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Review Article

A national portfolio of bone oncology trials—The Canadian experience in 2012

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ABSTRACT

Background: The impact of both cancer and its treatment on bone is an essential component of oncological practice. Bone oncology not only affects patients with both early stage and metastatic disease but also covers the entire spectrum of tumour types. We therefore decided to review and summarise bone oncology-related trials that are currently being conducted in Canada.
Method: We assessed ongoing and recently completed trials in Canada. We used available North American and Canadian cancer trial websites and also contacted known investigators in this field for their input.
Results: Twenty seven clinical trials were identified. Seven pertained to local treatment of bone metastasis from any solid tumour type. Seven were systemic treatment trials, five focused on bone biology and predictive factors, three evaluated safety of bone-targeted agents, three were adjuvant trials and two trials investigated impact of cancer therapy on bone health. The majority of trials were related to systemic treatment and bone biology in breast cancer. Most were small, single centre, grant-funded studies. Not surprisingly the larger safety and adjuvant studies were pharmaceutical company driven.
Discussion: Despite the widespread interest in bone-targeted therapies our survey would suggest that most studies are single centre and breast cancer focused. If major advances in bone oncology are to be made then collaborative strategies are needed to not only increase current sample sizes but to also expand these studies into non-breast cancer populations.

1. Introduction

Bone oncology is an increasingly important area of cancer therapeutics. It covers a number of areas including; the effects of normal aging on bone, the treatment and prevention of cancer therapy-induced bone loss and strategies for prevention of bone metastases and reducing skeletal related events in those with metastatic disease. Historically the greatest emphasis has been on bone metastasis management, as skeletal metastases are common and a significant cause of patient morbidity. Although any malignancy may ultimately metastasize to bone, it is most prevalent in advanced breast (70–80%), prostate (70–80%), thyroid (60%) and lung cancers (10–50%) [1]. Given that breast and prostate cancers are the most common cancers to afflict women and men respectively, it is not surprising that most research has focused on these sites. More recently there has been increased interest in the effects of cancer therapy-induced bone loss due to chemotherapy (directly and through induction of premature ovarian failure) and anti-estrogen/androgen therapies. Again, this is particularly pertinent in breast and prostate cancers. In addition, large adjuvant therapy trials with bisphosphonates and denosumab are also being evaluated in patients with breast and prostate cancers [2,3,4,5].

Research into bone health has to reflect the multi-modality, multi-disciplinary and broad interests of those involved. These can include such diverse groups as; medical oncologists, radiation oncologists, surgical oncologists, palliative care specialists, endocrinologists, nursing, orthopaedics, basic scientists, imaging and primary care providers, to name but a few. It is therefore essential that a portfolio of trials exists to reflect this. We also require a means of educating, identifying, and linking all those interested in bone oncology to help initiate and sustain relevant collaborations. The purpose of this paper is to briefly review and summarise bone oncology-related trials that are currently being conducted in Canada to facilitate this process.

2. Methods

We reviewed http://www.canadiancancertrials.ca/ and http://www.ontario.canadiancancertrials.ca/ in order to identify ongoing

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bone oncology-related trials. We used the keywords: bone, bone metastasis, bone treatment, cancer therapy induced bone loss and bisphosphonates for searching. We also used http://clinicaltrials.gov/ to identify Canadian participation in international studies. We also contacted colleagues in cancer centres across Canada for additional information about local studies at their own centres.

3. Results

Due to the diversity of effects of cancer and its treatment on bone health our search identified a number of bone oncology research themes including; local palliative therapy for symptomatic metastases, systemic treatment of bone metastases, the safety of systemic treatment, adjuvant therapy trials with bone-targeted agents and studies investigating cancer therapy induced bone loss. There were also a number of biomarker studies evaluating the utility of predictive factors for skeletal related events or designed to increase our understanding about fundamental bone biology. A number of Canadian groups perform basic and translational bone research. We will discuss each theme in turn.

3.1. Local therapy studies

A diverse range of local therapy trials are being performed (Table 1). These reflect the palliative effects of radiotherapy, focused ultrasound, or surgery on symptomatic bone metastases. These studies involved patients with a range of primary cancers. Six of the seven currently running trials of local therapy for bone metastases were multi-centre. Four of them were intergroup initiated, one was sponsored by industry, and one was academic grant-funded.

3.2. Systemic treatment trials for patients with bone metastases

Bisphosphonates and RANKL inhibitors have been shown to be effective in reducing the frequency and increasing time to onset of skeletal related events in patients with bone metastases. However, there are many unresolved questions around their use, including questions regarding; duration of use, optimal interval between treatments, choice of agent, as well as strategies to reduce side effects of therapy. Although current treatment recommendations are the same for all patients with metastatic bone disease (usually 3 to 4 weekly systemic therapy), patients with low risk of skeletal-related events probably need less aggressive dosing regimens, while patients at the highest risk of skeletal complications need more effective treatment.

Several ongoing trials are trying to optimise the management of patients with bone metastases using bone turnover markers as surrogates of skeletal related event risk (Table 2). These studies can be broadly split into those assessing the magnitude and/or duration of biomarker suppression [13–16], reduced bisphosphonate use [17], and those evaluating optimal care of patients with high risk disease [18]. Almost all these trials are in breast cancer patients. In prostate cancer there was one large randomized Phase III study evaluating the efficacy of early versus standard zoledronic acid in prevention of SREs in patients with prostate cancer metastatic to bone on androgen-deprivation treatment [19].

Unlike the local therapy trials described above most of the systemic therapy studies were small, single centre, investigator-initiated, and funded either by peer-reviewed grants or internal funding. One study was multinational, and sponsored by NCI and CALGB [19]. Another multi-centre study was initiated and sponsored by the Ontario Clinical Oncology Group with pharmaceutical funding [16]. Understandably systemic therapy safety (Table 3), adjuvant trials (Table 4) tended to be multinational and pharmaceutical company funded. Two Canadian prospective studies investigating cancer treatment induced bone loss in prostate

Table 1
Local therapy trials for patients with bone metastases.

Study title	Primary end-point	Number of centres	Number of patients	Cancer type
A Phase III international randomized trial of single versus multiple fractions for re-irradiation of painful bone metastases [6]	Compare pain relief in patients undergoing single-fraction versus multiple-fraction re-irradiation of painful bone metastases 2 months after treatment.	Multi-centre	850	Any
A phase III study of the effect of re-irradiation for bone pain on urinary markers of osteoclast activity [7]	To correlate the response of re-irradiation to the change of urinary markers of osteoclast activity	Multi-centre	130	Any
Dexamethasone versus placebo in the prophylaxis of radiation-induced pain flare following palliative radiation therapy for bone metastases [8]	Reduction in incidence of radiation-induced pain flare after single 8 Gy fraction from the time of radiotherapy treatment to 10 days after the completion of treatment	Multi-centre	300	Any
A prospective cohort study of the role of surgery and/or radiation therapy for bone metastases of the femur at high risk of pathological fracture (observational) [9]	To describe the ambulatory status at 3 months by intervention (surgery ± radiotherapy, and radiotherapy alone group)	2 Ontario centres	180	Any
Surgical versus non-operative treatment of metastatic epidural spinal cord compression. quality of life and cost-effectiveness outcomes (observational) [10]	Change in spine-associated pain intensity and neurological outcomes	Multi-centre	432	Any
A pivotal study to evaluate the effectiveness and safety of ExAblate (magnetic resonance-guided focused ultrasound surgery) treatment of metastatic and multiple myeloma bone tumors for the palliation of pain in patients who are not candidates for radiation therapy, phase III [11]	Improvement in pain scores	Multi-centre	148	Any
Phase II/III study of image-guided radiosurgery/SBRT for localized spine metastasis [12]	Efficacy and safety of radiosurgery	Multi-centre	280	Any