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RESEARCH PAPER

Short-course regimen of palliative radiotherapy in complicated bone metastases: a phase i–ii study (SHARON Project)

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Abstract

Metastases with soft tissues invasion, impending fractures or spinal cord compression (complicated bone metastases) represent a common clinical problem in advanced cancers and frequently lead to deterioration of patients' quality of life (QoL). A phase I–II study was planned to define the maximum tolerated dose (MTD) of a short-course radiotherapy (RT) and its efficacy in palliation of complicated bone metastases. A phase I trial was designed with three dose-escalation steps: 16, 18, and 20 Gy. Total dose at each level was delivered in 2 days, twice daily. Eligibility criteria were painful complicated bone metastases and ECOG performance status ≤ 3. The presence of acute toxicity $\geq$ Grade 3 (RTOG scale) was considered the dose limiting toxicity. The MTD was used to plan a phase II trial with pain response as the primary outcome. Pain was recorded using a Visual Analogic Scale (VAS), and QoL using CLAS scales. Forty-five patients were enrolled in this trial. In phase I no Grade ≥ 2 acute toxicities were recorded. Thus 20 Gy was established as MTD. In phase II, with a median follow-up of 4 months, rates of complete symptom remission, partial response, no symptomatic change, and symptoms progression were 32.0%, 52.0%, 8.0%, and 8.0%, respectively. This RT protocol tested in our study is effective and tolerable with comparable results to traditional RT treatments delivered in 5–10 daily fractions.

Keywords Complicated bone metastases · Radiotherapy · Palliative care · Pain · Quality of life

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Introduction

Complicated bone metastases represent a common complex clinical problem in advanced cancers leading to deterioration of patients' quality of life (QoL) due to symptoms such as pain, spinal cord or cauda equina compression, neurological disorders, hypercalcemia, and pathological fractures [1, 2]. Palliative radiotherapy (RT) is an effective and widely used treatment option associated with symptomatic relief and improved QoL while preserving the physical functioning and improving bone integrity [1, 3–6]. Based on several studies using different fractionation schedules, RT is considered a standard option in the palliative treatment of bone metastases [2–6].

Ideally, an effective palliative treatment should be delivered in few days to ensure patients' comfort and compliance. In fact, the clinical conditions of these patients are often very frail because of the cancer-related symptoms. Therefore, treatment duration of 2 days, instead of the traditional 2-weeks (30 Gy in 10 fractions), could solve some of the practical, economical, and logistic problems experienced by patients and RT departments. Moreover, very short treatments durations obviously favor integration with other therapies like chemotherapy and/or immunotherapy, frequently used in metastatic disease. Furthermore, this shorter duration could have a positive economic impact on the health systems. Finally, this choice could resolve potential coordination problems experienced with patients admitted to hospice preventing a prolonged interruption of the assistance.

Prescription of an accelerated hypofractionation RT scheme, in 2 days with twice daily fractionation, can represent a way to deliver a clinically relevant dose in a brief period. Obviously, this fractionation protocol could increase the risk of acute and late side effects and therefore of a QoL worsening. Therefore, a careful evaluation of the maximum dose deliverable without causing severe toxicity is needed before a large-scale evaluation of this treatment.

Previously our group published trials on RT regimens delivered in 2 days with twice daily fractionation in brain metastases and advanced pelvic malignancies [7–9]. Furthermore, our recent pooled analysis showed that this treatment is well tolerated even in older patients [10].

The objective of the present study was to assess feasibility and efficacy of short course palliative RT for complicated bone metastases. We used a dose-escalation trial to define the maximum tolerated dose (MTD) and the latter was used as the recommended dose to evaluate the treatment efficacy.

Materials and methods

Inclusion criteria and study design

Patients ≥ 18 years with pathologically proven diagnosis of solid tumor, CT-scan diagnosis of symptomatic complicated bone metastasis, performance status ≤ 3 according to ECOG, and not previously treated with RT in the same anatomical area were enrolled in the study. Particularly, patients had to have bone metastases with an extra osseous invasion and/or osteolytic lesions with impending pathologic fracture and/or spinal cord or cauda equina compression. The criteria of Mirels and Van der Linden et al. were used to identify patients with impending fracture (50% of bone mass destroyed by visualization on X-ray) [11, 12]. Chemotherapy administration was possible with a minimum of 10 days interval from RT. The presence and intensity of pain, the performance status and QoL were assessed at baseline and at each follow-up visit after RT. Pain intensity and use of analgesics were evaluated using the visual analogue self-assessment scale (VAS) and the IAEA scale (Pain and Drug scores) [13, 14]. Pain response was evaluated based on the International Bone Metastases Consensus Working Party Criteria [15]. The CLAS visual analogue scale was used to score QoL and, more specifically, well-being (CLAS1), fatigue (CLAS2), and ability to perform daily activities (CLAS3) [16].

Phase I

A dose escalation study with three dose levels was planned to define the maximum tolerated dose (MTD) of radiation. The MTD was used as recommended phase II dose and it was established as the next lower dose level below the one producing dose limiting toxicity (DLT) in at least one-third of patients [17]. DLT was defined as any acute toxicity ≥ Grade 3, according to the RTOG scale [18]. The minimum number of patients treated at each dose level was six. If DLT was observed in < 2 of 6 patients at a given dose level (provided a minimum follow-up of 3 months was available in at least 6 patients at that dose level), the trial proceeded to the next dose level. If DLT occurred in a third (2/6) of patients at a given dose level, 6 extra patients were enrolled in the trial using the same dose. In case of > 2 DLT recorded at a certain dose level, the interruption of enrollment was planned, and the lower dose level was defined as the recommended dose for the phase II trial. The same measures were respected even for DLT in ≥ 4 patients in the 12-patient cohort. In case of DLT in < 4 patients of the expanded 12-patient cohort, the trial was continued with the escalation of the dose to the next level.

Phase II

The two-stage design by Simon was used to calculate the sample size [19]. The design tested the null hypothesis that the symptomatic rate for this population would improve from 10% (without RT treatment) to 30%, using an α error of 0.05 and a β error of 0.2. Thus, the first step was planned to include 15 patients. Enrollment interruption and closure of the study were planned in case of ≤ 1 symptomatic response. However, with detection of at least 2 symptomatic responses, the study would enroll additional 10 patients bringing to a total number of 25 patients. The regimen would be considered inactive in case of ≤ 5/25 responses.

Treatment

All patients underwent CT-simulation in supine position using the immobilization systems more suited to the anatomical site. The Clinical Target Volume (CTV) was defined as the complicated bone metastases (considered as the Gross Tumor Volume, GTV) plus 1 cm margin. If the site was the spine, the CTV included the above and below vertebrae. An isotropic margin of 1 cm was added to the CTV to define the Planning Target Volume (PTV). RT was planned and administered using only three-dimensional (3D) conformal technique with multiple beams for optimal sparing of Organs at Risk (OaRs) using an Elekta Precise Linac equipped with standard multi-leaf collimators (MLC). In the three-consecutive planned dose level the total dose was 16, 18, and 20 Gy with 4, 4.5 and 5 Gy/fraction, respectively. Treatment was delivered in two consecutive days, 2 fractions a day, with an interval of at least 8 h between fractions. Based on the linear-quadratic model equation for late complications (α/β ratio: 3), the Equivalent Dose in 2 Gy fractions (EQD_2) relative to the three dose levels was 24.1 Gy, 27.8 Gy, and 32 Gy, respectively [19]. The dose prescriptions and specification were based on the ICRU Report 62 [20]. Dose-volume histograms (DVHs) were calculated for the PTV and OaRs evaluations. Both medical and physics staff independently performed quality assurance checks during treatment planning and delivery, as previously reported [21]. Setup and treatment reproducibility were checked before any fraction using electronic portal imaging, as previously described [22, 23]. A 5-HT3 antagonist (ondansetron, 8 mg b.i.d., p.o.) was prescribed to patients irradiated on the upper abdomen (last dorsal vertebrae or first lumbar vertebrae) during the two days of treatment.

Follow-up evaluation

Clinical history, physical examination and laboratory tests were performed 15 days after RT, and then every 2 months. RTOG and EORTC-RTOG toxicity scales were used to assess acute and late toxicities, respectively [18]. Data regarding pain level and score, drug score, and QoL were recorded. A zero VAS score defined complete pain relief, while a VAS, pain score, or drug score decrease defined a partial symptomatic response.

Table 1 Phase I–II: patients characteristics

	Number of patients	Percentage (%)
Patients	45	100
Age (years)		
Median	63	
Range	39–87	
Gender		
Male	22	48.8
Female	23	51.2
ECOG		
1	26	57.8
2	12	26.7
3	7	15.5

Table 2 Phase I–II: site of primary tumor in 45 patients

	Number of patients	Percentage (%)
Breast	15	33.3
Lung	13	28.9
Prostate	4	8.9
Rectum	3	6.7
Kidney	2	4.4
Bowel	2	4.4
Uterus	2	4.4
Stomach	1	2.2
Penis	1	2.2
Larynx	1	2.2
Thyroid	1	2.2

Results

Patient characteristics

A total of 45 patients were enrolled: 20 patients in the phase I and 25 in the phase II of the study. In both first and second dose level of the phase I, an extra patient was enrolled to assess the 6th patient's acute toxicity. Patients characteristics are detailed in Table 1. The primary tumor sites were: breast (33.3%), lung (28.9%), prostate (8.9%), rectum (6.7%), kidney (4.4%), bowel (4.4%), uterus (4.4%), stomach (2.2%), penis (2.2%), larynx (2.2%), and thyroid (2.2%) (Table 2). The treated metastatic sites were: vertebrae (42.2%), pelvic bones (24.4%), rib cage (15.6%), and others (17.8%).

Phase I

Since no patient in the first two dose levels experienced DLT, patient accrual proceeded up to the third level. Acute toxicities recorded in phase I are detailed in Table 3. Acute toxicities recorded in phase I are detailed in Table 3. Grade 1 skin erythema (1 patient treated on the sternum at 18 Gy dose level) and Grade 1 esophagitis (1 patient treated on cervical vertebrae at 20 Gy dose level) were the only two toxicities recorded. Overall, no patient developed Grade ≥ 2 acute toxicity. No patient died within 30 days.

Phase II

In the first stage of the phase II study, 15 patients were enrolled and treated with the recommended dose (20 Gy). Five patients (33.3%) showed complete symptoms remission, 6 patients (40.0%) partial remission, 2 patients (13.3%) had no change in symptoms, and 2 patients (13.3%) reported symptoms progression. Therefore, the palliative response rate (complete plus partial symptom remission) in the first stage was 73.3%. Consequently, 10 more patients were enrolled in the second stage to reach the total number of 25.

The overall (complete plus partial) pain remission was 84.0% (CI 0.95: 68.4–90.1%) and the overall median duration of palliation was 4 months (range 1–30 months). Pre- versus post-treatment mean VAS was 5.1 versus 1.6 (p: .0001). Particularly, 8 patients (32.0%) had complete symptom resolution (VAS = 0). Thirteen out of 25 patients (52.0%) presented partial symptom resolution (median ΔVAS: 60.0%, ΔVAS range 25.0–88.0%), 2 patients (8.0%) experienced an increased pain (median ΔVAS: 14.0%), while 2 patients (8.0%) had no pain changes.

At first follow-up, 8 patients (32.0%) had an improved ECOG performance status, 14 (56.0%) were stable and 3 (12.0%) had a worse ECOG performance. Furthermore, an improvement of CLAS1, CLAS2, and CLAS3 scores were recorded in 48.0%, 36.0%, and 44.0% of patients, respectively.

Among all patients who received 20 Gy in both phase I (6 patients) and phase II trials (25 patients), only 1 patient (3.2%) presented grade 3 acute toxicity. This patient, treated on the cervical spine, developed esophagitis with painful dysphagia requiring narcotic drugs for 2 weeks. Furthermore, 6 patients (24.0%) treated on the scapula (n = 2) and vertebrae (n = 2 cervical vertebrae, n = 1 cervical-dorsal vertebrae, n = 1 dorsal-lumbar vertebrae) developed Grade 1 skin toxicity. Five patients (20.0%) treated on cervical-thoracic vertebrae showed Grade 1–2 upper gastrointestinal toxicity (nausea or esophagitis). Two patients (8.0%) irradiated on dorsal-lumbar vertebrae (n = 1) and humerus (n = 1) had Grade 1–2 anaemia. Three patients (12.0%) treated on dorsal-lumbar vertebrae (n = 2) and sacrum (n = 1) reported Grade 1–2 lower gastrointestinal toxicity (diarrhea).

Discussion

To our knowledge, this is the first evaluation of multi-fractionation RT treatment for complicated bone metastases delivered in 2 consecutive days with two fractions per day.

The incidence of complicated bone metastases is around 35%, resulting most often from adverse features as pathological fractures (42.1%) and neurological symptoms (36.3%) [24]. These metastases are most common in lung cancers (24.2%) and the main site is the spine (68.5%), followed by the extremities (15.2%), and the pelvis (14.4%) [24]. Although single fraction RT is the standard treatment of uncomplicated bone metastases, multiple fractionation treatments are generally preferred in patients with complicated metastases [24].

The objective of this study was to assess feasibility and efficacy of a short course palliative RT in patients with complicated bone metastases. In the phase I of the study, the MTD (20 Gy) was defined from a dose-escalation protocol. This MTD was used in phase II trial to evaluate the treatment efficacy in terms of pain relief. Overall pain response was 84.0% with a complete response rate of 32.0%.

Table 3 Phase I: acute toxicity

Dose level		1st (16 Gy)		2nd (18 Gy)		3rd (20 Gy)	
		No	%	No	%	No	%
Enrolled patients		7	100	7	100	6	100
Acute toxicity	Grade						
Skin	1–2	0	0.0	1	14.3	0	0.0
	≥ 3	0	0.0	0	0.0	0	0.0
Gastrointestinal	1–2	0	0.0	0	0.0	1	16.7
	≥ 3	0	0.0	0	0.0	0	0.0
Patients experiencing DLT[a]		0	0.0	0	0.0	0	0.0

[a]Dose limiting toxicity

The main limitation of this study is the lack of late toxicity evaluation and long-term symptomatic control given the study design and the short follow-up. However, according to the linear-quadratic model, the MTD (20 Gy) used in phase II trial has the biological effect of approximately 32 Gy for late responder tissues (α/β: 3). Therefore, it can be estimated that the risk of late toxicity is very low. A further limitation of our study is represented by an outdated definition of CTV in the irradiation of vertebral metastases. In fact, evidences published after the approval of our study [25] showed that isolated local failures in unirradiated adjacent vertebral bodies may occur in only < 5% of patients with isolated spinal metastasis. Therefore, this unnecessary expansion of the CTV to the vertebrae adjacent to those involved could produce unjustified toxicity. Finally, a further limitation of our study is that the efficacy of the treatment was evaluated only in terms of toxicity and symptomatic response, without an evaluation of the impact on quality of life based on Patient Reported Outcomes Measures.

It is not easy to compare our results with the ones of published trials in terms of pain response, given the use of different pain scoring systems and different evaluation timing. However, our results (overall response: 84.0%, complete response: 32.0%), are at least comparable with those recorded in studies based on the traditional regimen of 30 Gy in 10 fractions (overall response rate: 66–86%; complete response rate: 13–18%) [26, 27]. Moreover, it should be noted that in those studies most patients had uncomplicated bone metastases, likely to be more sensitive to palliative RT.

If we consider some studies on palliative RT of complicated bone metastases, our response rate seems better compared to the results reported by Silva et al. [28]. In fact, the authors reported 12.5% and 37.5% complete and partial response rates, respectively, using a regimen of 16 Gy in 2 fractions, 1 week apart. Furthermore, our results compare favorably with the study of Maranzano et al. [29] who used the same protocol of Silva et al. or a split course regimen of 30 Gy in 2 weeks reporting 56.9% overall pain response rate. However, it should be noted that only patients with spinal cord compression were enrolled in that trial. This particularly unfavorable situation may have influenced the palliative effect on pain.

Similarly, it is not easy to compare toxicity with other studies since in most cases detailed analyses of side effects were not reported. However, we can observe that our rate of Grade ≥ 2 toxicity (16.1%) is very similar to the one reported by Hartsell et al. using the 30 Gy in 2 weeks protocol (17%) [27]. Furthermore, our rate of Grade 3 toxicity (3.2% in patients receiving 20 Gy) was lower compared to the study of Gaze et al. [30]. In fact, these authors reported 15% rate of Grade 3 nausea/vomiting using a regimen of 22.5 Gy in 5 fractions. Nevertheless, it is worth noting that in their study, RT was delivered with a single-beam or with two opposed beams technique, while a multiple-beam conformal RT was used in this study.

This technical aspect deserves to be strongly highlighted. Our results in terms of toxicity cannot be generalized for situations in which patients are treated with simpler techniques such as 2D-RT or with only 1–2 beams.

In conclusion, the RT protocol tested in our study seems to be effective and tolerable with comparable results to traditional RT treatments delivered in 5–10 daily fractions. This protocol has the advantage of RT completion in only 2 days. This can be particularly useful for patients living far from the RT centers or who need to start a systemic therapy or hospice care. However, due to the limitations of the study design, which do not allow definitive conclusions on the equal effectiveness of this regimen compared with traditional treatments, phase III studies are needed.

A multicenter randomized trial is currently ongoing in our centers comparing one arm based on the traditional treatment of 30 Gy in 10 fractions with one arm based on the scheme tested in the present study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the local Ethics Committee. The study is registered in an international public registry (ClinicalTrials.gov: NCT03455231).

Informed consent Informed consent was obtained from all individual participants included in the study.

Research involving animal and human participants This article does not contain any studies with animals performed by any of the authors.

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