An investigation into the incidence of pain flare in patients undergoing radiotherapy for symptomatic bone metastases

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Abstract

Introduction

External Beam Radiotherapy (EBRT) is a recognised intervention for symptomatic pain relief from bone metastases. Pain flare is a reported EBRT toxicity, described in 16-41% of steroid-naïve patients. This study aimed to determine incidence and duration of pain flare amongst patients within one Oncology Centre.

Methods

Patients receiving EBRT for bone metastases were recruited to a prospective cohort study. Baseline pain scores and a daily pain/analgesia diary were recorded during EBRT and for 14days thereafter. Pain flare was defined as a two-point increase on a pain scale or 25% increase in analgesia intake, with a return to baseline.

Results

Of the thirty-two participants, 69% (n=22) completed the diary. 41% (n=9) patients experienced pain flare, the median duration being 3 days. Of the evaluable patients, 55% (n=12) were male, 45% (n=9) female. The median age was 73years, (range 40-83). The common primary sites of disease were Breast (32%) and Prostate (32%), with other sites making up the remaining 36%. The most frequent EBRT site was the spine (63%), with other treatment sites including pelvis (23%) and extremities (14%). EBRT regimes were restricted to 20Gy in 5 treatments, received by 32% (n=7) of patients and 8Gy in 1 treatment (68% (n=14)). Of these two regimes, pain flare was reported by 29% and 47% respectively.

Conclusion

Pain flare is a common toxicity of EBRT for bone metastases. Taking the small sample size into consideration, the incidence and duration of pain flare in patients within this single-centre study are comparable with those found in international studies.

Key Words

Bone metastases, Pain flare, External Beam Radiotherapy

Introduction

Cancer incidence is rising due to longer life expectancy, and an improvement in systemic anti-cancer therapy (SACT) has led to greater numbers of patients living longer with metastatic disease[1]. In particular, bone metastases are a frequently occurring complication of many cancers, predominantly breast, prostate and lung, and are known to be experienced by approximately 70% of patients[2]. These can lead to poor quality of life (QoL), with patients experiencing many symptoms, including pathological fractures, hypercalcaemia and metastatic spinal cord compression (MSCC), some of which may require surgical intervention[3-5]. The main systemic management options for bone cancer are SACT (including bisphosphonates), surgery, chemotherapy and hormone manipulation, supported by analgesia. External Beam Radiotherapy (EBRT) provides a useful local treatment for pain relief. EBRT is widely used with approximately 23,000 episodes delivered due to metastatic bone cancer in England in 2013[6]. It has been evidenced to provide symptomatic relief and loco-regional control for approximately 50-80% of patients, and complete response for 30-50%[7].

Toxicities due to palliative EBRT vary, with patients experiencing erythema, fatigue and local side effects, e.g. nausea, diarrhoea. Furthermore, prospective studies have recognised that pain flare may be observed in up to 41% of patients in the period immediately post-treatment[9]. Pain flare is identified as a transitory increase of pain experienced within the irradiated site, and is thought to be caused by oedema of the periosteum compressing on nerves or the release of inflammatory cytokines[10]. Flare is generally quantified as i) an increase of 2 points on a numerical rating scale (NRS)

with no increase in analgesia, or ii) a 25% increase in analgesia to maintain the previous pain levels[8,9].

Limited evidence evaluating incidence of pain flare is available from within the literature, thus a corresponding pilot study was undertaken to identify and evaluate the experience within one UK Oncology Centre and subsequently compare the results with published literature.

Materials and Methods

Ethical approval was obtained from the Regional Ethics Committee (REC) and from the participating NHS Trust to undertake the study.

A prospective cohort study was undertaken with participation confined to one Oncology Centre within a 9 month period from December 2015 to August 2016. Patients were aged 18 years or over and capable of providing informed consent. A histological-proven diagnosis of any primary cancer or haematological malignancy was required, with radiologically-proven osseous metastases. Patients who were prescribed either 8Gy in a single treatment or 20Gy in five fractions of EBRT were eligible, conforming to the protocol within the Oncology Centre for prescription of EBRT to painful lesions. Participants were required to be assessed as having a performance status (PS) of 0-3 inclusive using the criteria developed by the Eastern Cooperative Oncology Group[11]. Due to differing EBRT protocols and treatment intent, patients prescribed EBRT for pathological fracture of a bone, MSCC, an area previously irradiated or non-proven osseous metastases were excluded.

Prior to EBRT, a questionnaire was completed using the Oncology Centre's electronic patient records and treatment management system, to ascertain baseline demographic data. The variables within this included gender, age, primary disease site, site and prescribed dose of current EBRT and any previous EBRT received. Baseline pain burden was assessed using the Brief Pain Inventory (BPI) and regular analgesia consumption registered[12]. The patient was provided with a pain diary, with written and verbal instructions regarding its completion, to record the worst pain score experienced each day on an NRS and any supplementary analgesia required. The diary was completed daily from the first day of treatment until 14 days following completion of EBRT. Patients were provided with a postage-paid envelope in which to return the diary and were contacted by telephone towards the end of the diary period to encourage them to do so.

Chow's definition of pain flare was used by the majority of the published studies, and was thus used within this study to enable comparison of results[8]. Consequently, pain flare was defined as a 2 point increase in pain on an 11 point NRS of 0 – 10 or a 25% increase in analgesia to maintain the previous pain level, with return to baseline following the flare.

Data from the completed diaries were collected on an excel® (Microsoft, Redmond, WA) spreadsheet to ascertain incidence of pain flare amongst the study population. Descriptive statistics were gathered to report percentages of the population experiencing pain flare; this was compared directly with the published studies. Demographic data was evaluated to ascertain statistical significance in gender, primary disease site, dose received, etc. Pearson's chi-square analysis was used to

test any associations between these variables, with the approximate P-value giving the probability of the observed differences happening by chance. A statistical significance threshold was agreed at 5%. Yates' continuity correction factor was applied to improve the accuracy if the cell values were less than 5. Incomplete data was analysed and assessed for suitability to be included in the overall results. Inclusion was dependent on the aspects of the data missing, for example, no indication on the NRS may be negated if the analgesia record was complete as this included the pain level at the time the medication is taken. Non-completion of the diary led to exclusion of the participant and therefore omission from the overall analysis.

Results

Thirty two patients were recruited into the study between December 2015 and August 2016, of which 47% (n=15) were males and 53% (n=17) were females. Of those enrolled, 69% (n=22) completed their daily pain diary to provide evaluable data which has been statistically analysed. Table 1 demonstrates the relevant data of the appraisable participants. Reasons for exclusion from the study included decline in patient condition or death during the study period, patient withdrawal from the study, non-return of the diary or insufficient data to allow for evaluation.

Daily pain levels were recorded by the participants using the BPI. Pain flare incidence was calculated, with the independent variables of pain experiences in the evaluated group indicated in Table 2. Ten of the evaluable patients experienced an increase of at least 2 points on the pain scale at some stage in their study period, however, using the Chow definition, 41% (n=9) of these actually experienced pain flare[8]. The 10th patient's pain did not revert back to the original level and thus cannot be recorded as

a flare. Severity and duration varied between participants. Pain flare occurred within the first 5 days in all of the patients (100%). 3 patients experienced intermittent pain flare and therefore provided more than one set of data, resulting in 13 reported episodes of flare in total. The mean duration of flare was 3 days (range 1-10 days).

Data was gathered regarding systemic and steroidal treatments, radiation dose and site as indicated in Table 2. The analysis of patients also receiving SACT, including Abiraterone and Tyrosine-kinase inhibitors, and steroid treatment was introduced part-way through the study period. Retrospective data was gathered where possible for early participants; however it was not possible to elicit this information from some annotations and records, reducing quantifiable data.

The age range of the evaluable patients within this study was between 40 and 83 years (median age 73 years). Of those experiencing pain flare, the range was 43-82 years, with an overall mean age of 67.4 years. Further analysis indicates that the male age range was 57-82 years, with a mean age of 73.8 years; the female population range was 43-72, the mean being 59.5 years. There was no statistical difference between patients who did or did not experience pain flare for the majority of variables, including gender, age range, primary cancer site, EBRT site, EBRT dose or SACT when using a significance of $p<0.05$. However, using Fisher's chi-square test for independence, a significant difference was found in pain flare experience between those who did and did not receive steroids during their evaluation period, with a probability (p-value) of 0.0253 ($p<0.05$). When the Yates correction factor was applied due to the small cell values, the p-value was recalculated at 0.0935; the statistical significance cannot be

confirmed. The calculations do not take into consideration the unknown steroidal status of 7 patients.

Discussion

This study provided further evidence that pain flare is experienced by patients receiving EBRT to secondary bone cancer, with 41% (n=9/32) of evaluable patients in the Oncology Centre reporting an increase in pain which conformed to the definition used[8]. The overall result is equivalent to the highest within the range identified in the reviewed publications (16-41%), although it is acknowledged that the results in our study may have been affected by imprecise patient annotation within the research tool and also the inclusion of participants who were also receiving SACT and steroid treatment. There is a wide range of results within published articles; however this may be due to inconsistent definition of pain flare. The definition used within our study is recognised to be the standard[8]. Furthermore, differing radiation dose schedules, pain flare measurement timescales and the allowance of steroids and SACT may account for some of the differences. The local incidence result may be seen as generally comparable, taking into consideration the small sample and restricted EBRT dose regimes allowed within the study criteria.

The timescale for recruitment was limited to a 9 month period, in which 32 patients were recruited. This study number is low compared to published data; however these recruited over longer periods of time or from more than one Oncology Centre. Other factors affecting enrolment included fluctuation in the suitable population, thus limiting

the availability of potential participants, and having just one member of staff recruiting to the study. Low accrual and high attrition rates within palliative clinical research are common, with barriers to recruiting participants including the patient or family perception of the onus of participating, patient PS and limited life expectancy, amongst others[13]. Such issues were identified within the recruitment period of this study, with further concerns including poor cognition of the study concept and lack of family support. Research within the palliative medicine setting requires careful consideration and management of the participants; there should be no notion of coercion or pressure to participate. As a result, gatekeeping by health care professionals is recognised as negatively impacting on palliative study recruitment[14] and this research acknowledges an element of this occurred when assessing the potential recruits' suitability to participate;

Statistical analysis of gender, age, primary disease site, EBRT dose and EBRT site has not identified any patient groups which may be at risk of pain flare; this concurs with published studies with the exception of one which reported Breast cancer patients to have a greater likelihood of experiencing an exacerbation of pain[9]. Initial statistical analysis showed a significant difference between patients who did or did not receive steroids during EBRT. The Yates correction factor was applied which indicated that the result could not be confirmed as statistically significant[15]. Furthermore, the details regarding steroids could not be ascertained in 32% (n=7/22) of patients. No patients were purposefully prescribed prophylactic steroids, and levels of Dexamethasone taken were between 0.75-2mg, far less than that prescribed in the studies investigating this topic[10, 16-19]. The results are contradictory to the expectation that Dexamethasone may reduce the incidence of pain flare.

The age range of the evaluable patients within this study was between 40 and 83 years, with flare experienced within the age range of 43-82 years. With the mean male age being 73.8 years, the female mean age was considerably lower at 59.5 years. This lower female age may be attributed to that 50% (n=2/4) patients had a primary Breast cancer. Over half (54%) of Breast cancer cases are diagnosed in patients under 65 years of age, compared to Prostate cancer in which 54% of diagnoses are in men over 70 years of age[20]. Within this study 32% (n=7/22) of the evaluable male population had a Prostate cancer primary, thus statistical analysis cannot be made between flare incidence and age. There is no link reported in the literature.

Attempts were made to encourage full participation in the study, with telephone calls made to patients to ascertain if there were problems and to serve as a reminder to return the diary. However, 60% (n=6/10) of those excluded were due to non-return of this, with further reasons for non-inclusion comprising deterioration in condition and withdrawal from the study. The previously published studies all experienced similar attrition reasons and rates; high attrition rates are common within supportive care and palliative oncology research studies, with the main reason being patient withdrawal, mainly due to a high symptom burden, which may or may not be related to the clinical trial intervention[21]. Patients within such studies generally have a poor PS due to the impact of their bone metastases and general disease burden, thus it may be predicted there could be a proportion that deteriorate in health or unfortunately die within their pain diary period. Whilst patients are assessed for suitability for treatment, there are occasions when the rate of decline in their health may not be foreseen; furthermore

they may be immuno-compromised due to previous or current systemic treatments, rendering them susceptible to infection which may impact further on their general health.

This project was undertaken as a pilot study to ascertain potential recruitment and suitability of the research tool. A second phase of the study will be undertaken, with the intention to expand our cohort of patients by increasing the size of the research team and recruiting over a greater length of time. A revision of the diary may be considered for the subsequent study to enhance the quality and depth of data, thus enabling improved reporting and statistical analysis

Conclusion

Despite the relatively small sample size, the incidence and duration of pain flare in patients within this single-centre study are comparable with those found in similar international studies and the results provide further evidence to support the assertion that pain flare may be a recognisable toxicity following palliative EBRT for painful bone metastases. The findings will support the information provided to patients regarding potential EBRT-related toxicities during the consent process. Greater consideration should be paid to analgesia available to the patients, with safe provision of supplementary medications made in case exacerbation of pain is experienced.

Future research is intended to extend our examination of this phenomenon and supplement our knowledge of the incidence and duration of pain flare.

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Table 1. Demographic, clinical and treatment details of patients recruited

	Non-evaluable patients (n 10)	Evaluable patients(n 22)
Gender		
Male	30% (3)	55% (12)
Female	70% (7)	45% (10)
Age (years)		
Mean +/- SD	62 +/- 12.99	65 +/- 14.45
Median (range)	60 (45-88)	773 (40-83)
Primary cancer site		
Breast	50% (5)	32% (7)
Prostate	0	32% (7)
Multiple Myeloma	10% (1)	9% (2)
Others	40% (4)	27% (6)
Radiation site		
Spine	50% (5)	63% (14)
Pelvis	10% (1)	23% (5)
Extremities	0	14% (3)
Axial skeleton	40% (4)	0

Radiation dose		
20Gy in 5#	10% (1)	32% (7)
8Gy in 1#	90% (9)	68% (15)

Table 2. Characteristics of pain experienced in evaluated patients			
	No pain flare (n 13)	Pain flare (n 9)	p-value
Gender			p=0.779
Male	62% (8)	55% (5)	
Female	38% (5)	45% (4)	
Age range (years)			P=0.760
40-49	30% (4)	11.1% (1)	
50-59	8% (1)	11.1% (1)	
60-69	8% (1)	22.2% (2)	
70-79	46% (6)	45.5% (4)	
80-89	8% (1)	11.1% (1)	
Primary cancer site			p=0.323
Breast	38% (5)	22.2% (2)	
Prostate	31% (4)	33.3% (3)	
Multiple Myeloma	0	22.2% (2)	
Others	31% (4)	22.2% (2)	
Radiation site			p=0.612
Spine	69% (9)	55% (5)	

Pelvis Extremities Axial skeleton	23% (3) 8% (1) 0	22.5% (2) 22.5% (2) 0	
Radiation dose 20Gy in 5# 8Gy in 1#	 38% (5) 62% (8)	 22% (2) 78% (7)	p=0.421
Steroids Yes No (Unknown)	 8% (1) 61% (8) (31% (4))	 45% (4) 22.5% (2) (33.5% (3))	P=0.0253
Systemic treatments Yes No (Unknown)	 23% (3) 62% (8) (15% (2))	 55.7% (5) 22.2% (2) (11.1% (1))	p= 0.661