Journal of Bone Oncology 3 (2014) 37–39

Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

Editorial

Bone metastases: Are we failing our patients?

ARTICLE INFO

Keywords:
Bisphosphonates
Bone metastases
Bone-targeted agents
Denosumab
Skeletal-related events

1. Editorial/opinion piece

Many patients with advanced cancer will develop bone metastases and associated complications, including severe pain and debilitating skeletal-related events (SREs), which require radiotherapy, surgery or changes to antineoplastic regimens [1–3]. Fortunately, there are effective treatments to prevent or delay the onset of SREs. Several intravenous and oral bisphosphonates have been used for over a decade. More recently, denosumab (120 mg monthly, subcutaneous injection) has been added to the field of bone-targeted agents, having demonstrated superior efficacy over zoledronic acid (4 mg every 3–4 weeks, intravenous injection), the previous standard of care [4]. However, a clinical practice survey of patients with bone metastases suggests that many patients have not been receiving optimal treatment [5].

This 2010 audit, conducted in France, Germany, Italy, Spain and the United Kingdom, was divided into two sections. In the first part, physicians completed a brief questionnaire about all patients who had bone metastases or who were being treated with bisphosphonates for cancer-related reasons. A detailed questionnaire was then completed for the next 11 consecutive patients the physicians saw who met the study criteria. Cases were weighted according to the probability of prospective inclusion in the study (i.e. based on patient consultation frequency and length of observation period).

Of the 17,193 patients included in the first part of the audit, 35% had prostate cancer, 21% of patients had breast cancer, 16% had multiple myeloma and 11% had lung cancer. The remaining patients had other solid tumors or non-Hodgkin's lymphoma. Patient characteristics were largely consistent across the five countries. Of concern, data from the brief questionnaires showed that, of the patients with bone metastases ($n=14,871$), only 53% were receiving bisphosphonates (the only bone-targeted agents available at the time of this study). One-fifth had discontinued treatment, 10% were expected to receive bisphosphonates in the future and 17% were expected never to receive bisphosphonates.

Detailed questionnaires were completed for a further 9303 patients to establish the reasons behind the clinical practice patterns. Reasons for bisphosphonate discontinuation were mainly (in 56% of cases) listed as 'end of treatment as planned'. Most individuals who stopped treatment received bisphosphonates for 2 years or less (83%) and many (36%) received treatment for 1 year or less. There was considerable variation across countries, from 14% of patients in Germany receiving bisphosphonates for 1 year or less, to 64% of patients in the UK. Assuming patients are tolerating bisphosphonates, the question remains why should physicians plan a specific treatment duration? Notably, most major guidelines do not recommend a restricted duration of therapy. There are limited data on long-term administration of these agents, but the information available suggests that the efficacy and safety profiles of bone-targeted agents are maintained over time [6]. Therefore, in the absence of a toxicity or adherence issue, there appears to be no obvious rationale to stop treatment.

Perhaps physicians are not fully aware of the risk-benefit profile of bone-targeted agents? A poor risk-benefit ratio and renal issues were key reasons for patients never receiving bisphosphonates, cited for 34% and 37% of individuals, respectively. Short life expectancy was another major reason for not treating patients (38%), despite 72% being at moderate-to-high risk of an SRE. Furthermore, over 60% of these patients were considered by their treating physician to be expected to live for more than 1 year. Considering that the mean time to an SRE is less than 2 months since diagnosis [7], with patients experiencing events every 3–6 months thereafter [8], patients with short life expectancies can still benefit from treatment. The chief objectives for treatment of patients with terminal cancer are palliation of symptoms and maintenance of quality of life; these are just as important when life expectancy is short. Bone-targeted agents can help to achieve these aims by preventing worsening of pain and avoiding the associated increased need for strong analgesics [9].

Abbreviations: SRE, skeletal related event

http://dx.doi.org/10.1016/j.jbo.2014.03.001

Reassuringly, for the majority of patients in whom treatment with bisphosphonates was delayed, the reason cited was 'bone metastases controlled by initial anti-tumour treatment' (56%). The audit also found, however, that a significant proportion of patients had their treatment delayed owing to safety concerns (31%), which included existing renal impairment (61%), dental health issues (28%) and avoidance of renal deterioration (20%). New bone-targeted agents that are not contraindicated in renal impairment, such as denosumab, may offer alternative options for patients whom physicians are reluctant to treat with bisphosphonates owing to renal issues. While maintaining dental health is important with both bisphosphonates and denosumab, studies suggest that it may be possible to reduce the risk of osteonecrosis of the jaw by carrying out preventive dental measures prior to treatment with bone-targeted agents and by avoiding invasive dental procedures while patients are on treatment [10–12].

The data also revealed notable differences in practice patterns across the countries. In France, Italy, Spain and the UK, patients were most likely to have multiple disseminated sites of metastases at the time of initial bone metastasis detection; however, patients in Germany were most likely to have a solitary bone metastasis. This suggests that bone metastases were more likely to be detected at an earlier stage in Germany than in other countries, meaning patients potentially received bisphosphonate treatment for longer than those in the other countries. Data from the audit on the circumstances surrounding bone metastasis detection supported this theory, with routine screening for metastases being much more common in Germany (38% of metastases were discovered this way) than in the other four countries (6–24%). Germany may offer a good example in this area as bone-targeted agents are beneficial even when initiated early in metastatic disease [1]. Thus, prompt diagnosis may result in patients experiencing fewer SREs overall.

The results of this audit suggest that the clinical management of bone metastases is at times suboptimal in these major European countries. Data from a study of a US claims database conducted by Hagiwara et al. [13] suggest that this issue is not confined to Europe. In their analysis, only 58.5% of patients with breast cancer received intravenous bisphosphonates in the first year after bone metastasis detection, and this proportion was even lower for those with prostate or lung cancer. Although it is some years since these studies were carried out, we believe that these data still have relevant implications for clinical practice. The recent introduction of denosumab may have improved access to treatment for patients with renal impairment, but other perceived barriers such as short life expectancy and short planned treatment duration are likely to persist in the clinic.

Encouragingly, the Skeletal Care Academy steering committee (composed of international experts in the field of cancer-related bone disease; oncologists, urologists, surgeons, nurses and patient advocacy groups) has put together a Patient Charter, setting out the basic requirements for standards of patient care in cancer-related bone disease [14]. This charter emphasizes the need for a multidisciplinary team who should understand the various management strategies available for patients with bone metastases. Increasing physicians' and nurses' awareness of different treatment strategies, together with improved clinical practice guidelines on optimal treatment duration and treatment of patients with short life expectancies, may help to improve patient access to effective therapies. Furthermore, prompt detection of bone metastases, as seen in Germany, may allow patients early access to bone-targeted agents, thereby delaying or avoiding debilitating bone complications and pain.

Conflict of interest statement

B. Tombal has received honoraria or speaker fees from Amgen, Astellas, Bayer and Sanofi-Aventis. I. Diel has received honoraria and consultations for Amgen, Novartis and Roche, and honoraria from Teva, GlaxoSmithKline and Medtronic. L. Drudge-Coates is a member of the Speaker's Bureaus for Amgen, Sanofi-Aventis, Ferring and AstraZeneca. I. Haynes is an employee of Amgen and owns Amgen stock and T. Brodowicz has received lecture fees from Amgen and Novartis.

Acknowledgments

Writing and editorial support was provided by Oxford PharmaGenesis™ Ltd. Funding for this support was provided by Amgen (Europe) GmbH.

References

[1] Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res 2006;12:6243 (–9s).
[2] Lipton A. Pathophysiology of bone metastases: how this knowledge may lead to therapeutic intervention. J Support Oncol 2004;2:205–13.
[3] Roodman GD. Mechanisms of bone metastasis. N Engl J Med 2004;350: 1655–64.
[4] Lipton A, Fizazi K, Stopeck AT, Henry DH, Brown JE, Yardley DA, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. Eur J Cancer 2012;48:3082–92.
[5] Casas A, Lebret T, Cavo M, Woll PJ, Deleplace C, Schoen P, et al. Insights into the management of bone metastases: a comprehensive European survey. Support Care Cancer 2012;20:S88.
[6] Saad F, Chen YM, Gleason DM, Chin J. Continuing benefit of zoledronic acid in preventing skeletal complications in patients with bone metastases. Clin Genitourin Cancer 2007;5:390–6.
[7] Delea T, Langer C, McKiernan J, Liss M, Edelsberg J, Brandman J, et al. The cost of treatment of skeletal-related events in patients with bone metastases from lung cancer. Oncology 2004;67:390–6.
[8] Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res 2006;12:6243s–49ss.
[9] Cleeland C, Patrick D, Fallowfield L, von Moos R, Body JJ, Egerdie B, et al. Effects of denosumab vs zoledronic acid (ZA) on pain in patients (Pts) with advanced cancer and bone metastases: an integrated analysis of 3 pivotal trials. Ann Oncol 2010;21(Suppl. 8) :viii 380 (Abstract 1248P).
[10] Dimopoulos MA, Kastritis E, Bamia C, Melakopoulos I, Gika D, Roussou M, et al. Reduction of osteonecrosis of the jaw (ONJ) after implementation of preventive measures in patients with multiple myeloma treated with zoledronic acid. Ann Oncol 2009;20:117–20.
[11] Ripamonti CI, Maniezzo M, Campa T, Fagnoni E, Brunelli C, Saibene G, et al. Decreased occurrence of osteonecrosis of the jaw after implementation of dental preventive measures in solid tumour patients with bone metastases treated with bisphosphonates. The experience of the National Cancer Institute of Milan. Ann Oncol 2009;20:137–45.
[12] Vandone AM, Donadio M, Mozzati M, Ardine M, Polimeni MA, Beatrice S, et al. Impact of dental care in the prevention of bisphosphonate-associated osteonecrosis of the jaw: a single-center clinical experience. Ann Oncol 2012;23:193–200.
[13] Hagiwara M, Delea TE, Cong Z, Chung K. Utilization of intravenous bisphosphonates in patients with bone metastases secondary to breast, lung or prostate cancer. Support Care Cancer 2014;22:101–13.
[14] Skeletal Care Academy. SCA patient charter. Available from: ⟨http://www.skeletalcareacademy.com/sca-charter.aspx⟩ (accessed 3.12.13).

B. Tombal *
Cliniques Universitaires Saint-Luc,
10 Avenue Hippocrate, B-1200 Brussels, Belgium
E-mail address: bertrand.tombal@uclouvain.be

I. Diel
CGG-Klinik Mannheim, Gynäkologischer Onkologe, Quadrat P7, 16-18, 68161 Mannheim, Germany

L. Drudge-Coates
Department of Urology, King's College Hospital NHS Foundation Trust, London, UK

I. Haynes
Amgen Ltd, Uxbridge, UK

T. Brodowicz
Comprehensive Cancer Center – Muscoloskeletal Tumors, General Hospital of Vienna, Medical University of Vienna, Vienna, Austria

Received 11 March 2014; accepted 13 March 2014
Available online 26 March 2014

* Corresponding author. Tel.: +32 2 7641415; fax: +32 2 7649083.