Radiotherapy and Oncology 115 (2015) 141–148

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Re-irradiation of bone metastases

Effect of re-irradiation for painful bone metastases on urinary markers of osteoclast activity (NCIC CTG SC.20U)

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ARTICLE INFO

Article history:
Received 5 November 2014
Received in revised form 2 February 2015
Accepted 5 February 2015
Available online 14 March 2015

Keywords:
Urinary markers
Osteoclast activity
Bone metastases
Re-irradiation

ABSTRACT

Purpose: The NCIC CTG Symptom Control.20 randomized trial (SC.20) confirmed the effectiveness of re-irradiation to painful bone metastases. This companion study correlates urinary markers of osteoclast activity with response to re-irradiation, survival and skeletal related events (SREs).
Methods: Pain response was assessed using the International Consensus Endpoints. Urinary markers of bone turnover-pyridinoline (PYD), deoxypyridinoline (DPD), N-telopeptide (NTX), Alpha and Beta cross-laps of C-telopeptide (CTX)-before and 1 month after re-irradiation were correlated to response to re-irradiation and then to both, either or none of the initial and re-irradiation: frequent responders (response to both); eventual responders (response to re-irradiation only); eventual non-responders (response to initial radiation only), and absolute non-responders (no response to both).
Results: Significant differences between 40 responders and 69 non-responders to re-irradiation existed for PYD ($p = 0.03$) and DPD ($p = 0.04$) at baseline. When patients were categorized as frequent responders ($N = 34$), eventual responders (6), eventual non-responders (59) and absolute non-responders (10), the mean values of all markers in the absolute non-responders at baseline and the follow-up were about double those for the other three groups with statistically significant difference for DPD ($p = 0.03$) at baseline. Absolute non-responders had the worst survival. The few occurrences of the SREs did not allow meaningful comparisons among the groups.
Conclusion: There were significant differences between responders and non-responders to re-irradiation for PYD and DPD at baseline. The urinary markers in the absolute non-responders were markedly elevated at both baseline and follow-up with a statistically significant difference for DPD at baseline.
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Radiation therapy is effective in alleviating painful bone metastases [1,2]. The exact mechanism of action is unclear. Although tumour cell kill plays an essential role, the rapid response, absence of a dose–response relation and correlation of efficacy with radiosensitivity suggest that an effect on host mechanisms of pain relief response may also be important [3]. The response to radiotherapy may take 3–4 weeks to occur. Biomarkers of bone turnover have primarily been applied to monitor medical therapy for bone metastases, especially bone modifying agents. Among the most commonly used biomarkers in this setting are: 1. the pyridinium cross-links: pyridinoline (PYD) and deoxypyridinoline (DPD), 2. N-telopeptide (NTX), and 3. C-telopeptide (CTX) [4–6].

In the UK Bone Pain Radiotherapy Trial [7], a supplementary study examined the effects of local radiotherapy for metastatic bone pain on PYD and DPD; baseline concentrations in the non-responding patients were greater than those of responders, and increased after treatment, whereas in responders, mean values remained unchanged ($p = 0.027$). The authors concluded that radiotherapy-mediated inhibition of bone resorption, representing osteoclastic activity, might predict for therapeutic responses [3].

Two systematic reviews have confirmed a beneficial response with repeat radiation therapy for patients who experience pain from bone metastases after initial radiation therapy [8,9]. In the NCIC Clinical Trials Group Symptom Control randomized controlled trial (SC.20) evaluating patients with bone pain after previous

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http://dx.doi.org/10.1016/j.radonc.2015.02.025
0167-8140/

irradiation, 45% of those receiving a single 8 Gy treatment and 51% treated with 20 Gy in multiple fractions had an overall pain response to repeat radiation. This benefit was observed in patients who did or did not respond to initial treatment [10]. However, there remains a small group of patients who appear to be non-responsive to any amount of palliative radiotherapy. The examination of urinary markers may help explain this observation. We therefore conducted a companion study (SC.20U) to primarily correlate response to re-irradiation with changes of urinary markers of osteoclast activity. The secondary aim included analysing the markers in relation to the response to both, either or none of the initial and re-irradiation. As biomarkers of bone metabolism may provide prognostic information [11], we also evaluated these markers as predictors for the survival and skeletal related events (SREs) such as pathological fractures and spinal cord compression.

Methods

The SC.20 randomized trial compared single with multiple treatment fractions in patients with painful bone metastases; the primary endpoint was pain response 2 months after re-irradiation. We have previously reported the trial design and outcomes, which demonstrated non-inferiority of a single 8 Gy treatment fraction and response was associated with meaningful patient-reported outcome differences using the Brief Pain Inventory (BPI) and the EORTC QLQ C30 quality of life instrument [10]. Patients enrolled in the SC.20 study at selected centres in Canada and the UK were approached to participate in SC.20U. Ethics approval was obtained at each participating institution and written consent from the patients.

Urine specimens

Patients submitted urine specimens prior to and 1 month after re-irradiation. The urine specimen before radiotherapy could be collected any time of the day in the clinic. The urine specimen one month after re-irradiation should be the second morning specimen [12]. Urine samples were analysed for PYD, DPD (MicroVue, Quidel Corp CA), NTX (Alere Scarborough Inc. ME), Alpha and Beta cross-laps of CTX (IDS, Immunodiagnostic Systems, AZ) and the results were normalized relative to urinary creatinine, calcium, phosphate, and magnesium concentration.

The response to initial radiation was assessed by the treating physician with patient's input. We employed international consensus endpoints to assess pain intensity and analgesic use [13]. Pain severity was scored with the BPI [14]. Analgesic use was converted into a daily oral morphine equivalent (OME) according to a schema (appendix in SC.20 and SC.20U study protocols). The primary endpoint was overall response to treatment in terms of pain relief, defined as the sum of complete and partial responses at 2 months after commencement of re-irradiation treatment [10].

Statistical methods

We previously reported the results at 2 months after re-irradiation therapy in the two randomized arms of the SC.20 trial with no important differences in outcomes between the two arms [10]. We therefore pooled both groups to perform current analyses. The level of the selected urinary markers was measured as the primary outcome. The increase/decrease (in both absolute and relative values) of the level from baseline was used in the analysis to account for differences in baseline values. Response to re-irradiation was categorized into two groups (responders vs. non-responders). Responders included those patients who achieved complete or partial response following re-irradiation. Others were considered as non-responders. The difference for each urinary marker variable (both at baseline and one month after randomization) between responders and non-responders was compared using Wilcoxon rank sum test [15].

We hypothesized the difference between responders and non-responders might be as large as 50% from baseline. The sample size was calculated with a two-sided significant level $\alpha = 0.05$ and power = 80%. The means and standard deviations (SDs) of PYD and DPD were derived from the UK study. The baseline mean value of PYD was 165 nmol/mmol creatinine and its SDs were 15 and 170 for responders and non-responders, respectively; whilst the corresponding numbers for DPD were: baseline mean 46 nmol/mmol creatinine, SDs 8 and 65 respectively [3]. The equation for calculating deltas is adopted from the sample size equation of Chow and Liu [16]. The proportion of the difference over baseline mean predicted the expected relative change. The required sample size for this companion study was therefore 130 patients. Assuming 20% of the patients did not submit the 1-month urine specimen, we needed to recruit 163 patients.

Moreover, the response to both, either or none of the initial and re-irradiation was classified into categories and the level of the urinary markers was examined via Kruskal–Wallis test [17]:

- Frequent responders (response to both initial radiation and re-irradiation).
- Eventual responders (no response to initial radiation but response to re-irradiation).
- Eventual non-responders (response to initial radiation but non-response to re-irradiation).
- Absolute non-responders (no response to both initial radiation and re-irradiation).

In the exploratory analyses, proportional hazards regression model [18] was used to correlate quartile of baseline urinary markers, age (continuous), gender (female vs. male), primary malignancy (breast vs. lung vs. prostate vs. others), performance status (50–60 vs. 70–80 vs. 90–100), worst pain score at baseline (2–4 vs. 5–6 vs. 7–10), site of painful bone lesion (lumbosacral spine vs. pelvis/hips vs. thoracolumbar spine vs. others), and reason for radiation (further pain relief desired vs. no response vs. pain returned) with the overall survival. A backward model selection method was applied to remove non-significant variables, with all urinary marker variables forced to be in the model. We also examined the correlation of the level of urinary markers with the SREs such as pathological fractures and spinal cord compression. *P*-value <0.05 indicated statistical significance. All analyses were performed in SAS version 9.2 (Carey, NC). This study is registered with ClinicalTrials.gov, number NCT00080912.

Results

A total of 169 patients were enrolled in SC.20U. There were 131 patients from Canada and 38 from the United Kingdom. One patient was ineligible due to baseline pain score less than 2 as per SC.20 study protocol. The 1-month urine sample was missing in 59 patients. A total of 109 patients with urine samples both at baseline and 1-month were therefore analysed (Fig. 1). There were 40 in the responder group and 69 in the non-responder group. Of the 109 evaluable patients, 34 were frequent responders, 6 eventual responders, 59 eventual non-responders and 10 absolute non-responders. Baseline characteristics of the 109 patients (49 female and 60 male) with the median age of 65 years (range 31–91) are shown in Table 1. The most common primary cancer sites were prostate (34.9%), breast (32.1%) and lung (19.3%). The quartile values for the five urinary markers at baseline are listed in Appendix Table 1.

For the 5 urinary markers (PYD, DPD, NTX, Alpha and Beta cross-laps) at baseline, there was a significant difference between responders and non-responders to re-irradiation for PYD (55.5 vs.