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ORIGINAL ARTICLE

Palliative radiotherapy in patients with multiple myeloma

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Summary

Purpose: *To analyse the therapeutic effect of palliative radiation therapy (RT) in multiple myeloma (MM) patients with bone lesions and soft tissue formations, to compare the therapeutic efficacy of two different RT regimens, the effect of RT on basic disease parameters, and its impact on survival in MM patients.*

Patients and methods: *162 patients with MM were diagnosed and followed for a 10-year period (1994-2004). Eighty-seven (53.7%) of them with myeloma bone disease (MBD) underwent palliative RT with two different regimens. The effect of RT on MBD and its complications was assessed. Patients with RT were compared in 10 parameters before and after RT. Survival was compared between the irradiated and non irradiated groups and also between patients treated with two different RT regimens, using Kaplan-Meier method and log-rank test.*

Results: *RT was applied in 92.1% of the patients with vertebral fractures, in 90.9% of the patients with non-vertebral fractures, and in 94.1% of the patients with extramedullary tumor formations. In 89.6% of the patients complete or partial pain palliation was achieved and in 58.6% resolution of neurologic symptoms occurred. The levels of hemoglobin (Hb), white blood cell (WBC) and platelet counts (PLT), bone marrow infiltration, serum calcium (Ca), creatinine, albumin, CRP, LDH, β2-microglobulin did not change significantly before and after RT. Median survival of patients on RT was 32 months (range 30-34) vs. 33 months (range 28-36) for patients without RT (p >0.05). Median survival was 32 months (range 27-37) for patients on 2×8 Gy vs. 34 months (range 25-39) for those on 5x4 Gy (p >0.05).*

Conclusion: *RT is a very effective method in bone pain palliation in vertebral and non-vertebral fractures and reduction of extramedullary formations, but does not influence the survival of patients with MM.*

Key words: bone pain, multiple myeloma, palliative radiotherapy, survival

Introduction

MM is a hematological malignancy characterized by clonal plasmocytic proliferation in the bone marrow and production of structurally homogeneous immunoglobulins or parts of them. In the last decade its morbidity had increased and among the lymphoproliferative disorders MM now is the second most frequent one (4-17/100,000) following the group of non-Hodgkin's lymphomas [1,2]. MM is still an incurable disease, although patients have now longer survival. This is due not only to the current chemotherapeutic regimens, but also to the multimodal treatment approaches known as best supportive care, which overcome the most common complications of MM such as anemia, bone disease and its consequences, renal function impairment and hypercalcemia.

The most common complication of MM is MBD. Over 70% of the patients present with bone lesions at the time of diagnosis. MBD and its related symptoms (bone pain, vertebral and non-vertebral pathological fractures, compression of central and peripheral nerves, cauda equina syndrome) and the clinical symptoms of hypercalcemia immobilize patients, impair their quality of life, influence negatively the therapeutic response and can be a cause for death. In these cases palliative RT is an important method in the multimodal treatment of MM.

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The purpose of this study was to analyse the therapeutic effect and complications of palliative RT in patients with MBD, to compare the therapeutic efficacy of two different radiotherapeutic regimens, the effect of RT on basic parameters of the disease, as well as its impact on survival in MM patients.

Patients and methods

From 1994 to 2004 162 patients with MM were diagnosed, treated and followed at the Clinic of Hematology. Eighty-seven (53.7%) of them with MBD underwent RT at the Clinic of Radiotherapy. Telegamma therapy was performed on "Rocus" apparatus. Two basic regimens of treatment were applied: 2 fractions of 8.5 Gy with an interval of 72 hours and 5 fractions of 4 Gy each consecutive day. Three patients were treated with 1 fraction of 8 Gy on one of the involved sites targeting the involved vertebra and parts of the neighboring not involved vertebrae.

According to the type and localization of the bone lesions, the patients were classified as follows:

a. 63 - vertebral fractures; 58 (92.1%) of them were irradiated (most common in the thoracic and lumbar spine).

b. 29 - spinal cord compression; 27 (93.1%) irradiated, 11 with preceding laminectomy.

c. 7- cauda equina syndrome; 6 (85.7%) irradiated.

d. 17- extramedullary soft tissue formations; 16 (94.1%) irradiated.

e. 11 - non-vertebral fractures (humerus, femur, clavicle, pubis, mandibula); 10 (90.9%) irradiated, 4 of them had undergone orthopedic stabilization.

Some of the patients had multiple bone lesions: 87 patients had 127 sites irradiated. The percentage represents the share of the treated sites from the whole group.

The characteristics of the patients on RT are presented in Table1.

The therapeutic response of RT was assessed as follows:

a. Frequency and degree of bone pain alleviation (subjective patient's assessment and intake of analgesic drugs)

b. Motor activity

c. Improvement of neurologic impairment and cauda equina syndrome

d. Reduction of the extramedullary tumor formations

e. Longest period free of bone-related symptoms, time to progression

f. Levels of Hb, WBC, PLT, degree (%) of bone marrow infiltration, serum creatinine, albumin, Ca, CRP, LDH and β2-microglobulin before and after RT

g. Toxicity

h. Survival of the group treated with RT; survival of the 2 subgroups on different radiotherapeutic regimens; survival of patients without RT.

Table 1. Patient characteristics

Characteristic	*n (%)*
Sex	
males	46 (52.8)
females	41 (47.2)
Age (years)	
mean	60.8 ± 9.6
range	38-81
age >65	34 (39.1)
Clinical stage (Durie and Salmon)	
I	4 (4.5)
II	25 (28.7)
III	58 (66.7)
Myeloma bone disease	
0	1 (1.2)
1	7 (8.05)
2	63 (72.4)
3	16 (18.8)
Bone marrow infiltration >50%	36 (41.4)
serum CRP > 10 g/l	40 (46.0)
serum LDH > 460 U/l	42 (48.3)
serum Ca >2.66 mmol/l	24 (27.6)
serum Hb <80 g/l	59 (67.8)
serum creatinine > 166 mkmol/l	30 (35.5)
Median survival (months)	33

Statistics

Statistical analysis was performed by the chi-square method, Student-Fisher method, variation analysis, alternative analysis, Kaplan-Meier survival curves and log-rank test using SPSS 11.0 for Windows.

Results

The mean period of follow up was 21 months (range 2-41). The response rates obtained are shown in Figure 1. In 78/87 (89.6%) of the patients bone pain palliation was achieved and in 21/87 (26.9%) of them pain was completely resolved for a median of 3.5 months (range 1.5-16). Improvement of motor function occurred in 62/79 (78.4%) patients; the range of movements was increased as well as the ability of walking without help (median duration 4.5 months, range 1.0-

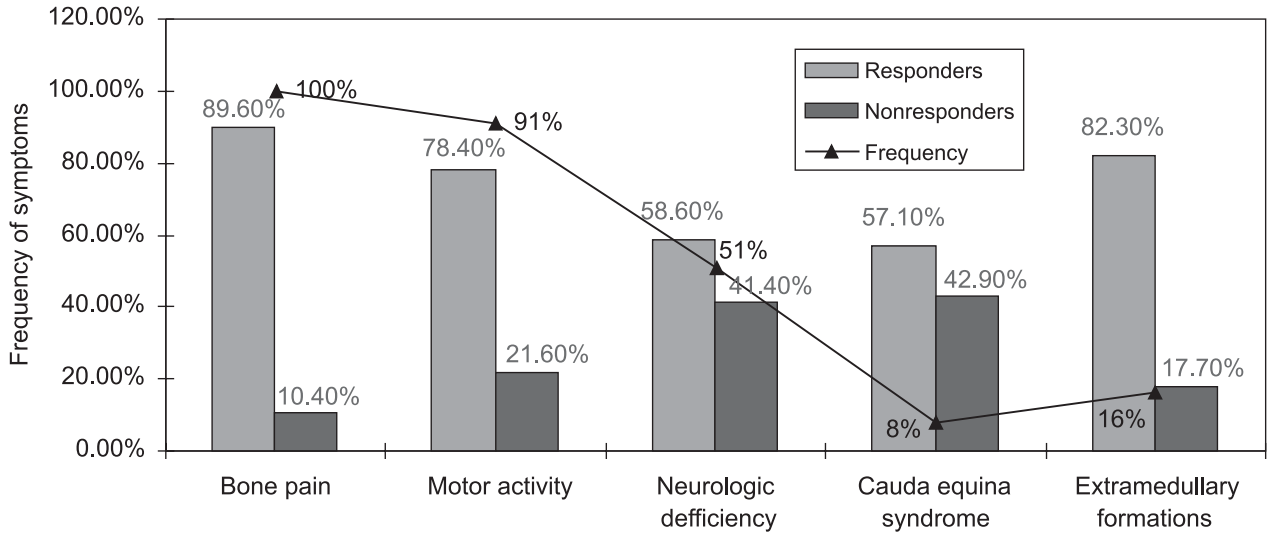

Figure 1. Therapeutic response after palliative radiotherapy.

16). In 25/44 (58.6%) patients neurologic symptoms such as radiculopathy, paresthesias, sensitivity for cold and warm, and weakened reflexes were improved. Resolution of cauda equina syndrome was registered in 4/7 patients who gained sphincter control, and 3 of these also gained partially their motor functions. The recovery of neurologic deficiency was usually partial and depended on the duration of compression or infiltration. Reduction of extramedullary tumor formations was observed in 14/17 (82.3%) patients and in 4/17 (23.5%) complete disappearance of these formations was found (on enhanced CT scan only fibrous tissue could be seen). The longest period free of bone-related symptoms following RT was 16 months (median 2.5). Relapses at previously treated sites were rather low: bone pain in 11.5%, neuropathy in 17.6%, and motor dysfunction in 15.7%. Progression was registered most frequently in the first 2-8 months.

Table 2. Basic laboratory parameters before and after RT

Parameter	*Before RT Mean value±SD*	*After RT Mean value±SD*	*p-value*
Hemoglobin (g/l)	99.5 ± 23.78	94.3± 22.96	NS
White blood cells ($\times 10^9$/l)	6.76 ± 2.8	6.01 ± 2.4	NS
Platelets ($\times 10^9$/l)	220 ± 93.94	203 ± 110.6	NS
Bone marrow infiltration (%)	50.87 ± 21.37	42.56± 20.189	NS
Ca (mmol/l)	2.59 ± 0.52	2.46 ± 0.38	NS
LDH (U/l)	587 ± 373.66	464.95 ± 225.1	NS
Albumin (g/l)	33.49 ± 7.33	35.40 ± 8.7	NS
Creatinine (μmol/l)	171.64 ± 152.39	210.0 ± 214.3	NS
CRP (g/l)	22.61 ± 11.21	17.47 ± 8.54	NS
β_2-microglobulin (mg/l)	9.13 ± 2.31	7.05 ± 1.53	NS

NS: non significant

Table 2 shows the basic laboratory data before and after RT. There was no significant difference in the levels of hematological and biochemical markers and markers of disease activity (CRP, LDH, β_2-microglobulin) before and after RT.

The hematological and non-hematological toxicity after RT were infrequent, low-grade, easily corrected and reversible (Tables 3,4).

Table 3. Hematological toxicity

	Grade 1 n (%)	*Grade 2 n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
Leucopenia	8 (6.96)	4 (3.84)	1 (0.87)	0
Neutropenia	6 (5.22)	4 (3.84)	0	0
Thrombocytopenia	5 (4.35)	2 (2.61)	0	0
Anaemia	5 (4.35)	1 (0.87)	0	0

Table 4. Non-hematological toxicity

	Grade 1 n (%)	*Grade 2 n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
Nausea	11 (9.57)	7 (6.09)	1 (0.87)	0
Vomiting	8 (6.96)	5 (4.35)	0	0
Pain aggravation	8 (6.96)	4 (3.84)	0	0
Fatigue	9 (7.83)	8 (6.96)	0	0
Diarrhoea	7 (6.09)	3 (2.61)	0	0
Cough	3 (2.61)	2 (1.74)	0	0
Shortness of breath	2 (2.61)	1 (0.87)	0	0
Tachycardia	2 (2.61)	1 (0.87)	0	0
Dehydration	1 (0.87)	0	0	0

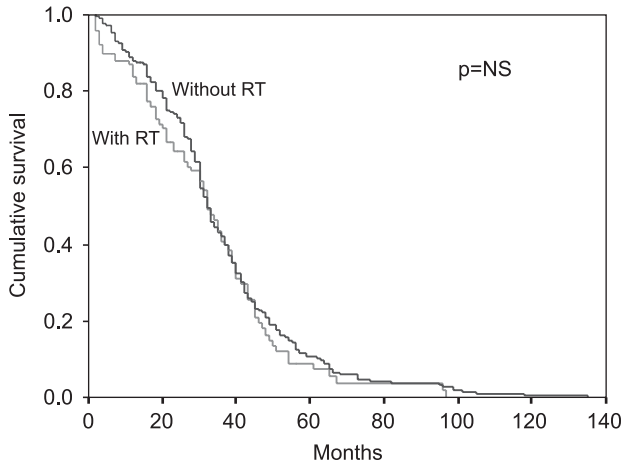

Figure 2. Survival of patients with MM with and without RT.

Comparison of survival between treated and non-treated patients showed no statistically significant difference (Figure 2). The median survival of non-irradiated patients was 33 months (range 28-36) vs. 32 months (range 30-34) for irradiated patients ($p > 0.05$). The median survival of patients treated with 5×4 Gy was 34 months (range 25-50), and of those treated with 2×8 Gy it was 32 months (range 27-37, $p > 0.05$) (Figure 3).

Discussion

In the last decade a large number of osteolytic cytokines was identified and the major mechanisms for development and manifestation of MBD were described. The highly specific markers of bone metabolism, modern imaging and osteodensitometric methods proved a serious disbalance in the bone remodelling in MM [3]. On the basis of these achievements, contemporary therapeutic and prophylactic methods of bone lesions and their complications are applied: calcitonin, biphosphonates, strontium^{99}, rhenium, recombinant osteoprotegerin and RANKL-FC. They block osteoclastogenesis and limit the development of MBD. Literature data show that the biphosphonates - the most widely used osteoprotective drugs - alleviate pain and bone-related events in 30-50% of the cases and they probably increase survival [3]. These are not concurrent but parallel therapies in the multimodal control of MBD, and palliative RT is a basic part of it.

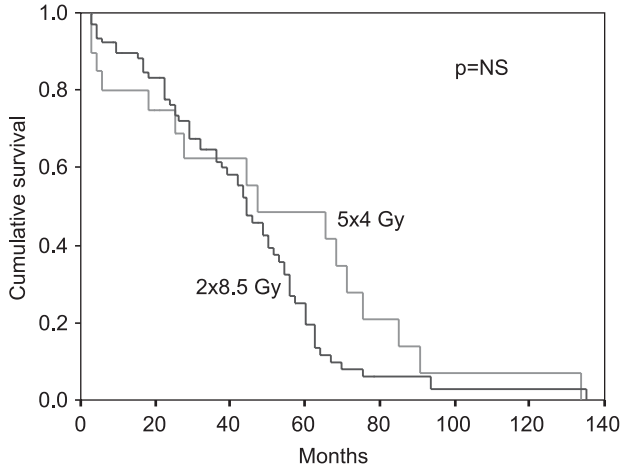

Figure 3. Survival of patients with MM, treated with two different radiotherapeutic regimens.

Since the 1920s, RT was the only effective treatment of MM for several decades. Local RT is one of the most important supportive methods with major indications bone pain, vertebral and non-vertebral pathological fractures, spinal cord compression, soft tissue formations and formations from destructive bone lesions [4,5].

Methods of whole body and hemibody irradiation result in pain alleviation but the frequent and high-grade adverse reactions do not give them advantage over chemotherapy [6,7]. These methods are nowadays a component of high-dose therapies followed by autologous stem-cell transplantation [5]. Today local RT is a method of choice in the solitary myeloma and isolated extramedullary forms of the disease [8-10]. To assess the role of RT in myeloma, in 1971 Bergsagel et al. [11] demonstrated the great radiosensitivity of myeloma cells: *in vitro* a single dose of 1.1 Gy destroyed 76-92% of myeloma cells. This became the radiobiological basis of the clinical implication and therapeutic efficacy of RT in MM. In cases of painful bone lesions not complicated by spinal cord compression or destruction, RT results in high response rates [12-14]. The response rate is not so high in cases with spinal cord compression and cauda equina syndrome, where complete response rarely occurs. An important factor for improved results is the early diagnosis and the immediate start of treatment (RT + high doses of corticosteroids ± surgical decompression). An 1/3 of the patients start walking, but only a minor part of completely paralysed ones get improved. Recovery of sphincter function precedes regaining the ability to walk. The slow evolution of the process is a beneficial factor for a better therapeutic outcome [15].

A large number of retrospective studies, and an increasing number of prospective studies confirm the good results in overcoming bone pain in 50-80% of the cases, but there is also some criticism concerning the enrollment of patients and the precise definition of the aim of the treatment, out of the analgesic effect and psychosocial support. Another debate in the literature

concerns the number and extent of a dose per fraction when irradiating the bone volumes [16,17]. The study of RTOG discusses the difficulties in controlling different factors, which can influence the data assessment. The basic point is that there is no correlation between the number of fractions and the therapeutic response [18]. In the last years the opinion settles that pain reduction can be achieved by a single fraction, but the expected survival and the general status of the patient must be taken in consideration [19-22]. In cases with expected longer survival, a 2- or multiple-fraction regimen has to be chosen, according to the decision of the radiotherapist [23]. The dose we apply 2×8.5 Gy and 4×5 Gy is considered to be optimal for our purposes.

Another problem open for discussion is the healing of bone lesions after RT. Norin et al. [24] found healing of vertebral fractures and reduction of the size of osteolytic lesions on X-ray examination, but other authors do not accept such an effect [25,26]. Mill and Griffith [11] report a successful treatment of 11 lesions of the long bones, but a patient with RT suffered a fracture immediately after RT because of a large osteolysis in the humerus. Some authors [27] describe 39 MM bone lesions treated with RT, which never developed fractures.

Conclusions

1. RT is a major method of treatment of MBD.
2. The most prominent effect of palliative RT is in bone pain palliation (89.6%), reduction of soft tissue formations (82.3%), improved motor function (78.4%) and resolution of neurologic deficiency due to compression (58.6%).
3. Palliative RT improves quality of life of MM patients.
4. Palliation of pain does not influence the activity of the disease and survival.
5. Conventional regimens of RT are well tolerated with minor hematological and non-hematological toxicities.

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