Clinical Oncology (2008) **20:** 83—89
doi:10.1016/j.clon.2007.09.009

Original Article

When Should we Define the Response Rates in the Treatment of Bone Metastases by Palliative Radiotherapy?

K. K. Li, S. Hadi, A. Kirou-Mauro, E. Chow

Rapid Response Radiotherapy Program, Odette Cancer Centre, University of Toronto, Toronto, Canada

ABSTRACT:
Aims: **It is well established that palliative radiotherapy provides effective pain relief for symptomatic bone metastases, but controversy remains regarding the optimal dose fractionation. Several meta-analyses and systematic reviews of trials comparing the efficacy of single vs multiple fractionated radiotherapy schedules noted that it is difficult to reach a consensus when inconsistent response end point definitions are used. The purpose of this study was to determine when the most appropriate time to evaluate a response is.**
Materials and methods: **Patients with symptomatic bone metastases treated with palliative radiotherapy between May 2003 and June 2005 were enrolled in the study. They were assessed with the Brief Pain Inventory at baseline, 1, 2 and 3 months after radiotherapy. Analgesic consumption during the preceding 24 h was recorded and converted into an equivalent total daily dose of oral morphine. The response to radiotherapy was assessed using the International Bone Metastases Consensus end point definitions at 1, 2 and 3 months of follow-up.**
Results: **One hundred and ninety-nine patients were treated with palliative radiotherapy. All pain scores and functional interference items improved after radiotherapy. The proportion of evaluable patients with a complete response or a partial response increased between 1 month (58%) and 3 months of follow-up (67%). However, when considering intention-to-treat percentages, which take attrition into consideration, overall response rates dropped from 35% at 1 month, to 32% at 2 months, and finally 24% at 3 months.**
Conclusion: **We conclude that 2 months after radiotherapy is the most appropriate time point to measure response rates for two reasons: (i) the maximum pain relief for some patients may take more than 4 weeks to achieve and (ii) attrition poses a major problem when response rates are measured at a later date. Future trials should use standardised criteria for end points to facilitate comparison and analysis across clinical trials. Given the limitations of this study, however, further investigations are needed to confirm the response time points for palliative cancer patients. Li, K. K. *et al.* (2008). *Clinical Oncology* 20, 83—89**

Key words: Bone metastases, cancer pain, international consensus, palliative radiotherapy end points

Introduction

A common cause of morbidity in patients with advanced cancer is painful bone metastases. Among the options for pain management, the primary treatment for most patients is external beam radiation therapy. It is well established that palliative radiotherapy provides effective pain relief [1]. However, there remains much controversy regarding the optimal dose fractionation among radiation oncologists despite clinical trials, systematic reviews and meta-analyses suggesting equivalence of response outcomes between single vs multiple fractionation schedules [2—5]. Wu and colleagues [6] noted five features that can influence reported primary outcomes of studies, namely: (i) the extent of pain reduction that constitutes a treatment response; (ii) the timing of which the response is assessed; (iii—iv) consideration of cointerventions such as systemic therapy and analgesic consumption; and (v) how the duration of the response is measured.

A systematic review by Chow *et al.* [5] and Wu *et al.* [6] found that many clinical studies of palliative radiotherapy measure pain response at varied time points. Wu and colleagues [6] found that most studies do not provide clear details regarding the timing of the assessment of the treatment response and suggested that it was probably related to the timing of the follow-up appointments. Response rates are different when evaluated at different time points, as illustrated by Arcangeli and colleagues [7]. Thus, variation in end point definitions can make it difficult to compare conclusions across trials [6].

To promote consistency among clinical trial design for palliative bone metastases, the International Bone Metastases Consensus Working Party on end point measurements was formed in 2002 [8]. This gave rise to an important

0936-6555/08/200083+07 $35.00/0

report outlining a set of commonly accepted end points, which was published and disseminated as guidelines for trial design. There were 13 items listed in the guidelines, including end point definitions, timing, frequency and duration of follow-up assessment, and when to determine a response. The Consensus Working Party agreed upon the timing of the response evaluation, which was suggested to be determined at 1, 2 and 3 months after radiotherapy [8]. However, little is known about the differences in response rates when measured at such time points, and if one is more appropriate than the others. The purpose of this study was to determine the best time to evaluate the response to palliative radiotherapy in patients with bone metastases.

Materials and Methods

All patients referred for palliative radiotherapy for symptomatic bone metastases at the Rapid Response Radiotherapy Program clinic were enrolled into this study if: they were able to speak and understand English, were competent to complete the survey questions, had radiographic evidence of bone metastases and gave verbal consent. Ethics approval for the current study was obtained from the Sunnybrook Health Sciences Centre Research Ethics Board.

At the initial consultation, patient characteristics and baseline symptom profiles were collected, including the Karnofsky Performance Score, and the Brief Pain Inventory (BPI) [9]. Using the BPI, patients rated their worst, average and current pain intensity on a scale of 0 (no pain) to 10 (pain as bad as you can imagine), as well as the level of pain interference with seven items of function: general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life on a scale of 0 (no interference) to 10 (complete interference). The BPI has been validated and shown to be reliable in measuring pain intensity and interference with function [9].

Analgesic consumption in the previous 24 h was recorded and all opioid analgesics were converted to an oral morphine equivalent dose. Non-opioid analgesics were accounted for as 0 for oral morphine equivalent dose. Follow-up assessments by telephone were conducted at 1, 2 and 3 months after palliative radiotherapy.

Response outcomes were determined at 1, 2 and 3 months, where recommendations of response definitions by the International Bone Metastases Consensus were adopted [8]. A responder to radiation was defined as one with a complete (CR) or partial response (PR). CR was defined as a worst pain score of 0 at the treated site with no increase in analgesic intake. PR was defined as: (i) reduction in worst pain score of 2 or more at the treated site without analgesic increase, or (ii) analgesic reduction of 25% or more from baseline without an increase in pain. Individuals who experienced pain progression or who did not fall into one of the response categories outlined by the consensus were considered non-responders. Pain progression was defined as (i) two or more points increase above the baseline at the treated site with stable analgesic use or (ii) pain score stable or one point above the baseline with an increase of 25% or more in analgesic intake compared with the baseline. Patients who had missing pain scores or analgesic intake were not included in the analysis. The time (months) to first CR/PR was recorded for each patient. Patients without CR/PR at the end of the study or by the time they withdrew had censored lifetimes.

All analyses were carried out using the Statistical Analysis System [10]. Descriptive statistics and frequency distributions were generated for the patients' demographic and disease-related characteristics, as well as response rates at various time points.

Results

Patient Characteristics

Between May 2003 and June 2005, 199 patients (51% men and 49% women) who received radiotherapy for painful bone metastases consented to participate in the study and were included in the analysis. At baseline, their median age (lower quartile [LQ]—upper quartile [UQ]) was 66 years (54—74) and the median Karnofsky Performance Score (LQ—UQ) was 70 (65—80). Lung, breast and prostate were the most common sites of primary cancer. The most common painful bony sites were the lower limbs (34%), hip (24%) and pelvis (23%). Half of the patients (51%) had 8 Gy in one fraction and 43% had 20 Gy in five fractions. The remaining 6% received other dose fractionations. The median total daily oral morphine equivalent (LQ—UQ) was 47.5 mg (0—150). The median (LQ—UQ) pain relief from medication and other therapies was 70% (50—80) before palliative radiotherapy, and 80% (60—90), 80% (60—90), 80% (70—90) at 1, 2 and 3 months after radiotherapy, respectively. Patient characteristics at baseline and follow-up at 1, 2 and 3 months are summarised in Table 1.

The number of patients that could be reached for a follow-up was 134 at 1 month, 101 at 2 months and 79 at 3 months. The main contributors to the loss of follow-up were death and hospitalisation, accounting for the attrition of 25 patients at the first follow-up, a total of 41 patients by the second follow-up and 44 patients by the third follow-up. Additional reasons for the loss to follow-up included inability to be reached by telephone ($n = 23$ at 1 month, $n = 16$ at 2 months, $n = 31$ at 3 months), and patient's request to discontinue participation in the study ($n = 8$ at 1 month, $n = 21$ at 2 months, $n = 24$ at 3 months), and others ($n = 9$ at 1 month, $n = 20$ at 2 months, $n = 21$ at 3 months).

Pain and Functional Interference

The baseline median worst, average and current pain scores were 8, 5 and 3.5, respectively. All three pain scores improved at 1 month after radiotherapy. Figure 1 shows the median pain scores and their LQ and UQ at baseline and 1, 2 and 3 months of follow-up.

The functional items and their corresponding median scores and LQ and UQ at baseline were as follows: general activity = 8 (5—10), mood = 6 (3—8), walking ability = 8 (3—10), normal work = 8.5 (5—10), relations with others = 2