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Research Article

De-escalated administration of bone-targeted agents in patients with breast and prostate cancer—A survey of Canadian oncologists

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ABSTRACT

Objective: Questions remain regarding the optimal use of bone-targeted agents in patients with metastatic bone disease. The purpose of this study was to assess current clinical practice regarding the use and administration of bone-targeted agents by Canadian oncologists in patients with metastatic breast and prostate cancer.
Methods: A survey was designed to explore; bone-targeted agent use in metastatic bone disease, variability in the choice and the frequency of administration of these agents. Opinions were sought on potential outcomes for future trials.
Results: A total of 193 clinicians were contacted and 90 completed our survey (response rate 49% after adjustment for inactivity). Survey respondents were medical oncologists (71.1%), radiation oncologists (21.1%) and urologists (7.8%). The findings suggest that once bone-targeted agents are started they are rarely discontinued. More agents are used in breast cancer than in prostate cancer. There was considerable interest in performing studies of de-escalated therapy in both breast and prostate cancer. Physicians requested (86%) that the primary study endpoint be the occurrence of skeletal related events and not biomarker driven.
Conclusions: Despite clinical practice guidelines and widespread use, significant areas of clinical equipoise with respect to use of bone-targeted agents exist. Findings from this survey suggest that physicians are interested in de-escalated therapy for both breast and prostate patients. However, the use of multiple agents in breast cancer and the desire for skeletal related events to be the primary endpoint means that very large randomized studies will be required.

1. Background

Despite the widespread use of bone-targeted therapies such as bisphosphonates (e.g. zoledronate, pamidronate, clodronate) or receptor activator of nuclear factor kappa-B ligand (RANKL) antibodies (i.e. denosumab) in patients with metastatic bone disease, many questions remain about their optimal use [1,2]. One question in particular pertains to identification of the optimal dosing frequency [3]. Bone-targeted agents are usually given every 3–4 weeks, a dosing interval that is based predominantly on their clinical development as an add-on treatment to standard anti-cancer therapies such as chemotherapy [4], along with data derived from the treatment of hypercalcemia from malignancy [5–7].

This "one size fits all" approach to the dosing intervals [8] is sub-optimal however, as it ignores the long half-life of these agents in bone [9] and the substantial variability in individual patient risk of skeletal related events (SREs) [10]. Given the modest magnitude of absolute benefit of bone-targeted agents on skeletal related event reductions, [2] it is important to investigate whether to not less frequent administration could affect the efficacy of these agents. This would not only result in reduced financial costs to both the patient and to the health care system, but would also likely reduce drug-associated toxicity. The latter is particularly important as toxicity of these agents has been shown to be related to both the potency and the cumulative dose of the bone-targeted agent [11].

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To date, two trials have been presented assessing reduced frequencies of administration of these agents in metastatic breast cancer patients [12,13] and others are still on going [17]. Despite this, the results of the published trials would suggest that there is still a need for larger definitive studies. In addition, we are not aware of any similar studies planned for prostate cancer where again the benefits of bone-targeted agents in reducing SREs are likely even more modest than that seen in breast cancer patients. We are however aware of considerable variability in clinical practice, not only between cancer centers, but also within centers with respect to a number of questions around optimal use of bone-targeted agents, despite various clinical practice guidelines [3].

Before contemplating a trial to formally assess the feasibility of de-escalated bone-targeted treatment in both prostate and breast cancer patients, we wished to conduct a survey of potential collaborating physicians at Canadian hospitals regarding their current clinical practice in these populations and their views on this matter to assist with design of future trials. In particular, we hoped a survey would help establish current standards of care, the extent of clinical equipoise with respect to de-escalation, physician comfort with entering patients on such a trial, and finally, what the most important outcomes and related effect sizes might be for clinicians in order to establish the comparability of these approaches to treatment.

2. Methods

2.1. Questionnaire design

The survey was designed by the authors through three rounds of question development and refinement, and consists of three components. The first component was devised to collect pertinent demographic information of the population of respondents, as well as to determine what proportion amongst them use bone-targeted agents to treat their patients. The second component was designed to collect information from those respondents who prescribe bone-targeted agents with regard to intended benefits from bone-targeted agent use, scenarios in which they prescribe bone-targeted agents, and choice of agent for their patients in order to gain an understanding of current Canadian clinical practice. In the third component, respondents were presented with a series of questions related to the design of a future clinical trial geared toward studying the clinical benefits of de-escalated therapy, with topics of interest including outcome selection and patient inclusion criteria.

2.2. Survey frame and implementation

A member of the authorship team (MC) has held a national annual meeting related to the study of bone in oncology patients since 2005, and participants from past years' meetings were considered an accessible, representative, and appropriate group to approach as a population for this survey [3]. A list of all participants' email addresses was compiled, and these individuals were then sent a link via electronic mail inviting them to participate in the survey. The survey was designed and implemented using the online tool www.FluidSurveys.com. The survey was initiated at the start of July 2012 and remained open until September 1, 2012. Two reminder notices were sent to participants in July and August of 2012. Local research ethics board approval was received before commencing the study. The survey questions used in this study can be found in the online supplement.

2.3. Data analysis

Electronic invites were sent to a total of 193 clinicians, and a total of 90 invitees responded; 11 of the email invites were associated repeatedly with automatic out of office responses, and were thus excluded from the denominator (survey response rate=49.5%). All measures of respondent characteristics including profession, type of center for clinical practice, province, populations treated (breast cancer, prostate cancer, or both), number of new patients and follow up patients seen annually, and use of bone-targeted agents were compiled and reported as proportions of the total number of respondents. For summary statistics calculated in relation to components two and three of the survey as described above, a denominator of 66 respondents was used as physicians not using bone-targeted agents in their practice were not asked to respond to the questions associated with these components. We tabulated proportions of different responses for each question. Where relevant, we stratified findings according to the type of patients treated by the respondents (i.e. breast or prostate cancer; where respondents treated both populations, they were included within both groups). Data were analyzed using Microsoft Excel 2010 (Microsoft Corporation, Seattle, Washington).

3. Results

3.1. Survey component 1: characteristics of the respondent population

Physician demographics from the population of respondents are shown in Table 1. The distribution of characteristics shows that the majority work in teaching hospitals, consistently manage moderate to large numbers of patients, and that 55.6% (50/90) see at least one new patient per month, suggesting the population is an experienced group of oncologists. Approximately two thirds of the respondents were medical oncologists, with the remainder consisting of radiation oncologists and urologists. Physicians were located predominantly in Ontario (60%), Quebec (13.3%) and Alberta (11.1%). Totals of 43, 26 and 18 respondents treated breast cancer, prostate cancer, or both, respectively; 3 respondents failed to indicate their specialty. Amongst the 90 respondents, 73.3% (43/43 treating breast cancer patients, 12/26 treating prostate cancer patients, and 11/18 treating both) indicated that use of bone-targeted agents is a part of their clinical practice, and thus continued on to complete component two of the survey.

3.2. Survey component 2: bone-targeted agent use in Canadian practice

3.2.1. Rationale for bone-targeted agent use

Respondents were first asked to describe the primary reasons they provide bone-targeted agents to their patients, with the ability to select multiple reasons as deemed relevant (see online questionnaire in supplementary data). Fig. 1 provides a quantitative summary of the reasons that were reported. Most respondents primarily provide bone-targeted agents to reduce fracture risk (95.45%), to reduce risk of surgery to bone or radiotherapy (87.88%), to reduce metastasis pain (89.39%), to improve quality of life (72.13%), to reduce hypercalcaemia risk (71.21%), and to reduce risk of spinal compression (68.18%). Few do so based on beliefs that these agents will improve progression-free survival (18.18%) or overall survival (4.55%). Response profiles were generally consistent across sub-populations of those treating breast cancer, prostate cancer, or both diseases (Fig. 1).

To assess the situations in which bone-targeted treatment might be prescribed, respondents were presented a series of five