Original article

Which bisphosphonates do oncologists prescribe for women with metastatic breast cancer and why? Results of a UK survey

Lesley Fallowfield a,*, Valerie Jenkins a, Robert Coleman b

a CRUK Psychosocial Oncology Group, Brighton & Sussex Medical School, Brighton, East Sussex, UK
b Academic Unit of Clinical Oncology, Weston Park Hospital, Sheffield, UK

Received 31 October 2007; received in revised form 8 January 2008; accepted 20 February 2008

Abstract

In breast cancer, many bisphosphonates are approved for use in metastatic bone disease which significantly delay and reduce the risk and rate of skeletal complications. There is a paucity of evidence about the relative efficacy of different drugs, routes of administration or optimal doses. Oral and IV administration have various advantages and disadvantages. A total of 112/144 (78%) UK oncologists completed a postal survey about their bisphosphonate prescribing practices and reasons for them. Fifty three percent gave both oral and IV drugs, 40% only IV and 7% only oral. In the absence of scientific evidence, financial constraints often dictated choice and route of administration or local guidelines which were extremely varied. The primary advantages perceived for oral drugs were patient convenience (48%) and for IV to ensure compliance or bioavailability (37%). Adherence to oral bisphosphonates is often poor, but 44% oncologists expected good adherence in >71% patients. More clinical trial data are needed to inform practice.

© 2008 Elsevier Ltd. All rights reserved.

Keywords: Bisphosphonates; Metastatic bone disease; Adherence; Oncologists’ prescribing preferences

Introduction

At any one time in the UK there are approximately 20,000 women with bone metastases from breast cancer. Median survival for women with breast cancer following this diagnosis is approximately 2 years. Bone involvement leads to uncoupling of the bone remodelling process, typically associated with accelerated bone resorption and considerable skeletal morbidity. Appropriate multi-disciplinary management of bone metastases is vital to ensure the maintenance of a good quality of life. Treatment with bisphosphonates, which are effective inhibitors of bone resorption, reduce the number and rate of skeletal complications. Some of these skeletal related events (SREs) such as fractures and cord compression may at worst be life-threatening whilst others contribute to considerable pain and immobility, compromising quality of life.1

A recent Cochrane systematic review of bisphosphonates found that their use in women with advanced breast cancer and clinically evident bone metastases significantly reduced not only the risk and rate of SREs but also increased the time to developing an event.2 Some bisphosphonates reduced bone pain and improved overall quality of life. Direct evidence as to when to start treatment and the optimum duration of treatment remain uncertain,3 but clinical guidelines4 recommend that bisphosphonates are started once radiological confirmation of bone metastases is obtained and continued for at least 2 years or until treatment is deemed clinically inappropriate.

Although bisphosphonates are a standard part of the clinical management of breast cancer patients with bone metastases, there are variations in the specific drugs used and in the route of administration. Both oral and intravenous (IV) bisphosphonates have been approved for use in advanced breast cancer
within Europe, but the route of administration may affect efficacy, is associated with different side effect profiles, and has convenience and cost implications for hospitals and for patients. One underestimated problem of oral administration of any therapy is the potential for poor patient adherence. Lack of adherence in the context of the long-term therapy needed with bisphosphonates, may severely compromise any putative benefits. In non-cancer settings the average adherence rates for patients in clinical trials receiving chronic therapy are between 43 and 78%, and the ability of clinicians to recognise non-adherence is poor.5 Also a recent systematic review showed sub optimal persistence and compliance with oral bisphosphonates for osteoporosis in patients on both daily and non-adherence is poor.5 There are no comprehensive studies of adherence of any therapy is the potential for poor patient adherence. Lack of adherence in the context of the long-term therapy needed with bisphosphonates, may severely compromise any putative benefits. In non-cancer settings the average adherence rates for patients in clinical trials receiving chronic therapy are between 43 and 78%, and the ability of clinicians to recognise non-adherence is poor.5 Also a recent systematic review showed sub optimal persistence and compliance with oral bisphosphonates for osteoporosis in patients on both daily and weekly therapy.6 There are no comprehensive studies of adherence to the different bisphosphonate regimens available to women with metastatic bone disease but there is little reason to suppose that cancer patients would be any more adherent to oral bisphosphonate therapy than non-cancer patients. We know from other studies that a surprising number of patients with advanced breast cancer do not take their oral hormonal therapy as prescribed especially if they experience side effects.7,8 In the absence of clear evidence from randomised trials to guide management, clinicians may be compelled by financial constraints imposed on them, or chose to offer patients a wide variety of drugs, dosing schedules and routes of administration.

In this study medical and clinical oncologists in the UK were surveyed to identify their prescribing practices, perceptions of adherence and factors influencing their treatment recommendations to patients with metastatic breast cancer.

Materials and methods

Respondents & procedure

A database of clinical and medical oncologists in the UK treating women with metastatic breast cancer was compiled from Internet searches and the membership lists of academic breast cancer groups. This database was not exhaustive, but comprised a wide geographical spread of oncologists working in UK cancer centres. The clinicians were sent a covering letter explaining the purpose of the survey together with a questionnaire probing their bisphosphonate prescribing practices and reasons for them. Clinicians were asked to complete the questionnaire anonymously and return it in a pre-paid envelope.

Questionnaire

A short study specific questionnaire was designed to elicit the factors that might influence different prescribing practices with bisphosphonates in metastatic breast cancer (see Appendix A). Clinicians indicated their speciality and the numbers of breast cancer patients with bone metastases they treated annually. They were asked to identify from a list, the bisphosphonates they prescribed most frequently, the routes of administration for these and the primary reasons for their prescribing choices.

Further questions probed the clinicians’ perceptions of the primary advantages, disadvantages and side effects associated with both oral and IV bisphosphonates. Finally they estimated the percentages of patients they expected to adhere to the different therapy regimens.

The study had full ethical approval (Ref no: 07/Q1907/08).

Two coders checked all responses to the questions in the survey. Data were analysed using SPSS v.11.5.

Results

Respondents

One hundred and forty four clinicians identified as likely to be treating women with metastatic breast cancer were invited to join the survey. Questionnaires were completed and returned by 112 of these (response rate of 78%). The sample comprised 38 (34%) medical and 74 (66%) clinical oncologists. The number of breast cancer patients with bone metastases they treated annually is shown in Table 1. Seventy-nine (70%) oncologists stated they had been involved in bisphosphonate clinical trials such as AZURE (neoadjuvant chemotherapy and/or neoadjuvant hormone therapy ± zoledronic acid in high risk breast cancer), ZICE (IV zolendronic acid versus oral ibandronate in MBC) & BISMARK (standard, 3–4 weekly IV zoledronic acid versus bone-marker directed dosing in MBC).

The majority of oncologists 77/105 (73%) said that they offered patients a choice of different bisphosphonate treatments.

Prescribing practices

Eight oncologists (7%) only prescribed oral bisphosphonates, 45 (40%) only IV and 59 (53%) gave both. The primary reason for prescribing oral drugs was that ‘health authority/primary healthcare trust will only pay for this’. Some had no personal choice in the matter as “Guidelines exist in our Network as to who starts with IV or oral” or “I can’t get IV preparations onto the formulary”.  

Oral bisphosphonates

Table 2 shows the numbers of oncologists who prescribe oral drugs. Of the 67/112 (60%) oncologists who ever gave oral bisphosphonates to their patients, the drug most frequently prescribed was ibandronic acid, 44 (66%), followed

<table>
<thead>
<tr>
<th>Patients</th>
<th>Oncologists</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>11–50</td>
<td>66</td>
<td>64</td>
</tr>
<tr>
<td>51–100</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>&gt;101</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>No response</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

Table 1
N of breast cancer patients with bone metastases treated annually
by clodronate, 17 (25%). Six (9%) oncologists gave both drugs. None of the oncologists surveyed prescribed risedronate or alendronate, the other oral bisphosphonates available in the UK although only approved for benign bone diseases. There were restrictions as to which oral drug could be given.

“trying to move to more ibandronate in community but resistance from GPs who won’t prescribe”

“submissions for use of oral ibandronate (my preferred option) turned down by PCT commissioning groups”

“another example of treatments being driven by fiscal rather than medical considerations + PCT will not fund ibandronate which is better tolerated than sodium clodronate”

### Intravenous bisphosphonate prescribing practices

Table 3 shows that 104 (93%) oncologists give IV bisphosphonates. Zoledronic acid was the most frequently prescribed with 58 (56%) of clinicians reporting it as the only IV preparation they prescribed. Twenty-four (23%) oncologists reported prescribing disodium pamidronate. A further 22 (21%) prescribed both zoledronic acid along with either disodium pamidronate and/or ibandronic acid. Again there were inconsistencies across different health authorities as to which drugs could be prescribed.

The primary reasons influencing prescribing practices given by the 45 oncologists who only ever gave IV bisphosphonates are shown in Table 4. For those prescribing pamidronate, 9/13 (69%) said it was the only one that their health authority would pay for.

The primary reason given by 12/26 clinicians (46%) who only prescribed zoledronic acid was that it was the drug best supported by the data. For others it was the only drug they were permitted to prescribe.

“Zoledronic acid is only one on approved pharmacy list”

### Expected worst side effects of bisphosphonate therapy

The worst side effects associated with oral and IV treatments are shown in Table 5. One hundred and three oncologists generated 120 side effects for oral treatments, which were grouped into 5 main categories. The most frequently generated problem cited was gastrointestinal effects (92%). Only two doctors felt that side effects were minimal and nine did not comment.

The 133 worst side effects that clinicians felt were associated with IV therapy were also grouped into 7 primary categories. The most frequently cited were acute phase flu-like reactions 54/133 (41%) and osteonecrosis of the jaw 32/133 (24%).

### Primary advantages of different bisphosphonates

Table 6 shows the primary advantages perceived by oncologists for oral and IV bisphosphonates. One hundred and five oncologists provided 169 advantages for oral drugs. These
Table 6
Perceived primary advantages of oral and i.v. bisphosphonates

<table>
<thead>
<tr>
<th>Oral advantages (n = 169)</th>
<th>N (%)</th>
<th>i.v. advantages (n = 207)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convenience for pts</td>
<td>81 (48)</td>
<td>Ensures compliance/ bioavailability</td>
<td>76 (37)</td>
</tr>
<tr>
<td>No need for i.v. access</td>
<td>39 (23)</td>
<td>Prevention of GI complaints</td>
<td>45 (22)</td>
</tr>
<tr>
<td>Cheaper/fewer resources</td>
<td>29 (17)</td>
<td>Efficacy</td>
<td>30 (15)</td>
</tr>
<tr>
<td>Efficacy</td>
<td>7 (4)</td>
<td>Convenience for hospital</td>
<td>29 (14)</td>
</tr>
<tr>
<td>Fewer side effects</td>
<td>6 (4)</td>
<td>Convenience for pts</td>
<td>19 (9)</td>
</tr>
<tr>
<td>Miscellaneous other</td>
<td>7 (4)</td>
<td>Miscellaneous other</td>
<td>8 (4)</td>
</tr>
</tbody>
</table>

were grouped into 6 categories; the most frequently cited being general convenience for the patients (48%) and no need for IV access (23%). One hundred and eight oncologists generated 207 advantages for IV bisphosphonates, which were grouped into 7 categories, the most frequently cited being to ensure adherence/compliance (37%) and the prevention of GI complaints (22%).

Adherence to oral bisphosphonate therapy

The distribution of the proportion of patients clinicians’ expected to adhere to oral bisphosphonates is displayed in Fig. 1. Anticipated adherence varied however, 99/110 (90%) oncologists expected more than 40% of patients to adhere to their treatment regimen. More than a third of oncologists thought adherence to be more than 71%.

Adherence to intravenously administered preparations

Clinicians were asked to indicate the percentage of patients they thought failed to return for further doses of IV bisphosphonates. The vast majority (99/109, 91%) of oncologists expected fewer than 25% of patients would fail to return for further IV infusions of bisphosphonates.

Discussion

In the absence of definitive clinical trial data to support evidence-based practice, oncologists have adopted a pragmatic approach offering predominantly IV bisphosphonates where possible and if permitted to do so by their health authority or primary care trusts. More than half the sample surveyed provided bisphosphonates via both oral and IV routes but there were inconsistencies in the reasons for offering one or the other. Some oncologists felt that many patients preferred the convenience of oral drugs with avoidance of hospital visits and the necessity for cannulation whilst others claimed that their patients “valued regular and continued contact with the Cancer Centre via attendances for infusional treatment and for this reason have declined oral therapy”. It was clear that some clinicians had problems not only with unwillingness of trusts to pay for IV drugs but had other resource issues “We would find it difficult to cope with all the patients if they needed it IV and monthly”.

Some clinicians expressed their frustration at the lack of evidence to guide practice and wanted to get involved in more research. Others were aware that a number of patients being treated in some centres were being denied any choice of optimal therapy because of financial constraints e.g. “This is an important topic to be evaluated because of the need for patient choice, NHS capacity issues etc. Please contact me if I can help further with this”. Many were anxious to provide better, effective treatment and acknowledged the importance of the ongoing trials. “We all want a well tolerated oral preparation with proven efficacy. Reductions in SREs have been lower in IV preparations but no real head to head data and cross study comparisons dangerous. We await outcome of SWOG and ZICE study”. This last quote demonstrates the necessity to acquire a much firmer evidence base from properly conducted trials (SWOG is a head to head comparison of adjuvant oral zoledronate, clodronate or ibandronate). The quote is interesting for other reasons however as it implies that oral preparations are the preferred route and assumes that there will be good adherence to therapy. There is evidence from other studies of patients receiving breast cancer treatments that although a majority of patients do seem to prefer oral routes of administration to either intra-muscular or intravenous, a sizeable minority, approximately 25%, does prefer injectable routes.7 The primary reason for this is patients’ desire to receive optimal doses of drugs and their own acknowledgement that they often fail to adhere either accidentally due to forgetting or not understanding the dosing schedule, or deliberately to avoid unpleasant side effects. Several studies have reported patient compliance or adherence for breast cancer treatment therapies and for chronic therapy to be <50%.5,9 In our survey the vast majority of clinicians over-estimated likely patient adherence with more than 90% expecting that adherence was likely to be >40% and over a third of doctors thinking that it was more than 71%. Given the polypharmacy due to co-morbidities, as well as the other breast cancer drugs that patients are prescribed, these are optimistic estimates.10 Furthermore taking oral bisphosphonates makes unpleasant, troublesome demands on sometimes quite frail and elderly patients who have to stand upright and not eat breakfast or drink milk for at least an hour after taking their pill. In an overview describing the safety and
compliance with different dosing regimens associated with intravenous and oral bisphosphonates, four randomised clinical trials are cited where there was low compliance to oral therapy and high rates of GI adverse events.\[11\] There are arguments for prescribing higher doses of oral bisphosphonates less frequently to improve adherence but again appropriate comparative trials are required urgently before this approach could be adopted.

**Conflict of interest statement**

None declared.

**Acknowledgements**

The authors would like to thank Novartis for an unrestricted educational grant to conduct this survey, the doctors who commented on early drafts of the questionnaire and those who completed the final version. Louise Parlour, Rachel Cane, Grace Gelliatry and Louise Atkins for help identifying eligible doctors, administration and data entry.

Cancer Research UK funds Lesley Fallowfield and Valerie Jenkins.

**Appendix A. Postal questionnaire**

**CONFIDENTIAL**

Clinicians’ Attitudes Towards and Factors Influencing Treatment with Bisphosphonates in Metastatic Breast Cancer in the UK

Your Specialty: - Med Oncologist □  Clin.Oncologist □  Other □

1) How many breast cancer patients with bone metastases do you treat annually?……………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………