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Palliative Fractionated Radiotherapy for Bone Metastases Clinical and Biological Assessment of Single Versus Multiple Fractions

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ABSTRACT

Background: Radiotherapy is effective in controlling pain from bone metastases which is a direct result of bone resorption. The urine resorption marker DPD proved important in assessing effectiveness of palliative radiotherapy to bone metastases. There is still controversy about the optimum adopted fractionation regimen.

The aim of this study is to compare single fraction 8Gy with the standard treatment course of 30Gy/10 fractions/2weeks and to a third regimen of 20Gy/5 fractions/1week regarding factors impacting on QoL in terms of improved pain, mobility, analgesia scores, PS. The decrease of urine DPD was included as an objective parameter of response.

Patients and Methods: A prospective phase lll controlled study of palliative radiotherapy was conducted on 60 patients with bone metastases from known primary sites divided into 3 groups each of 20 patients balanced in age, sex, and type of malignancy, to be treated with one of three RT regimens. Assessment was done before and 6 weeks after treatment completion according to an established scoring system.

Results: Pain and analgesia scores were improved in the group receiving 30Gy/10 fr. regimen (p=0.002 & 0.003) with no significant improvement of mobility (p=0.16) or PS (p=0.08). Urine DPD was decreased in this group by 43% in 9/20 patients. The group receiving single fraction of 8 Gy showed a significant improvement of scores of pain (p=0.008), analgesia (p=0.01), mobility (p=0.001), PS (p=0.01) and decrease in urine DPD by 33% in 7/20 patients. The group receiving 20Gy/5 fr. protocol achieved improved scores of pain (p=0.002), analgesia (p=0.008), mobility (p=0.03), and a decrease of u-DPD by 56% in13/20 patients which was significantly better than the group receiving single 8Gy fraction, (p=0.03). There was a trend towards an increased number of reirradiations in patients receiving single fraction 8Gy, though not significant, whereas reirradiation was significantly correlated with the high initial u-DPD level within all groups.

Conclusion: The 20Gy/5fr. regimen seems to be superior to both the standard 30Gy/10fr. and the single fraction 8Gy as it achieved significant improvement of three clinical criteria, pain, analgesia and mobility concomitantly with significant decrease in urine DPD. Urine resorption markers confer subjective evaluation of radiotherapy response in patients with bone metastases. The high initial u-DPD level was significantly correlated with the need to reirradiation.

Key Words: *Fractionated radiotherapy – Bone metastases – Bone resorption markers.*

INTRODUCTION

Bone metastases is a major complication of many solid tumors as prostate, lung and thyroid cancers **[1,2]**. Although bone metstastases often start clinically silent, yet they may lead to serious sequalae as pain, fractures, and hypercalcemia **[3]**. These complications usually impact on the performance status (PS) and quality of life (QoL) of the patient. Most patients experiencing bone pain eventually require opiates which can significantly alter the patient QoL. Over many years, radiationtherapy (RT) had been the main indication that proved to be effective in the treatment of pain of osseous metastases **[3]**. There have been many randomized trials addressing the issue of optimal fractionation schedules and total dose of external beam radiotherapy. Many of them have shown that lower doses of radiotherapy are equivalent

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to higher doses for the end point of pain response rates **[4-6]**. Studies have also demonstrated increased rates of retreatment and of fractures when using shorter low dose-schedules **[7,8]**. The use of different hypofractionation schedules other than conventional fractionation allowed to obtain variable clinical responses at better cost effectiveness. However, the continued debate over the appropriate fractionation scheme for the most effective regimen of palliative radiotherapy has not yet ceased. Pain scores, analgesic consumption, and QoL scores are all subject to observer bias and are difficult to compare with different patient populations. In view of better assessing the response to the used fractionation scheme, some studies included bone resorption markers to the evaluation parameters of the efficacy of the treatment **[9]**. Biochemical markers of bone metabolism can provide subjective insight into tumor and bone interactions and on the effect of therapy on this dynamic process **[10]**. These include pyridinoline -cross-linked peptides (DPD), bone specific alkaline phosphatase and osteocalcin. Pyridinoline-cross-linked peptides appear to have the best association with clinical status and response to treatment **[10]**.

The aim of the present study: is

* To compare the clinical and biological palliative effect of single fraction RT 8Gy for painful bone metastases of solid malignant tumors with other two types of fractionation schedules: 20Gy, 5 fractions over one week and another one of 30Gy, 10 fractions over two weeks.

* To investigate the value of the urine bone resorption marker DPD in assessing response to palliative RT regimens.

PATIENTS AND METHODS

Sixty patients with bone metastases from different primary histologically proven solid tumors presented to Nasser Institute Oncology Department during the years 2003-2004. All patients had known malignancy metastatic to bone causing neuropathic pain and had a life expectancy of at least three months. Evaluation included complete history taking, clinical examination including performance status (PS), pain scale, mobility, previous or current medication, the type and dose of analgesia. Routine blood investigations, radiological examination and bone scanning were mandatory. Urinary bone resorption marker DeoxyPyridinoline Dipeptide (u-DPD) was performed on the second morning voided urine sample and normalized to urine creatinine level. All patients below 18 years of age, patients with clinical or radiological evidence of cord or cauda equina compression, and patients with bone metastases who received irradiation or hormonal treatment, bisphosphonates or chemotherapy within 10 weeks prior to study were excluded. Evaluation depended on a scoring system for each of clinical and biological items before treatment and six weeks after treatment completion. Patients were divided into 3 balanced groups, each of 20 patients, according to the Fractionation Radiotherapy regimen. The first group received 30Gy in 10 fractions over 2 weeks (30Gy/10fr), the second group received 20Gy in 5 fractions (20Gy/5fr) over one week, and the third group received a single fraction of 8Gy. Radiotherapy regimen specified the use of photons from LA 6 or 10MV. Bone metastases in thoracic, lumbar spine, sacrum or rib were treated with single field at depth 3-6cm according to the depth of the vertebrae. Other sites including cervical spine were treated with parallel opposing fields to mid plane. The prescribed dose was the maximum absorbed dose at depth in single fields and the central dose for opposing fields. Pain assessment was based on questioning the patient. Patients rated their index pain as intolerable (score 4), severe (score 3), moderate (score 2), mild (score 1), or none (score 0). A scoring scale for the dose, frequency, and type of analgesia (simple, NSAI, opiates) from 0-4 was recorded. A similar scoring scheme from 0-4 was also adopted for mobility and ECOG scale for performance status (PS). Response to treatment was assessed 6 weeks after completion of treatment **[11-13]**. Urinary DPD (u-DPD) was measured using an ELISA Kit (Biometra, USA), before treatment and six weeks after treatment completion. The normal u-DPD excretion was assessed in 40 apparently healthy individuals within the same age range of the patients for comparison. Clinical response was defined as a decrease of 25% of the initial score before starting treatment reflecting an improvement in pain, mobility, performance status and decrease of analgesia. Biological response wasdefined as a decrease of u-DPD excretion by 25%, 6 weeks after treatment. The analysis of data was done on eligible patients who received all

their assigned treatment. Mean and standard deviation were used as descriptive values of quantitative data. Friedman test was used to compare means of more than two dependent groups.

RESULTS

All patients subject of this study met the assigned inclusion criteria and filled a written informed consent. Their age ranged from 35 to 85 years old. All of them had painful bony metastases from breast cancer (36 patients), prostate cancer (4 patients), renal cell carcinoma (4 patients), bronchogenic cancer (4 patients) and 12 patients with other different primaries. The three groups of the study, each of 20 patients, were balanced in age, sex, type of malignancy and number of bone metastatic sites and have shown no significant difference regarding any of these clinical features (Table 1). The majority of cases had multiple metastatic sites, mainly involving the pelvis and the spine. All patients received appropriate treatment delivered by LA 6MV and 10MV photons. The number of fields ranged from 1 to 3 in most of the patients using single or two parallel opposing fields and sometimes up to 6 fields (Table 1). Factors impacting on quality of life (QoL) as pain, analgesia consumption, mobility and performance status were assessed before and six weeks after radiation therapy according to the established scoring system. The three groups of patients showed no significant difference regarding any of these factors before treatment. After treatment, the data in Tables (2-5) demonstrate variable significant degrees of improvement in patients belonging to each of the three groups 30Gy/10 fr, 20Gy/5 fr and single fr. 8Gy regarding pain score (p=.002, .002 & .008), frequency and dose of analgesia (p=.003, .008 & .01), mobility (p=.16, .03 & .001), and performance status (p=.08, .16 & .01). The total score of all clinical parameters showed a similar significant response in all groups receiving single or fractionated palliative irradiation (p=. 04, .04 & .001) (Table 6).

Urinary DPD excretion represented an objective criteria of biological response. The u-DPD was elevated in the group receiving the standard regimen (30Gy/10 fr.) with a mean level of 37.8±14.5nmol/mmole creatinine compared to 5.6±1.5nmol/mmol creatinine in normal individuals. The initial u-DPD was 44.5±30.3 nmol/mmol creatinine in the 20Gy/5fr. group and 41.6±34.6nmol/mmol creatinine in the 8 Gy single fraction group. The patient achieving 25% reduction in the u-DPD level was considered a responder to radiation therapy. A significant decrease in the mean u-DPD level after radiation therapy was observed in the three groups of patients. However, the number of responders in group 20Gy/5fr. (13/20 patients) was significantly higher than the 8Gy single fraction group (7/20 patients) and the 30Gy/10 fr. group (9/20 patients). There was also a significant difference in the mean percent decrease in u-DPD of responders of this group compared to single fraction of 8Gy group (Table 7).

Seven patients (35%) of the group receiving single fraction 8Gy had pain recurrence at the irradiated sites and needed reirradiation at week 8. Only 3 patients in the 30Gy/10 fr. group and 5 patients in the 20Gy/5 fr. group needed to be reirradiated at weeks 10 and 11. The data in Table (8) show that reirradiated patients had a significantly higher initial u-DPD level than the non reirradiated patients within each group, p<0.05, Table (8).

Table (1): Patient characteristics and radiotherapy details.

	Gp 30Gy /10fr	Gp 20Gy /5fr	Gp 8Gy /1fr	Significance (p)
Number of patients	20	20	20	
Age range (years):				
35-60	8	9	7	
61-85	12	11	13	Ns
Type of malignancy:				
Breast	12	12	12	Ns
Prostate	1	1	2	
Bronchus	2	2	0	
Kidney	1	1	2	
Other	4	3	4	
Bone metastatic sites:				
1-5	20*	9	12	Ns
> 5	0*	11	8	Ns
high u-DPD level (No)	15	17	20	.04
Radiotherapy modality:				
LA 6 MV	20	17	16	Ns
LA 10 MV	0	3	0	
LA 6 MV & 10MV	0	0	4	
Radiotherapy fields:				
Single field (1-5)	6	5	9	
Two opposite fields (2-5)	9	3	3	Ns
Both (4-6)	5	12	8	

Ns: Not significant. *: Not included in comparison.

Table (2): Pain status in response to the different RT fractionation schedules.

	Pain status			Significance (*p*)
	Gp 30Gy/10fr	Gp 20Gy/5fr	Gp 8Gy/1fr	
Number of responders	14/20	15/20	14/20	Ns
Pain score ± SD:				
Before RT	1.65±0.21	2.0±0.26	2.15±0.44	Ns
Week 6 after RT	0.75±0.08	1.1±0.05	1.35±0.1	.037
p value	.002	.002	.008	

Ns: Not significant

Table (3): Analgesia status in response to the different RT fractionation schedules.

	Analgesia status			Significance (*p*)
	Gp 30Gy/10fr	Gp 20Gy/5fr	Gp 8Gy/1fr	
Number of responders	11/20*	16/20	12/20	.05
Analgesia score ± SD:				
Before RT	1.9±0.17	1.15±0.27	1.15±0.3	Ns
Week 6 after RT	0.75±0.11	0.45±0.05	0.65±0.1	Ns
p value	.003	.008	.01	

*: Not included in comparison. Ns: Not significant.

Table (4): Mobility status in response to the different RT fractionation schedules.

	Mobility status			Significance (*p*)
	Gp 30Gy/10fr	Gp 20Gy/5fr	Gp 8Gy/1fr	
Number of responders	11/20	10/20	12/20	Ns
Mobility score ± SD:				
Before RT	1.65±0.3	2.11±0.08	2.75±0.7	Ns
Week 6 after RT	1.05±0.4	1.1±0.08	1.05±0.05	Ns
p value	.16	.03	.001	

Ns: Not significant.

Table (5): Performance status (PS) in response to the different RT fractionation schedules.

	Performance status scale (PS)			Significance (*p*)
	Gp 30Gy/10fr	Gp 20Gy/5fr	Gp 8Gy/1fr	
Number of responders	9/20*	6/20	13/20	.02
PS (ECOG scale±SD):				
Before RT	1.7±0.15	1.7±0.3	2.3±0.5	Ns
Week 6 after RT	1.25±0.2	1.3±0.4	1.65±0.4	Ns
p value	.08	.16	.01	

Ns: Not significant. *: Not included in comparison.

Table (6): Total clinical score variation in response to the different RT fractionation schedules.

	Total score			Significance (*p*)
	Gp 30Gy/10fr	Gp 20Gy/5fr	Gp 8Gy/1fr	
Number of responders	17/20	15/20	19/20	Ns
Total score±SD:				
Before RT	6.8±0.35	6.96±0.56	8.4±1.1	Ns
Week 6 after RT	3.8±0.41	3.95±0.71	4.4±0.7	Ns
p value	.004	.04	.001	

Ns: Not significant.

Table (7): Bone resorption markers (U-DPD) in response to different RT fractionation schedules.

	Urinary DPD status (n:5.6+1.5nmol/mmol creatinine)			Significance (*p*)
	Gp 30Gy/10fr	Gp 20Gy/5fr	Gp 8Gy/1fr	
Number of patients	20	20	20	
Mean u-DPD (nmol/mmol creatinine):				
Before RT	37.8±14.5	44.5±30.3	41.6±34.6	Ns
6 Wks 6 after RT	27.3±12.4	24.6±19.8	31.4±26.9	Ns
p value	.04	.045	.05	.04
Number of responders:	9/20 (45%)*	13/20 (65%)	7/20 (35%)	.03
% decrease in u-DPD at wk 6 after RT±SD	43%±19%*	56%±14%	33%±11%	

Ns: Not significant. *: Not included in comparison.

Table (8): Correlation between initial u-DPD level (nmol/mmol creatinine) and re-irradiation.

	Radiotherapy regimen			Significance (*p*)
	Gp 30Gy/10fr	Gp 20Gy/5fr	Gp 8Gy/1fr	
Reirradiated:				
No of patients	3 (15%)	5 (25%)	7 (35%)	Ns
Median time to reirradiation	wk 11	wk 10	wk 8	NS
Mean u-DPD±SD (nmol/mmol creatinine)	50.5±18.6	65.4±21.3	53.9±27.2	Ns
Non reirradiated:				
Mean u-DPD±SD	35.7±11.3	40.1±19.6	35.2±18.7	Ns
p value	.045	.04	.035	

Ns: Not significant.

DISCUSSION

The diagnosis of bone metastases is a devastating occurrence for patients with malignant solid tumors as it leads to major alteration of their QoL and to serious skeletal related events (SRE), a result of bone resorption **[14]**. Pain is the most common symptom of bone metastases in actual practice that occurs in 50-90% of patients **[15]**. Several therapeutic measures have been proposed for pain management, ranging from a wide spectrum of analgesics to more effective modalities as palliative RT and bisphosphonates **[15-17]**. However a recent study reported that bisphosphonates on their own are ineffective in controlling pain **[18]**. Although palliation of pain caused by bone metastases is one of the most frequent indications of radiotherapy, yet the optimum fractionation regimen of external beam irradiation is subject to controversy **[19-22]**. Many controlled randomized

trials and overviews were addressed to this issue and recorded efficacy results based on patient self assessment of pain and QoL. Such results could be subject to patient or observer bias and is difficult to compare among different patient populations. The data in the present study indicate that pain response and analgesic consumption improved in more than 70% of patients treated with single fraction RT (8Gy) as well as with both other fractionation regimens. A significantly improved score of pain and analgesia, was observed in all patients treated with single fraction, 20Gy/5 fr. regimen, and in patients receiving 30Gy/10fr. regimen, yet this improvement did not impact or correlate with the PS, probably due to the advanced disease stage of these patients. In order to allow an objective estimation of the efficacy of the different fractionation palliative RT regimens, we included the measurement of a biological parameter of bone turnover, the u-DPD. The results obtained indicate a significant increase of the number of responding patients in the group treated with 20Gy/5fr. regimen compared to single 8Gy or 30G fr. p=0.04. Also, the percent reduction in u-DPD 6 weeks after therapy completion was significantly different in favor of the 20Gy/5fr. regimen.

It is known that radiotherapy mediated inhibition of bone resorption and perhaps of tumor cell killing reduces the production of osteoclast activating cytokines predicting the improvement of pain response **[18,23]**. Therefore, it is likely to consider the decrease in u-DPD after RT in the group receiving the 20Gy/5fr. regimen, a reliable measure of its subjective palliative response and directly correlated with pain improvement.

In all randomized trials, patients receiving a single fraction were more likely to have the same site reirradiated compared to those treated with fractionated RT, mainly due to pain relapse **[24,25]**. Although not statistically significant, a trend towards this finding is evident in the present study as 35% of patients receiving single fraction were reirradiated versus 25% in 20Gy/5 fr. regimen and 15% in 30Gy/10fr. regimen. There was no evident time dependence regarding the need to reirradiation as all cases were in late stage disease, however the need to reirradiation seemed to be significantly related to the initial higher level of u-DPD within each group. In this issue several studies have reported on the ability of bone turnover markers to predict negative clinical outcome in patients with bone metastases from solid tumors and the frequency of reirradiation **[9]**. Another study recommended their routine measurement in such patients at regular intervals to identify responses to irradiation or bisphosphonate therapy **[26]**. Although the Dutch bone metastases study **[5]** stressed on the lower medical and societal cost of single fraction radiation treatment, yet according to other reports, single fraction treatment is overweighed by the higher rate of retreatment **[14]**, a view which is supported by the present study.

In conclusion, twenty Gy over five daily fractions seemed to be the optimum fractionation regimen for palliation of pain from uncomplicated bone metastases. A significant improvement of pain, mobility and PS were recorded with this regimen consolidated by the significant decrease in u-DPD compared to single 8Gy fraction. Urine DPD is a useful tool in assessing the response to palliative radiotherapy of bone metastases and its predictive value regarding reirradiation should be considered.

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