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Research Article

Incidence, consequences and treatment of bone metastases in breast cancer patients—Experience from a single cancer centre

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ABSTRACT

Background: There is a paucity of literature about the benefits of bone-targeted agents for breast cancer patients with bone metastases treated in the non-trial setting. We explored the incidence, consequences, and treatment of bone metastases at a single cancer centre.
Methods: Electronic records of metastatic breast cancer patients were reviewed and pertinent information was extracted.
Results: Of 264 metastatic breast cancer patients, 195 (73%) developed bone metastases. Of these patients, 176 were eligible for analysis. Median age at bone metastases diagnosis was 56.9 years (IQR 48–67) and initial presentation of bone metastases included asymptomatic radiological findings (58%), bone pain (40%), or a SRE (12.5%). Most patients (88%) received a bone-targeted agent, starting a median of 1.5 months (IQR 0.8–3.30) after bone metastasis diagnosis. 62% of patients had ≥ 1 SRE. The median time from bone metastasis diagnosis to first SRE was 1.8 months (IQR 0.20–8.43 months). Median number of SREs per patient was 1.5 (IQR 0–3). Overall, 26.8% of all SREs were clinically asymptomatic. Within the entire cohort, 51% required opioids and 20% were hospitalized due to either an SRE or bone pain.
Conclusions: Despite extensive use of bone-targeted agents, the incidence of SREs remains high. Nearly half of SREs occur prior to starting a bone-targeted agent. Use of opioids and hospitalizations secondary to bone metastases remain common. More effective treatment options are clearly needed.

1. Introduction

Despite advances in the treatment of early stage breast cancer, bone remains the most common site of distant metastasis [1]. The consequences of bone metastases include reduced survival, morbidity, pain and reduced quality of life [2]. While the care of these patients is multidisciplinary, possibly the most attention in recent decades has been given to the role of bone-targeted agents (BTAs) such as bisphosphonates and denosumab. Clinical trials of BTAs have shown statistically significant reductions in the incidence of, and time to, skeletal related events (SREs) (defined as need for surgery or radiotherapy to bone, pathological fractures, spinal cord compression, hypercalcemia) and reduced bone pain in patients with bone metastases from breast cancer [3–7] (Table 1). As a result of these trials, BTAs have become a standard of care, with treatment starting at the time of bone metastasis diagnosis until evidence of a substantial decrease in performance status [8,9].

With the widespread use of BTAs there is a growing body of data that suggests that their benefits in routine clinical practice are more modest than that observed in randomised trials [10–14] (Table 2). We therefore decided to evaluate the incidence, consequences, and management of bone metastases in an unselected cohort of breast cancer patients at a large Canadian cancer centre. In addition, we assessed less commonly reported clinical outcomes of importance to patients and the health care system, such as the use of opioids and the need for hospitalization due to skeletal complications.

2. Methods

2.1. Data collection

Registry information was available for all patients seen with a diagnosis of breast cancer at The Ottawa Hospital Cancer Center between January 2008 and June 2012. Electronic charts were

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screened manually (IK, PM, TN) to identify eligible patients. Eligibility criteria included: radiologically and/or pathologically confirmed bone metastases, breast cancer as the only diagnosed malignancy, and complete electronic chart data (i.e., radiologic imaging, serum calcium levels, reports of radiation/surgical procedures, and clinic dictations). Data collected included demographic

Table 1
Overview of SREs on BTA in randomised trials.

Reference	Study	Patients with bone disease only (%)	Radiologic screening	Outcomes on BTAs	Overall survival
Hortobagyi [3]	Pamidronate 90 mg IV vs. placebo	62 (pam) 60 (placebo)	Radiographic surveys of the skeleton were performed before entry into the study and after 3, 6, and 12 cycles of treatment	Median time to SRE—13 months Proportion of SREs—46%	14.8 vs. 14.2 months, no difference
Theriault [4]	Pamidronate 90 mg IV vs. placebo	66 (pam) 72 (placebo)	Radiologic bone survey within 1 month before entry and then at cycle 3, 6, 12, 18, 24 or at last visit if came off prematurely	Delay in 1st SRE-10.4 months SRE rate—56%	23.2 vs. 23.5 months, $p=0.685$
Conte [26]	Pamidronate 45 mg IV vs. control	55 (overall)	Bone survey on study entry , then at 3 and 6 month	Delay in 1st SRE—13.1 months	pam-592 control—642 days, no difference
Hultborn [33]	Pamidronate 60 mg vs. control	54 (pam) 57 (placebo	Bone scan and directed X-ray at study entry, then every 6 months	SRE-free survival 11.8 months	n/a
Body [6]	Ibandronate 2 mg or 6 mg vs. placebo	66 (6 mg) 69 (2 mg) 67 (placebo)	Not specified	SMR-1.19 for 6 mg median time to 1st SRE 50 weeks	8 patients died in IBA, 15 in placebo
Kohno [5]	Zoledronic acid 4 mg IV vs. placebo	Not specified	Radiologic bone survey on study entry, then at 3, 6, 9, 13 months, bone scan on study entry and at 6 and 13 months	Proportion of patients with SREs—30% SRE rate ratio at 1 year—0.61Time to 1st SRE not reached	n/a
Rosen [21]	Zoledronic acid 4 mg IV vs. pamidronate 90 mg IV	Not specified	Radiologic bone survey on study entry, then at 3, 6, 9, 13 months, bone scan on study entry and at 6 and 13 months	Time to 1st SRE Zoledronic acid—356 days Pam—376 days SMR Zoledronic acid—1.04 Pam—1.39	More than 2 years, no difference between arms
Stopek [28]	Zoledronic acid 4 mg IV vs. denosumab 120 mg SC	Not specified	Skeletal surveys or any of radiological assessment (X-ray, CT , MRI) every 12 weeks	Time to 1st SRE Zoledronic acid—26.4 months Denosumab-not reached SMR Zoledronic acid—0.58 Denosumab—0.45	No difference between treatment groups

Table 2
Overview of retrospective data of SREs on bone-targeted agents.

Reference	Study	*N*	Proportion of patients with only bone disease (%)	Frequency of radiologic assessment	Outcomes	Overall survival
Trinkaus [11]	Retrospective study SREs on pamidronate	87	35	N/a	Time to 1st on pamidronate SRE—267 days Proportion of patients with SRE—38%	N/a
Liauw [14]	Retrospective study SREs on IV bisphosphonates	110	58	N/a	Time to 1st SRE—365 days Proportion of patients with SREs—30%	818 Days from start of bisphosphonates
Murphy [34]	Retrospective study SREs on IV bisphosphonates	62	N/a	N/a	Proportion of patients with SREs—zoledronic acid—75% Pam—62%	N/a
Young [12]	Retrospective study SREs on zoledronic acid	11	7.2 at diagnosis	N/a	Proportion of patients with SREs—42.3%	1.9–1.6 years, median 1.5 years
Crawford [35]	Retrospective study SREs on IV bisphosphonates	181			Proportion of patients with SREs—30%	
Ding [13]	Retrospective study SREs on bisphosphonates 181 patients		37	N/a	Proportion of patients with SREs—34.8%	Median 64 months (range 57–70)
Current study	Retrospective study Patients diagnosed with bone metastases	177	20.4	Q 3–5 months in 54% of patients	Time to 1st SRE on BTA—8.3 months Proportion of patients with SRE on BTA—48%	Median 40.0 months (IQR 22.3–93.3 months)