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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

Table 2
Systemic therapy trials for patients with metastatic bone disease.

Study Title	Study arm	Primary end-point	Number of centres	Number of patients	Cancer type
A randomized pilot study comparing the efficacy of 4-weekly versus 12-weekly intravenous bisphosphonate therapy in women with low risk bone metastases from breast cancer using bone resorption markers [13]	Randomised comparison of 4 weekly versus 12-weekly pamidronate	To demonstrate that the administration of pamidronate once every 12 weeks is equivalent to 3–4 weekly administration	1	37	Breast
Suppression of bone turnover following treatment with zoledronic acid in patients with metastatic breast cancer: duration of effect [14]	Single arm, single infusion of zoledronic acid	To estimate the proportion of patients with suppression of bone turnover at 12 weeks after administration of a single dose of zoledronic acid	1	35	Breast
Duration of suppression of bone turnover following treatment with zoledronic acid in men with metastatic castration resistant prostate cancer [15]	Single infusion of zoledronic acid	Duration of suppression of bone turnover in prostate cancer patients with bone metastases following a single infusion of Zoledronic Acid and its effect on quality of life.	2	50	Prostate
A phase ii, multi-centre, randomized, double-blind trial to evaluate the therapeutic benefit of Fulvestrant in combination with ZACTIMA or Fulvestrant Plus Placebo in postmenopausal women with bone only or bone predominant, hormone receptor positive metastatic breast cancer [16]	Fulvestrant + Zactima versus Fulvestrant + Placebo	Significant change in NTx level defined as $a \geq 30\%$ reduction in urinary NTx level from baseline	Multi-centre	126	Breast
A multicentre study assessing 12-weekly intravenous bisphosphonate therapy in women with low risk bone metastases from breast cancer using bone resorption markers [17]	Single arm, 12-weekly pamidronate	To demonstrate that in women with biochemical evidence of lower risk bone metastases following at least three months of regular 3–4 weekly pamidronate, the administration of pamidronate once every 12 weeks is sufficient to maintain this biochemical stability for one year	1	68	Breast
A randomized, double-blind, placebo controlled, Phase III trial evaluating the palliative benefit of either continuing pamidronate or switching to second-line zoledronic acid in breast cancer patients with high risk bone metastases [18]	4 weekly pamidronate versus zoledronic acid	To compare the proportion of high-risk metastatic breast cancer patients with bone metastases that will achieve a decrease in sCTX in the zoledronic and pamidronate treatment arms.	1	84	Breast
A randomized, double-blind, placebo-controlled phase iii study of early versus standard zoledronic acid to prevent skeletal related events in men with prostate cancer metastatic to bone [19]	4 weekly zoledronic acid versus placebo	Time to 1st SRE	Multi-centre	680	Prostate

Table 3
Trials assessing safety of systemic therapies.

Study title	Primary end-point	Number of centres	Number of patients	Cancer type
An Open-label, multi-centre, phase 2 study of denosumab in subjects with giant cell tumour of bone [20]	Safety profile of denosumab characterized in terms of the type, frequency, and severity of adverse events and laboratory abnormalities	Multi-centre	375	Giant cell tumour of bone
A double-blind, placebo-controlled study to evaluate new or worsening lens opacifications in subjects with non-metastatic prostate cancer receiving denosumab for bone loss due to androgen-deprivation therapy [21]	Subject incidence of cataract event development or progression on denosumab by month 12 exceeding a predefined level at any of 3 key lens locations using LOCS III score	Multi-centre	760	Prostate non-metastatic
Feasibility and dose discovery analysis of zoledronic acid with concurrent chemotherapy in the treatment of newly diagnosed metastatic osteosarcoma [22]	Safety, dose-limiting toxicity and maximum tolerated dose of zoledronic acid	Multi-centre	30	Osteosarcoma

Table 4
Adjuvant bone-targeted therapy trials.

Study title	Primary end-point	Current status	Number of centres	Number of patients	Cancer type
A randomized, double-blind, placebo-controlled, multi-centre phase 3 study of denosumab as adjuvant treatment for women with early-stage breast cancer at high risk of recurrence (D-CARE) [23]	DFS	Recruiting	Multi-centre	4500	Breast
Randomized phase iii trial of bisphosphonates as adjuvant therapy for primary breast cancer [24]	DFS, OS	Closed for accrual	Multi-centre	5400	Breast
A clinical trial comparing adjuvant clodronate therapy versus placebo in early-stage breast cancer patients receiving systemic chemotherapy and/or hormonal therapy or no therapy [4]	DFS	Closed to accrual	Multi-centre	3323	Breast

DFS = Disease free survival, OS = Overall survival.

Table 5
Studies related to cancer therapy induced bone loss.

Study title	Primary endpoint	Current status	Number of centres	Numbers of patients	Cancer type
A randomized, single-blind, placebo-controlled, multicentre study to evaluate the effect of risedronate and placebo on bone mineral density in men undergoing androgen deprivation therapy with leuprolide acetate [25]	Bone mineral density of the lumbar spine after 12 months	Completed- results awaiting	Multicenter	160	Prostate
A prospective study to evaluate the incidence of skeletal related events in prostate cancer patients undergoing Androgen Deprivation Therapy (ADT) [26] prospective observational	Bone mineral density of the lumbar spine	Ongoing but not recruiting patients	Multicenter	300	Prostate

Table 6
Studies evaluating bone biology and biomarkers of skeletal risk.

Project title	Primary end-point	Number of centres	Number of patients	Cancer type
Prospective identification of risk factors for skeletal related events in breast cancer patients receiving bisphosphonates for bone metastases [27]	Identification of risk factors for SREs in breast cancer patients	1	60	Breast
Histomorphometric and microarhitectural analyses using the 2 mm bone marrow trephine in metastatic breast cancer (MBC) patients on long term bisphosphonate therapy—a feasibility study [28]	Feasibility of bone biopsy using 2 mm needle to look at the way bisphosphonates change the structure of the bone after extended use	3	30	Breast
Bone repository feasibility study in breast, prostate and lung patients [29]	To evaluate if 2 mm needle bone biopsy can provide enough tissue to make all	1	30	Breast, prostate, lung
Breast cancer to bone (B2B) metastases research program: a multidisciplinary approach to the investigation of bone metastases from breast cancer [30]	4 Subgroups: identification of predictor factors for bone metastases in patients with early stage breast cancer	1	600	Breast
A Phase 2 trial exploring the clinical and correlative effects of combining doxycycline with bone-targeted therapy in patients with metastatic breast cancer [31]	To assess the palliative benefit (reflected through changes in validated pain scores and the bone resorption marker serum C-telopeptide) of adding doxycycline to standard bone-targeted therapy in women with breast cancer and bone metastases	1	37	Breast

cancer patients were conducted in collaboration with pharmaceutical companies (Table 5).

3.3. *Studies of bone biology and predictive markers*

A number of investigations are ongoing to evaluate fundamental biology in bone and also prospectively identify useful biomarkers of bone metastasis aggression and behaviour, or prediction of future bone metastasis risk (Table 6). Again these studies tended to be focused on breast cancer patients. Prospectively collected specimens from three studies [13,17,18] have been used to identify risk factors for skeletal related events in breast cancer patients receiving bisphosphonates and also risk for developing bone metastases in the first place.

Given the paucity of in vivo information about the effects of bone targeted agents on human tissue two studies are of particular interest. In one study [27], patients with bone metastases from breast cancer are being prospectively evaluated to determine whether standard or novel assessment of bone density, bone quality, and/or markers of bone breakdown are useful in stratifying the skeletal related event risk of individual patients. In another study [28] evaluating long term bisphosphonate therapy on bone homeostasis, quality, quantity, and bone architecture is being explored. Patients with metastatic breast cancer on long term bisphosphonate are undergoing histomorphometric and micro-architectural analyses of 2 mm bone marrow trephine biopsies to assess bone quality, as well as standard DEXA assessments of bone quantity. Another bone biopsy study will evaluate whether trephine needle bone biopsy

can provide enough tissue for banking in patients with lung, prostate and breast cancers [29].

The, "Breast cancer to bone (B2B)" metastases research program is a large multidisciplinary population study funded by the Alberta Cancer Foundation. This project collects clinical, pathological and biochemical data for the investigation of predictive factors for bone metastases in patients with early stage breast cancer. Patients are followed prospectively from the time of diagnosis of breast cancer until they develop bone metastases. This study has recently been expanded to collect tissue and data from patients with a range of malignancies [30].

Preclinical studies showed that doxycyclin enhance an antitumour activity of bone targeted agents on bone metastases models. A phase II study exploring clinical efficacy of combination bone targeted agents with doxycyclin is open to accrual. Predictive and prognostic role of multiple bone formation and bone resorption markers will be assess in this trial [31].

3.4. Basic research programs

There are currently a number of Canadian groups performing basic and translational bone research. The overall goal of these programs is to obtain a better understanding of changes in bone and its microenvironment related to cancer and its treatment as well as discover new important targets for therapeutic interventions. For example, the Singh laboratory (McMaster University) is currently investigating impact of glutamatergic signalling mechanisms on cancer-induced bone pain and cancer-induced depression [32,33].

The Whyne laboratory (University of Toronto) is focused on understanding of biomechanics of musculoskeletal system using translational bioengineering research with emphasis on structural changes in bone involved in metastatic process [34]. They are also performing preclinical and Phase 1 trials assessing effects of photodynamic therapy in metastatic bone lesions [35].

Extensive bone programs are also running at McGill University with the Siegel laboratory identifying molecules and pathways that facilitate organ specific breast cancer metastases [36]. This is close collaboration with the Park laboratory where the influence of the metastatic microenvironment on breast cancer metastasis is being explored [37]. Finally our own group is working in collaboration with the Kremer laboratory on a number of projects relating to the role of vitamin D and parathyroid hormone related peptide (PTHrP) in cancer and musculoskeletal disorders [38]. The Addison laboratory in Ottawa are performing translational studies look at the role of Focal Adhesion Kinase and β1 integrin in animal bone metastases models [39].

4. Discussion

Bone oncology is a broad and multidisciplinary area of cancer therapeutics. Given the significant impact bone health management has across a broad range of disciplines we hope this paper will be an important step in allowing people to see the nature of studies available and potential collaborators. To further enhance these communications we have also organised a yearly bone meeting in Canada. This meeting aims to cover a wide range of topics from normal bone function, to the effects of cancer on bone as well as effects of cancer therapies on normal bone and metastatic bone disease [40].

The purpose of this paper was therefore to briefly review and summarise what types of bone oncology-related trials are currently being conducted in Canada. We have specifically not included pure bone-related basic science projects as there is no systematic reporting structure for identifying these studies. This is certainly something we could consider working on in the future. It is clear that the portfolio of clinical bone oncology trials is broad. However, while most of the local therapy trials are intergroup initiated and multicentre, the majority of systemic therapy and bone biology trials are small, single centre studies, mainly focused on analysis in breast cancer patients. Fortunately an increasing number of these trials do include prospective specimen collection for future correlative studies.

It is clear however, that if major advances are going to be made in patient management we need more people to get involved in these types of trials and to also ensure that sustained collaborative efforts are being made. The nature of these collaborations can be both national and international but should also occur between diverse research groups and across multiple disciplines. For example, our own centre has an established reputation in performing bone biopsies [41,42] and thus attempts are being made to work more closely with those groups who are experts in the analysis of the bone structure of these specimens.

Recently a multidisciplinary consensus conference was held around understanding bone biology and pathophysiology, prevention of bone metastases and cancer treatment induced bone loss [43]. It is clearly pleasing that the spectrum of basic and clinical research being performed in Canada that we had shown in this current manuscript covers almost all of consensus statements. In addition, Canadian groups are making considerable contributions to many international trials [4,23,24]. It is clear however that if major advances are going to be made in the treatment of patients—especially those with prostate, lung, renal and thyroid cancers that frequently spread to bone, that we need to change our paradigm of research. This clearly requires more discussion and coordinated research efforts.

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