapy was observed. Chow

Table 5. Toxicity. GI: gastrointestinal tract.

	Grade 1, N (%)	Grade 2, N (%)	Grade 3, N (%)	Grade 4, N (%)
Leukopenia	6 (13.04)	5 (10.9)	0	0
Neutropenia	3 (6.5)	3 (6.5)	0	0
Thrombocytopenia	4 (8.7)	1 (2.2)	0	0
Upper GI	13 (28.3)	4 (8.7)	0	0
Lower GI	8 (17.4)	3 (6.5)	0	0
Mucous membrane	1 (2.2)	1 (2.2)	0	0
Skin	2 (4.4)	0	0	0
Genitourinary	1 (2.2)	0	0	0

et al. analyzed 16 randomized trials comparing SF versus MF for bone metastases and no significant difference was found in response rates (37). An increased risk for pathological fractures and spinal cord compressions was observed in the SF regimen, which was statistically insignificant, while retreatment in the SF regimen was 2.5-fold higher (37). Koswig and Budach found that MF regimens resulted in significantly increased bone density and better stabilization compared with SF (15). The role of different palliative radiotherapy regimens for MM is not well established due to lack of clinical trials. There are only a few studies in the literature regarding dose-response relationship with pain relief and recalcification (3–11,22,23).

Mill et al., in a retrospective review, reported pain relief in MM patients with a radiation dose of 15–20 Gy but did not analyze the dose-response relationship, analgesic reduction, or recalcification (9). Adamietz et al. (4) and Mose et al. (8) reported that concurrent chemotherapy had a significant impact on a positive response to radiotherapy, but other studies did not show this relationship (3,5,6,9). Some studies did not find a significant difference between radiation dose in pain reduction (5,6,9,10,22,23); however, Minova et al. (7) and Stolting et al. (3) reported the need for higher doses to obtain adequate pain relief. Adamietz et al. affirmed that local long-term palliation effect can only be achieved by a high radiation dose (4), but Leigh et al. observed durable symptom relief after a total dose of 10 Gy (6).

The current study confirms the efficacy of radiotherapy in pain relief as evaluated by VAS and analgesic consumption. Overall response of pain relief of 78.3% was obtained in the first 12 weeks and remained so until the end of the follow-up period. The use of opioid analgesics was reduced in 68.4% cases and in 31.6% stopped totally. The mean opioid dose at admission was 60 mg/day; at 24 weeks after radiotherapy the mean dose remain at about 25 mg/day. Thus, the 8 Gy SF regimen is effective for pain relief and reduction of drug intake without significant toxicity. The significant parameters in pain relief were age of <65 years and IgG-type MM.

4.2. Recalcification

According to the literature, recalcification is achieved after some months and occurs in 40%–50% of cases of irradiated bone destructions (3,8,11–13). Mose et al. found that stabilization of the irradiated bone could be achieved in 80% of cases, and concurrent chemotherapy reinforces this effect (8). Stolting et al. also reported the importance of concurrent chemotherapy for recalcification (3). Koswig and Budach (15) found that a MF regimen (3 Gy × 10) significantly increased the bone density in the area of metastases from solid tumor as compared to SF treatment (8 Gy), in contrast to pain relief effect; Stolting et al. also reported that recalcification was detected at total doses of >20 Gy for MM patients (3). The same was reported by Rades et al. in the treatment of spinal cord compression due to metastases or MM (38,39). Balducci et al. found recalcification in 50% of cases with a median total dose of 38 Gy and reported the importance of the early use of radiotherapy to avoid pathological fractures (23).

In this study, we found recalcification in 55% of cases; in 15%, radiotherapy failed because of progressive disease and pathological fractures that we think require higher doses for recalcification. We found only 1 significant parameter for recalcification, which was age of <65 years; the same was determined by Stolting et al. (3).

4.3. Quality of life

A global analysis of the Dutch Bone Metastasis Study did not show significant differences in quality of life between SF and MF regimens (40). Some other studies reported that patients who have pain relief after radiotherapy also

have a better quality of life (41–43); however, Sauer et al. considered that even though palliative radiotherapy leads to pain relief, quality of life is not affected positively due to the side effects of radiotherapy (44). Others showed significant improvement only in functional capabilities and social aspects in patients undergoing radiotherapy for spinal metastatic disease (43). In our current study, we did not discover a significant difference between QLQ scores before and at 4 weeks after radiotherapy.

In conclusion, this study confirms SF's effectiveness in pain relief and reduction of drug intake without significant toxicity. A higher dose should be used in order to achieve better recalcification or for patients who are at risk for pathological fractures.

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