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Clinical Investigation

Comparing the Effectiveness of Combined External Beam Radiation and Hyperthermia Versus External Beam Radiation Alone in Treating Patients With Painful Bony Metastases: A Phase 3 Prospective, Randomized, Controlled Trial

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Summary

Bone pain recurrence after palliative radiation therapy (RT) to bony metastases is a common scenario. In this randomized phase 3 trial, we aimed to compare the rate, duration, and time to achieve complete pain relief and radiologic responses between RT alone (30 Gy/10 fractions) and hyperthermia

Purpose: To compare the response, duration of pain relief, and time to achieve complete pain relief after radiation therapy (RT) with or without hyperthermia (HT) in patients with painful bony metastases.

Methods and Materials: Cancer patients with bony metastases and pain score $\geq$4 on the Brief Pain Inventory (BPI) were randomized to RT of 30 Gy in 10 fractions combined with HT (RT + HT) versus RT alone. Hyperthermia was performed by the Thermotron RF-8, with maintenance of the target temperature for 40 minutes per treatment within 2 hours after RT, twice weekly for 2 weeks. Patients were stratified by lesion number (solitary or multiple), BPI score (4-6 vs 7-10), and primary site. The primary endpoint was complete response (CR) (BPI = 0 with no increase of analgesics) within 3 months after treatment. This study was registered with ClinicalTrials.gov.

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(HT) (by Thermotron RF-8) combined with RT. The addition of HT to RT significantly increases pain control and extends response duration compared with RT alone for painful bony metastases.

Results: The study was terminated early after an interim analysis of 57 patients, 3 years after the first enrollment (November 2013 to November 2016): 29 patients in the RT + HT group and 28 patients in the RT-alone group. The CR rate at 3 months after treatment was 37.9% in the RT + HT group versus 7.1% in the RT-alone group ($P = .006$). The accumulated CR rate within 3 months after treatment was 58.6% in the RT + HT group versus 32.1% in the RT-alone group ($P = .045$). Median time to pain progression was 55 days in patients with CR (n = 9) in the RT-alone group, whereas the endpoint was not reached during the 24-week follow-up in the RT + HT group ($P < .01$).
Conclusions: The addition of HT to RT significantly increases the pain control rate and extends response duration compared with RT alone for painful bony metastases.

Introduction

Bone metastases lead to significant morbidities, such as unbearable pain, pathologic fractures, or cord compression. Many randomized trials have confirmed the mainstay role of radiation therapy (RT) to alleviate pain or control the progression of osseous metastatic disease (1, 2). A dose of 30 Gy in 10 fractions is generally regarded as the standard palliative RT dose. Although symptom relief has been seen in 50% to 80% of patients who received RT, only less than 50% of patients have been reported as pain-free after 4 weeks (3), and 50% have experienced pain relapse at approximately 12 weeks (median, 9.6-15 weeks) after treatment (4). An impact of bone ossification usually has been seen at 10 to 12 weeks after RT (5).

It has long been recognized that hyperthermia (HT) in the range of 40° to 43°C and higher acts as a radio- and/or chemo-sensitizer (6, 7). The increased RT or chemotherapy effect is called thermal sensitization. The Thermotron RF-8 (Yamamoto Vinita, Osaka, Japan), which delivers 8-MHz radiofrequency (RF)-based deep HT, is one of the most commonly used HT machines. The RF-8 requires a pair of capacitive electrodes placed on opposite sides of the body to treat superficial, subsurface, or deep-seated tumors, especially at 5 to 7 cm depth; it has been used in combination with RT for the past 2 decades in Japan (8). Dielectric heat with high power has been produced after rapid changes in the electric field (8 MHz) to reach the goal temperature in a specific region (9). Since the 1990s, increased local control or overall survival by combining RF-8 with RT have been reported in multiple randomized trials in the settings of esophagus cancer (10), advanced cervical cancer (11, 12), advanced head and neck cancer (13), and advanced non-small cell lung cancer (14). Hyperthermia also stimulates osteoblast activity to improve osteogenesis and decrease fracture risk (15).

Despite the high incidence of bony metastases and the relatively short duration of treatment response, the clinical experience of combining HT with RT has never been reported. We aimed to conduct the first phase 3 study comparing the rate, duration, and time to achieve complete pain relief and radiologic responses between RT and the combination of HT with RT.

Methods and Materials

Study design

The primary objective of the study was to evaluate the rate of complete response (CR) in indicated lesions, defined as a Brief Pain Inventory (BPI) score of zero plus no concomitant increase in analgesic use within 3 months after RT. Secondary objectives included time and duration of pain relief; differences in radiologic tumor response on measurable lesions at week 12; quality of life changes recorded by the European Organization for Research and Treatment of Cancer C30 questionnaire; and treatment-related adverse events. This randomized phase 3 study was approved by the institiutional review board of Shin Kong Wu Ho-Su Memorial Hospital and is registered with ClinicalTrials.gov. NCT 01842048.

Patients

Eligible patients had a histologically or clinically (computed tomography [CT], magnetic resonance imaging, bone scan, or positron emission tomography/CT scan) confirmed solid tumor bony metastases with the index lesion involving or abutting bone; Eastern Cooperative Oncology Group performance status score of 0 to 3; age between 20 and 75 years; and life expectancy $\geq$3 months. The index lesion was defined as a lesion $<$20 cm with worst pain (BPI $\geq$4) over the last 24 hours, in the irradiated field contoured from CT simulation, and effectively covered by electrodes (maximal diameter 30 cm). Each patient could have only 1 index lesion for treatment and evaluation. Radiation to other metastatic lesions was allowed after treatment of the index lesion, to prevent the influence on analgesic dose evaluation. Systemic therapy (chemotherapy, hormonal therapy, target therapy, or bisphosphonate), analgesics, or prior surgery without metal implants were allowed. The strength of analgesics and systemic therapy should not have been changed for 4 weeks before and during RT. Exclusion criteria included index lesion involving the skull, pathologic fracture requiring immediate