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Review Article

Incidence of pain flare in radiation treatment of bone metastases: A literature review

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ABSTRACT

Purpose: Pain flare is a temporary increase in pain and is a potential side effect of radiotherapy treatment. However, its incidence has been reported only in recent studies, and with great variability. A few studies have reported on the use of dexamethasone as a prophylactic agent in the prevention of pain flare. The objective of this study is to present a review of the available literature regarding the incidence of pain flare and use of dexamethasone as a preventative measure.

Methods: A literature search was conducted in PubMed using subject keywords including: "radiation therapy", "stereotactic radiation therapy", "bone metastases", "pain flare", and "dexamethasone". The search was limited to English only but not restricted to any time period. Additionally, a search was also conducted in the American Society for Therapeutic Radiology and Oncology (ASTRO) 2014 book of published abstracts. Inclusion criteria were primary studies published with full text and/or abstracts only. Letters to the editor were excluded.

Results: A total of 11 studies were selected, two of which were abstracts published by ASTRO in 2014. Seven articles investigated pain flare and/or dexamethasone use for conventional external beam radiation therapy (EBRT) while the remaining four investigated stereotactic body radiation therapy (SBRT). Pain flare incidence ranged from 2 to 44% for EBRT and 10 to 68% in SBRT. The use of dexamethasone also showed to be effective in both the prophylaxis and treatment of pain flare.

Conclusions: Pain flare has been established as an acute toxicity of both EBRT and SBRT, although its incidence is widely variable due to differences in data collection. The use of dexamethasone in the prophylaxis of pain flare is efficacious. Future studies are required in order to both optimize the reporting of pain and the dexamethasone regimens in the prevention of pain flare.

1. Introduction

Bone metastases are exceedingly common among advanced cancer patients, especially in those with breast, prostate, and lung carcinomas [1,2]. They are a cause of great morbidity and result in significant pain in 50–75% of patients at some point throughout the course of their illness [2–4]. Bone metastases can also lead to hypercalcemia, skeletal complications including pathological fractures and spinal cord compression, and have a negative impact on quality of life (QOL) [1,5,6].

External beam radiation therapy (EBRT) is recommended for the relief of symptomatic bone metastases [1,5,6]. Studies have proven it to be both cost-effective and efficacious, with up to 80% of treated patients experiencing at least some pain relief [3,6]. Moreover, it has few associated toxicities, many of which are temporary and minor in nature [6].

Recent technological developments have led to an increased use of stereotactic body radiation therapy (SBRT) for the treatment of select tumors, most commonly to the liver, lung, or bone [7,8]. This technique is employed with a locally curative intent and delivers more radical doses of radiation with great accuracy [9]. For spinal metastases, SBRT allows for locally ablative doses of radiation to the target and limits the spinal cord or cauda to thresholds below the dose of myelopathy [6]. SBRT to the spine delays tumor progression and provides long-term pain control and maintenance or even improvement in QOL [7]. Long term complications of spine SBRT, unique from conventional EBRT, include vertebral compression fractures and, much less likely, radiation myelopathy. Acute adverse events are similar to conventional radiotherapy and are usually self-limiting [8].

Pain flare, defined as a "temporary worsening of bone pain in the treated metastatic site" [2], has been previously documented as a side effect of radiopharmaceutical and hormonal therapy [2,10,11]. Although it is a recognized side-effect of radiation treatment as well,

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only recent studies have attempted to accurately document its incidence in patients treated with EBRT or SBRT [2,4,7–13]. These studies report incidences reaching as high as 68% for SBRT and 44% for EBRT [8]. A qualitative study published by Hird et al. [14] discusses patient perspectives and the impact of pain flare on QOL. Overall, patients describe interference with daily activities and general functioning, as well as anxiety and worry regarding the success of the treatment. Typical pain flare management entails an increase in analgesic use, leaving the patient at risk of associated adverse events including dry mouth, drowsiness, and constipation [14]. Moreover, the majority of patients felt that their pain was not adequately relieved by increased analgesics. Rather, 85% of patients stated that the optimal management of pain flare requires prophylaxis [14].

Dexamethasone is an anti-inflammatory steroid medication that has been shown to be effective as a prophylactic agent against pain flare [4,8,12]. It is hypothesized that the dexamethasone reduces edema within the periosteum of the treated bone [15]. With a half life of 36–54 h, it may be administered to patients throughout the duration of treatment and for a few days post treatment in order to curb the debilitating effects of pain flare [12].

The objective of this report is to present the currently available literature documenting the incidence of pain flare in both conventional and stereotactic radiation therapy techniques. Furthermore, it will summarize the use of dexamethasone in early clinical trials as a prophylactic measure against the occurrence of pain flare.

2. Methods

A literature search was conducted in PubMed. It was limited to English articles only, but was not restricted to any time period. The American Society for Therapeutic Radiology and Oncology (ASTRO) 2014 book of published abstracts was also screened for potential relevant studies. Keywords and subject headings for searches included “radiation therapy”, “stereotactic radiation therapy”, “bone metastases”, “pain flare”, and “dexamethasone”. Inclusion criteria were primary studies published with full text and/or abstracts only. Letters to the editor and commentaries were excluded.

Abstracts and articles generated by the search were screened based on title first, then abstract or full text, independently by RM and LR. If there was a disagreement for inclusion or exclusion of an article, a discussion ensued until a consensus was reached.

3. Results

A total of eleven studies published between 2005 and 2014 were identified as relevant. This includes nine full text articles and two abstract publications extracted from the ASTRO 2014. Seven studies investigated EBRT with two additionally investigating prophylactic treatment of pain flare with dexamethasone and one investigating prophylaxis with a methylprednisolone infusion. Four studies investigated pain flare resulting from stereotactic radiation therapy, only one of which included dexamethasone as a prophylactic agent. A summary of the studies and their characteristics is presented in Table 1. The incidence of pain flare, duration of pain flare, and possible use of dexamethasone, if applicable, is reported in Table 2.

3.1. External beam radiation therapy

A total of seven studies have documented the incidence of pain flare in patients treated with EBRT to symptomatic bone metastases, three of which included an investigation of pain flare prophylaxis with a steroid medication [2,4,10–13,16]. All studies collected data such as pain score and analgesic intake prospectively using questionnaires at baseline, daily during, and daily after treatment completion for a set duration of time. Specific data collection methods can be found in Table 1.

The first study to investigate the incidence of pain flare was published in 2005 [10]. Pain flare was defined in their study as either a 2-point increase in worst pain on a scale of 0–10 with no decrease in analgesic intake, or as a 25% increase in analgesic intake with no decrease in worst pain score. Between June 2000 and February 2001, 88 patients were accrued to the study. The incidence of pain flare was 14% on day one for patients who received 8 Gy in 1 fraction, and 15% on day one for patients who received 20 Gy in 5 fractions [10].

Following up with this study in 2007, the authors [12] published a study investigating the use of dexamethasone for the prophylaxis of pain flare. All 33 patients accrued to the study were prescribed two tablets of 4 mg dexamethasone by mouth one hour before treatment. Using the Brief Pain Inventory (BPI) to collect analgesic information and worst pain score, pain flare incidence in this population was reported to be 24% [12].

In contrast to the previous two studies, Loblaw et al. [11] collected pain scores using the Present Pain Intensity (PPI) questionnaire and developed two working definitions of pain flare: (1) a 2-point increase in the PPI with no decrease in analgesic score, or a 50% increase in analgesic score with no decrease in PPI on at least two consecutive days; and (2) a 2-point increase in PPI with no decrease in analgesic score or a 25% increase in analgesic score with no decrease in PPI on at least two consecutive days. The authors collected pain scores prospectively using the PPI at baseline, in a daily diary for the first week following treatment, and then at 14, 30, and 60 days post treatment. The incidence of pain flare was 34.1% and 40.9% using each definition, respectively [11].

Hird et al. [2] published a comprehensive study in 2009 with results on pain flare incidence from three Canadian Centres. A total of 111 patients were included in the study, of which 41% documented pain flare. Eighty percent of those who experienced pain flare also reported it to be within the first five days following treatment. A phase II trial was then published in 2009 by Hird et al. [4], in which 8 mg of dexamethasone was prescribed to all patients and taken at least one hour before daily radiotherapy and for three consecutive days following completion. Twenty-two percent of the 41 accrued patients reported pain flare with a median duration of one day.

A recent study published in abstract form only reported the incidence of pain flare in patients treated with EBRT to bone metastases [16]. This study collected worst pain scores and analgesic consumption prospectively before, daily during, and for ten days post-treatment. Of a total patient population of 94, 42 (44.7%) were documented to have pain flare. The median duration of pain flare was two days and the majority (88%) occurred between days one to five post-treatment [16].

In a double-blind randomized study, one hundred twenty patients with vertebral metastases during the two week short-course EBRT were randomized to methylprednisolone versus placebo resulting in pain flare incidence of 6.6% versus 20% respectively [13].

3.2. Stereotactic body radiation therapy

Four studies investigated the incidence of pain flare in patients treated with SBRT [7–9,17]. Three of the four studies defined pain flare as (1) at least a 2-point increase in worst pain score, (2) at least a 25% increase in opioid intake, or (3) the initiation of steroids [7,8,17]. The fourth study measured pain flare according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [7].

Chiang et al. [8] published the first study in March 2013 and focused specifically on SBRT for patients with spinal metastases. Data was collected prospectively using the BPI at baseline, during treatment, and ten days post follow-up. The authors found that 28 of 41