DO PHYSICIANS FOLLOW SYSTEMIC TREATMENT AND FUNDING POLICY GUIDELINES? A REVIEW OF BISPHOSPHONATE USE IN PATIENTS WITH BONE METASTASES FROM BREAST CANCER

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ABSTRACT

Background
The use of bisphosphonates for the prevention of skeletal related events in women with bone metastases from breast cancer is well established. We undertook an evaluation of bisphosphonate use in clinical practice in three Canadian cancer centres. In addition we assessed whether or not physicians at these centres are following their local treatment guidelines and funding policies.

Methods
Charts and electronic files of patients who had received either clodronate or pamidronate at any time between January 2000 and December 2001 at three Canadian cancer centres were retrospectively reviewed.

Results
There has been a marked improvement in the time between the diagnosis of bone metastases and the commencement of bisphosphonates from a median of 155 days in 1998 to 24 days in 2001. However, despite a local funding policy requiring that oral clodronate be the first bisphosphonate used, this was the case in only 67% of patients. In addition, despite one centre's guidelines recommending that bisphosphonates be stopped once the patient was progressing, 90% of their patients remained on bisphosphonates until they died.

Conclusions
A considerable amount of effort is spent on the creation of "evidence based" treatment guidelines. Funding agencies develop policies based on these treatment guidelines, but often funding is more restrictive than the treatment guideline would suggest. It is clear from this review that physicians still appear to manage a substantial proportion of patients outside of funding policies, but within evidence based recommendations. Therefore, a need exists for either the creation of guidelines and policies that physicians will follow or the implementation of methods to ensure that restrictive policies are actually followed.

Key words: *Bisphosphonates, guidelines, drug use evaluation, breast cancer*

The majority of women with metastatic breast cancer will either present with or subsequently develop bone metastases.[1, 2] The development of bone metastases has significant consequences for patients in terms of both morbidity and mortality.

With respect to morbidity, two-thirds of patients with bone metastases will subsequently develop a complication, including non-vertebral and vertebral pathological fractures, hypercalcemia of malignancy and spinal cord compression.[3, 4] Many of these patients will require medical, radiation and surgical interventions to manage or prevent further bone metastasis-related complications.

With respect to prognosis, women with bone-only or dominant disease typically have a median survival of 2-3 years. However, patients with bone related complications, such as pathological fractures, spinal cord compression or hypercalcemia of malignancy have a shorter median survival of 12, 4 and 3 months, respectively.[5, 6]

Bisphosphonates are potent inhibitors of bone resorption. The results of randomized controlled trials comparing a bisphosphonate with either placebo or no treatment in secondary prophylaxis (i.e. in patients with breast cancer and established bone metastases) [4,7-19] have shown that once bone metastases are present, the use of bisphosphonates in addition to first-line chemotherapy or hormonal therapy can significantly reduce skeletal related events (SREs).[12-14, 19]

As a result of these studies, the use of bisphosphonates in patients with bone metastases has increased dramatically. In the province of Ontario alone, 20% of the $50 million Cancer Care Ontario (CCO) New Drug Fund budget was spent on pamidronate in 2001.

Bisphosphonate use has also increased because of their inclusion in many systemic treatment guidelines. International, provincial and local practice guidelines (Table 1) state that bisphosphonate therapy should be initiated at the time of diagnosis of bone metastases. However, differences between guidelines exist not only for which bisphosphonate should be used but also whether or not they should be stopped after further bone progression while on bisphosphonate therapy.[20-23]

These differences between guidelines are important as they lead to inconsistencies in clinical practice. They also have cost implications, as these agents are expensive, not only in terms of drug cost, but also in terms of nursing and patient time.

Therefore, following on from previous work in this area,[24] we evaluated how bisphosphonates are being used in actual clinical practice in three cancer centres in Ontario, Canada. We also assessed whether or not physicians are following their local treatment guidelines and funding policies. The questions we proposed to address in this study were:

1. What is the current standard clinical practice of physicians with respect to the use of bisphosphonates in women with metastatic breast cancer?
2. Is this practice consistent with their local treatment guidelines and funding policies?
3. What proportion of patients on a bisphosphonate for bone metastases from breast cancer continue on a bisphosphonate despite progression either in their bones or at any other disease site?

METHODS

Data collection

This review was performed at two large cancer centres in Toronto (centres 1 and 2), and a smaller community cancer centre outside of Toronto (centre 3). The protocol was approved by the ethics committees of each participating centre.

Patient charts, progress notes, diagnostic imaging, laboratory reports and computerized records were used to retrospectively assess all breast cancer patients receiving pamidronate or clodronate at any time from January 2000 to December 2001. These dates were chosen to allow sufficient time for both short and long-term tumor related complications to occur.

TABLE 1 International (ASCO), provincial (CCO) and local (UHN) Guidelines for commencement and stopping of bisphosphonates for metastatic breast cancer.

GUIDELINE/ Jurisdiction	ASCO	Cancer Care Ontario/ Ontario, Canada	University Health Network/Toronto, Canada
Recommended BP for prevention of skeletal complications	IV pamidronate	Oral Clodronate or IV Pamidronate	Oral Clodronate, (IV Pamidronate on progression or ADR)
Initiation	Diagnosis of bone metastases	Diagnosis of bone metastases	Diagnosis of bone metastases
Discontinuation	Continue BP until evidence of substantial decline in a patient's general performance status	None *"There is insufficient evidence to recommend continuation of pamidronate after bone progression while on pamidronate"*	Progression of bony disease
Prophylactic use in patients without bone metastases	None	Not recommended *Insufficient evidence*	None
Funding restrictions	N/A	Oral Clodronate (IV Pamidronate only funded if ADR)	Oral Clodronate (IV Pamidronate only funded if ADR)

BP = bisphosphonate, ADR = Adverse drug reaction

The data collected included: patient demographics, current and previous chemotherapy or hormonal treatments and reasons for discontinuation or switch of bisphosphonate treatment.

Clinical outcomes were identified and quantified including all skeletal related events (SREs) occurring between the time the bisphosphonate was initiated and the end of the study period. SREs were defined as pathological bone fracture, spinal cord compression, radiological bone metastases progression, tumour induced hypercalcemia, surgery to bone and radiation to bone.[14, 24] Pharmacy records were used to confirm the type and dose of bisphosphonate prescribed as well as the duration of use. Data was collected using a standardized data collection form.

Inclusion Criteria

Women with metastatic breast cancer were eligible for this study if they had received either oral or intravenous clodronate or intravenous pamidronate for the secondary prophylaxis of complications due to bone metastases between January 2000 December 2001.

Exclusion Criteria

Patients were excluded from this analysis if they were documented as receiving other bisphosphonates for the management of osteoporosis. Other exclusion criteria included

the presence of other malignancies and patients who received intermittent doses of bisphosphonates for the treatment of tumor induced hypercalcemia.

Sample Size and Statistical Considerations

Pharmacy records were used to identify all patients who received intravenous bisphosphonates at each of the three centers. Two centers also had centralized records of those patients receiving oral clodronate (centres 1 and 3). At centre 2 there was no central record keeping and so we were unable to collect information about oral clodronate prescriptions. For each of the participating centers, lists of all eligible patients were created.

All eligible patients from centers 1 and 3 were included in the study because the total sample size from each center was relatively small. From center 2, a sample of 52 patients was selected using a random numbers table.

With a final sample size of 190, the proportion of patients remaining on pamidronate despite bone progression was measured with a precision that extends to ± 7, with a 95% probability. All clinical and drug utilization data were presented as descriptive statistics as means, medians, or proportions. Parametric and non-parametric inferential statistics were used in an exploratory analysis to compare bisphosphonate prescribing patterns between centers.

RESULTS

Patient Demographics

Two hundred and twenty-two charts were reviewed, of which 190 were for women with bone metastases secondary to breast cancer and who had received treatment with a bisphosphonate for the prevention of skeletal events during the study period.

The mean age of the patients at the time of breast cancer diagnosis was 52.1 years (range: 26-86) and 48%, 47% and 3.7% were pre-, post- or perimenopausal at that time (Table 2). At the time of this analysis 88 (44%), 84 (44%) and 21 (11%) patients were alive, dead or lost to follow up, respectively.

TABLE 2 Patient demographic and clinical characteristics.

Characteristics (range)	N=190
Mean age in years	52.1 (26-86)
Treatment Centre	
Centre 1	58.3%
Centre 2	24.1%
Centre 3	17.6%
Menopausal status	
Peri-	3.8%
Pre-	48.4%
Post-	47.8%
ER Status	
Positive	73.4%
Negative	17.6%
Unknown	9.0%
HER-2 Status	
Positive	16.4%
Negative	34.9%
Unknown	48.7%

Number of Positive Nodes at Diagnosis	
0	32.8%
1-3	41.8%
≥4	25.4%
Unknown	15.9%
Tumor Size (cm)	
<1 cm	16.4%
1-3 cm	61.1%
≥4 cm	21.7%
Unknown	16.4%
Tumor Histology	
Ductal	77.8%
Lobular	9.5%
Other	6.3%
Unknown	6.3%
B-R Grade of Tumor	
I	3.7%
II	32.3%
III	28.0%
Unknown	36.0%
Anticancer Therapy at the Start of BPs[1]	
None	0.5%
Chemotherapy	32.3%
Hormonal therapy	64.1%
Both chemo and hormonal therapy	2.1%
Trastuzumab (Herceptin®)	1.5%
Median Time to Metastatic Disease [months]	39 (0-194)
Median Time to Metastatic Bone Disease [months]	44 (0-194)

[1]Bisphosphonate (BP) utilized for the prevention of skeletal related events.

TABLE 3 Median time from diagnosis of bone metastases to start of bisphosphonate therapy (days) for patients diagnosed after 1998.

Year	No. patients	Total days	Centre 1	Centre 2	Centre 3
1998	28	155	137 (n=20)	56 (n=5)	591 (n=3)
1999	30	32	29 (n=17)	34 (n=10)	181(n=3)
2000	39	38	46(n=22)	8.5(n=7)	78 (n=10)
2001	38	24	21 (n=24)	52.5 (n=4)	59 (n=11)
Total	**136**		**81**	**26**	**27**

Current clinical practice of physicians with respect to the use of bisphosphonates in women with metastatic breast cancer

Of the 190 patients, 136 were diagnosed with bone metastases after January 1, 1998, which was the effective date of the local bisphosphonate guidelines. The median time from diagnosis to commencement of bisphosphonates steadily declined in all centres from a median of 155 (range 0-1179) days in 1998 to 24 (range, 0-238) days in 2001 (Table 3). There was no significant difference overall between centres with respect to the time taken to commence bisphosphonates.

In 7.3% (14/190) of patients, there was no evidence of bone metastases at the time of starting bisphosphonates. Comments in these patients' charts suggest that this was done either for the treatment of osteoporosis or for the primary prevention of bone metastases.

TABLE 4 Patient clinical characteristics following the diagnosis of bony disease.

Characteristics (range)	N=190
Median Time to BP initiation[1] [days]	89
Mean Time to BP initiation[1] [days]	381 (range 0-4236)
First BP prescribed	
PO clodronate	67.0%
Pamidronate	28.7%
IV clodronate	4.7%
Other	0.7%
Type of BP received at any time	
IV Pamidronate	74%
PO Clodronate	66.8%
IV Clodronate	16.4%
Received IV Pamidronate for prevention at some point	72.6%
Received both PO Clodronate and IV Pamidronate	42%
Received PO Clodronate before IV Pamidronate[2]	97.5%
Developed an SRE[3]	71.6%
Mean number of SREs	2.2 (0-13)
Median time to first SRE [days]	89 (0-4236)
Types of SRE	
Pathological fracture	18.1%
Spinal cord compression	2.8%
Progression	40.6%
TIH	1.2%
Surgery	2.0%
XRT	35.3%
Continued BP Despite SRE	90.3%

Non-Skeletal Related Events	
Developed a Non-SRE	58.4%
Mean Number of Non-SRE's	1.2 (0-9)
Continued BP Despite non-SRE	90.0%
Median Duration of initial BP therapy [months]	12.5 (0 – 59)
Reason for discontinuing BP	
Adverse drug reaction	17.9 %
Progression of bone disease	10.2%
Death	18.5%
Not stated	24%
Ongoing, not discontinued as time of analysis	21 %
Other	7.5 %
Patient Status at time of Analysis	
Alive	44.4%
Dead	44.4%
Lost to follow up	11.1%

[1]From the diagnosis of metastatic bone disease. The BP was for the prevention of skeletal events.
[2]As stated in the Cancer Care Ontario New Drug Fund policy.
[3]SRE = Skeletal Related Events, defined as bone fracture, spinal cord compression, bone metastases progression, tumour induced hypercalcemia, surgery to bone, radiation to bone.

TABLE 5 Patient clinical characteristics following the diagnosis of metastatic bone disease by center.

Variable	Centre 1 (N-112)	Centre 2 (N=45)	Centre 3 (N=33)	P-Value
Mean DFI (all sites) mo. (Range)	55.8 (0-280)	55.0(0-189)	47.7 (0-120)	NS
Mean DFI (bone) mo. (Range)	60.3 (0-314)	56.2(0-189)	48.7 (0-156)	NS
Mean Time to BP initiation[1] [days]	359	464	379	NS
Received PO Clodronate as first therapy	96/112 (86%)	13/45(29%)	18/33 (54%)	<0.001
Received pamidronate as first therapy	13/112(12%)	25/45(56%)	15/33(46%)	<0.001
Received IV Clodronate as first therapy	3/112 (3%)	6/45 (13%)	0/33 (0%)	<0.001
Received PO clodronate for prevention at some point	86%	31%	55%	<0.001
Received IV Pamidronate for prevention at some point	63%	97.8%	81.2%	<0.001
Received IV clodronate for prevention at some point	24%	20%	0%	0.019
Median Time to first SRE (days)	182	225	185	NS
Developed an SRE[2]	79.8%	71.1%	51.5%	0.006

Mean number of SREs	2.8	1.9	0.91	0.003
Continued BP Despite SRE	90.7%	90.3%	88.2%	NS
Developed a non-SRE[3]	63.3%	68.1%	30.3%	0.004
Continued BP Despite non-SRE	88.7%	96.7%	80.0%	NS
Duration of first BP therapy [months]	14.1	9.8	11.8	NS

[1]From the diagnosis metastatic bone disease. The BP was for the prevention of skeletal events.
[2]SRE = Skeletal Related Event and defined as, bone fracture, spinal cord compression, bone metastases progression, tumour induced hypercalcemia, Surgery to bone, radiation to bone.
[3]Non-SRE = Metastatic spread outside of bone
NS = not statistically significant.

According to the provincial funding policy, all patients should be started on oral clodronate and indeed 67% (127/190) of patients were so treated (Table 4). There were however, marked differences between cancer centres (Table 5). At centre 1, 86% and 12% of patients were started on oral clodronate and IV pamidronate respectively.

In contrast, at centre 2, 29% and 56% were initiated on oral clodronate and IV pamidronate respectively ($p<0.001$). Seventy-four percent of all patients eventually received pamidronate at some point during their illness. Unfortunately, the reasons for discontinuation or change of a bisphosphonate were rarely stated in patients' charts (Table 4).

Proportion of patients on bisphosphonates continuing treatment despite SREs or progression at other disease sites

In this study 136 patients (71.6%) had a SRE while on a bisphosphonate (Tables 4 & 5). The mean number of SREs for all 190 patients was 2.2 (range 0-13). The most common SREs were progressive bone disease and radiotherapy to bone. The median time from initiation of a bisphosphonate to a SRE was 89 days (mean = 381, range = 0-4236). Of the patients who had an SRE, 90.3% (123/136) were continued on their bisphosphonate treatment despite the occurrence of a skeletal event.

Only the remaining 9.7% had a change in treatment (either discontinuation or switching) within 1 month of the SRE and of these patients, 3 of 13 were switched to another bisphosphonate at the time of the first SRE.

Of the original 190 patients, 111 (58.4%) had at least one episode of progressive disease at a non-bony site while on bisphosphonate therapy (Table 4). Of these patients, 90.0% (100/111) continued on bisphosphonate therapy following the progression, and 10% (11/111) had a change in bisphosphonate therapy. There were 136 non-SRE events within 1 month of the progressive disease. The mean number of non-SRE events while on bisphosphonates was 1.2 (range, 0-9). In total, the median number of events (including both SRE's and non-SRE events) was 3 (range 0-15).

DISCUSSION

The use of bisphosphonates in the management of bone metastases from breast cancer is well established. There are, however, differences in systemic treatment guidelines regarding not only which bisphosphonates should be used initially, but also whether or not bisphosphonates should be continued after disease progression. These differences have important consequences first in terms of inconsistencies in patient care between physicians and second in terms of cost as these agents are expensive.

With respect to the budget impact of these agents, $8 million of the $50 million Cancer Care Ontario New Drug Fund Program was spent on pamidronate alone in 2001. Since pamidronate is infused over at

least 2 hours in the ambulatory care clinic, there are additional costs such as nursing time, infusion apparatus and monthly hospital visits.

The differences between guidelines and the significant financial impact are important in view of Cancer Care Ontario's mandate for improved quality of care and evidence based practice. This study presented an opportunity to gain practical information about how these high cost agents are being used.

The purpose of this retrospective review was to establish current clinical practice at two tertiary Canadian cancer centres and one community centre and to determine if the local and international treatment and funding guidelines were being followed. Since the establishment of local bisphosphonate treatment guidelines in 1998, there has been a marked improvement in the time to initiate a bisphosphonate after the diagnosis of bone metastases. While this suggests that the guidelines are being followed the provincial treatment funding policy recommends that oral clodronate be used first (Table 1).

It is clear, however, that a large number of patients are being started on pamidronate (28.7% of all patients) and that this was particularly so at one centre (56% at centre 2) In addition, many physicians start patients on oral clodronate and appear to switch to pamidronate on progression, but there was a large difference between centres.

In all instances, the opinion of the treating physician was that the bone metastatic disease process had not been arrested by the bisphosphonate in question (i.e., either oral or intravenous clodronate) and pamidronate therapy was initiated in these patients. Thus, the results of this study would suggest that 74% of women with bone metastases from breast cancer would receive pamidronate at some stage of their illness. However, no scientific evidence exists to support the practice of using pamidronate as second line therapy as a result of bone disease progression while already on a bisphosphonate.

Although intravenous clodronate has been demonstrated in short-term studies to relieve bone pain, it has not been evaluated to determine its efficacy in reducing fractures, the requirement for radiation therapy or the optimal frequency of administration. Therefore, intravenous clodronate was not recommended by any of the guidelines. In spite of this, 16% of patients received intravenous clodronate as first line therapy for the prevention of SREs (Table 4).

As this was a retrospective review, evaluation of prescribing patterns relied upon the presence of filed copies of outpatient prescriptions and progress notes in patient charts. This approach for tracking prescriptions is limited to the extent of accuracy of recording in the medical charts. It was not feasible to obtain refill records as a proxy for tracking adherence, since patients filled their outpatient prescriptions at different pharmacies and they relied on a variety of sources for drug funding, including self-coverage. Patients who received oral clondronate might not be fully represented due to differences in where patients obtained their prescriptions.

Accepting these caveats, what can be extracted from this study? First, a considerable amount of effort is spent on the creation of "evidence based" treatment guidelines. Funding agencies develop policies based on these treatment guidelines, but often funding is more restrictive than the treatment guideline would suggest. It is clear from this review that physicians still appear to manage a substantial proportion of patients outside of funding policies, but within evidence based recommendations. Therefore, a need exists for the creation of guidelines and policies that the majority of physicians will follow or the implementation of methods to ensure that these policies are actually followed.

Second, the choice of guideline that healthcare providers follow will have different budgetary implications.[23, 25, 26] There may be more effective ways of controlling the rapidly rising cost of bisphosphonate therapy. One would be to limit bisphosphonate use to those patients who are most likely to benefit from them i.e. patients with predominantly bone disease and to delay or avoid the initiation of bisphosphonates in patients with a particularly poor prognosis i.e. those with predominantly visceral metastases.[5, 27] Indeed, both of the

large pamidronate studies had as eligibility criteria a prognosis of at least 6 months survival.[4,12-14] In addition, a large majority of patients had bone-only metastases (61% in the Hortobagyi studies[12,13] and 70% in the Theriault study[4] with a median survival of approximately 18 months in the Lipton et al. combined analysis[14]). The overall 13% absolute reduction in SREs reported in these trials was therefore achieved in a population with a relatively favourable prognosis. Thus, treating patients with a poor prognosis will be even less cost effective.

The question as to whether or not bisphosphonates should be continued after progression of bone metastases is important.[28] Bone progression was included in this study as an SRE[24] even though it is not considered an SRE in the randomized bisphosphonate trials.

It is clear from the data reported here that the vast majority of patients (90%) continue on bisphosphonates until death despite bone progression. Even though this is consistent with provincial guidelines, it is important to realize that despite the use of bisphosphonates, most patients with bone metastases will eventually progress in their bones. The lack of data supporting the efficacy of bisphosphonates after progression suggests that the majority of patients receiving these agents are the group for which there is no proven benefit.

Despite citing the level of evidence as "Insufficient data. N/A", the ASCO guidelines for the continuation of pamidronate after progression suggest that intravenous bisphosphonates be continued until evidence of substantial decline in a patient's general performance status.[23]

In summary, the use of bisphosphonates for bone metastases has led to a major improvement in the management of women with metastatic breast cancer. However, a real need exists for randomized trials looking at the continued use of bisphosphonates following skeletal events while on a bisphosphonate and also their role in the management of patients with poor prognosis disease. These studies could also incorporate quality of life measures, patient preference, treatment compliance and possibly correlation with bone markers to determine if the benefit is confined to subgroups with a marker response or at least no early increase. One possible trial could include patients progressing while on a bisphosphonate, randomized to either placebo, continuation of the same bisphosphonate or to another bisphosphonate.

Such a study would provide important evidence for the cost effective use of these agents. However, given the lack of commercial incentive associated with such a trial, funding would have to come from public sources.

Until these studies are done, there will continue to be major differences between treatment, funding guidelines and the clinical management of these patients.

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