The use of bisphosphonates in the management of bone involvement from solid tumours and haematological malignancies – a European survey

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Bone metastases in patients with solid tumours (ST) and bone lesions in patients with haematological malignancies (HM) are common. Associated skeletal-related events (SREs) cause severe pain, reduced quality of life and place a burden on health care resources. Bone-targeted agents can reduce the risk of SREs. We evaluated the management of bone metastasis/lesions in five European countries (France, Germany, Italy, Spain and the UK) by an observational chart audit. In total, 881 physicians completed brief questionnaires on 17 193 patients during the observation period, and detailed questionnaires for a further 9303 individuals. Patient cases were weighted according to the probability of inclusion. Although a large proportion of patients with bone metastases/lesions were receiving bisphosphonates, many had their treatment stopped (ST, 19%; HM, 36%) or will never be treated (ST, 18%; HM, 13%). The results were generally similar across the countries, although German patients were more likely to have asymptomatic bone lesions detected during routine imaging. In conclusion, many patients who could benefit from bone-targeted agents do not receive bisphosphonates and many have their treatment stopped when they could benefit from continued treatment. Developing treatment guidelines, educating physicians and increasing the availability of new agents could benefit patients and reduce costs.

Keywords: bisphosphonate, bone metastases, bone-targeted agent, haematological malignancy, skeletal-related event, solid tumour.

INTRODUCTION

Bone complications are common in patients with advanced solid tumours (ST) and haematological malignancies (HM; Coleman 2001). Skeletal metastases are most frequently found in individuals with advanced breast cancer or prostate cancer, affecting 65–90% of patients,
and bone lesions are present in up to 96% of patients with newly diagnosed multiple myeloma (Coleman 2001; Kyle et al. 2003; Parker et al. 2013). Bone metastases also occur frequently in patients with other ST such as advanced lung and kidney cancer, but are rare in patients with gastrointestinal tumours. This pattern of occurrence may result from the route of blood drainage from the breast and pelvis to the skeleton. In addition, interactions between cancer cells and the bone marrow stroma may result in the promotion of secondary tumour growth (Coleman 2001).

As the treatment of cancer improves and patients live longer, the prevalence of bone involvement is predicted to rise. Bone metastases and lesions are associated with severe pain and debilitating skeletal-related events (SREs), which include pathologic fractures, spinal cord compression and the need for therapeutic radiation or surgery to bone (Coleman 2001; Ibrahim et al. 2013). SREs are associated with increased mortality (Saad et al. 2007b; Norgaard et al. 2010) and reduced quality of life (Weinfurt et al. 2004, 2005; Depuy et al. 2007; Costa et al. 2008; von Moos et al. 2013), and place a considerable burden on hospital resources (Delea et al. 2006; Lage et al. 2008; Pockett et al. 2010; Hechmati et al. 2011; von Moos et al. 2013; Hoeferl et al. 2014; Body et al. 2015). Therefore, the effective management of metastatic bone disease and bone lesions is of increasing importance in order to improve clinical outcomes and the quality of life of patients. This management requires a multidisciplinary approach involving specialists in areas such as oncology, radiotherapy, orthopaedics, nursing and palliative care (Ibrahim et al. 2009, 2013).

Bisphosphonates are bone-targeted drugs that have been shown to reduce the risk of SREs in patients with bone metastases secondary to ST (Body 2003; Lipton 2007) and in patients with multiple myeloma and bone involvement (Berenson et al. 1996; Rosen et al. 2003). The use of bisphosphonates, particularly nitrogen-containing agents such as pamidronate and zoledronate, is associated with side effects which, although rare, should be considered when initiating treatment. Osteonecrosis of the jaw (Woo et al. 2006; EMA 2015a) and a modest risk of renal toxicity (<10%) (Conte & Guarneri 2004) have been associated with bisphosphonate use. The benefit–risk ratio should be taken into consideration before initiating bisphosphonate treatment and careful monitoring should be carried out once treatment has commenced. The risks are typically outweighed by the fact that bone-targeted agents can delay the onset of the first and subsequent SREs (Lipton 2007; Saad et al. 2007a), therefore the clinical benefit for patients with bone metastases or lesions is considerable.

The aim of this patient chart survey was to assess the management of bone metastases and lesions in patients with ST and HM across five European countries, in order to evaluate the use of bisphosphonates and to identify any barriers to their use.

**PATIENTS AND METHODS**

This was an observational chart audit performed over 2–3 weeks in March 2010 in France, Germany, Italy, Spain and the UK. In total, 881 physicians (307 oncologists, 164 haematologists, 196 urologists, 120 oncological haematologists, 41 pulmonologists, 31 gynaecologists, 12 radiation oncologists and 10 internists) who treated patients with advanced cancer were selected to form a representative sample. Eligible physicians had to manage at least five patients per week with advanced cancer involving bone. The number of patients intended to be included in this survey was 16 500.

The audit was divided into two parts that were completed concurrently by participating physicians. In the first part, physicians completed a brief questionnaire (Appendix 1) for every patient they saw with bone metastases associated with ST [prostate cancer, breast cancer, lung cancer, renal cell carcinoma, bladder cancer, colorectal cancer or other ST], or with bone lesions associated with HM [multiple myeloma, or non-Hodgkin lymphoma [NHL]], and for all additional patients who were being treated with a bisphosphonate for cancer-related reasons. Disease was staged using a scale of I–IV (Ann Arbor staging system) in patients with ST or NHL, and a scale of I to III in patients with multiple myeloma (Durie and Salmon staging system). The observation period was 2–3 weeks, as dictated by the caseload of the physician. In the second part of the audit, physicians completed a detailed questionnaire (Appendix 2) on the next 11 consecutive patients that they saw who met the pre-defined criteria. These criteria were: the first six patients treated with bisphosphonates; the first three patients with bone involvement who had never received bisphosphonates. Data on these patients were collected retrospectively via chart survey.

The frequency with which a patient visits their physician is usually determined by the type of cancer they are being treated for. Therefore, in order to avoid an under-estimation or over-estimation of the prevalence of different cancers, cases from the first part of the audit were weighted according to the probability of inclusion in the study. The weighting coefficient was estimated based on
the consultation frequency and the length of the observation period (i.e. the probability of the patient seeing the physician within the observation period; patients seeing the physician more frequently, e.g. those receiving chemotherapy every 3 weeks, were more likely to be included than those seeing the physician less frequently, e.g. those taking oral targeted therapy). To correct for any recruitment bias, data were weighted by the date of next consultation, with patients returning sooner allocated a lower coefficient than those returning later.

In each country, the evaluation an individual physician’s caseload obtained in the first part of the audit was also used to weight each detailed patient case appropriately in the second part. This ensured that the representative proportions of the patient populations according to treatment status (currently treated with bisphosphonates, previously treated, treatment planned, or will never be treated) measured in the first part of the audit were maintained in the second part, and in any analysis based on data from the detailed questionnaires.

RESULTS

Physicians and patients

In the first part of the audit (brief questionnaires), the 881 participating physicians provided data on 17,193 patients. These data showed that patient characteristics were largely consistent across the five countries (Table 1). The median ages of patients in each malignancy group were similar (ST, 67.7 years; HM, 67.5 years). For patients with ST, the youngest were in Germany (median age, 62.6 years) and the oldest in Italy (70.3 years). The median age of patients with HM was consistent across countries (64.3–68.3 years) (Table 1).

Detailed data were provided for 9,303 patients who were included in the second part of the audit. From these questionnaires, the most common cancer types associated with bone metastases or lesions ($n = 8,768$) were prostate cancer, breast cancer, lung cancer and multiple myeloma (Table 2). In Germany, there was a slightly higher proportion of patients with bone metastases who had lung cancer (20%) than in the other countries (Spain, 13%; France, 12%; Italy, 9%; UK, 8%; Table 2). Eastern Cooperative Oncology Group (ECOG) status and life expectancy (according to the treating physician’s opinion) in patients with bone metastases or lesions are listed in Table 3. Most patients had an ECOG status of 1 (ST, 47%; HM, 38%) or 2 (ST, 27%; HM, 22%). Only 1% of all patients had an ECOG status of 4. Most patients with ST (82%) and HM (96%) had a life expectancy of 1 year or more (Table 3).

### Table 1. Patient characteristics by malignancy type and by country: data from the brief questionnaire

|                  | Total ($N = 17,193$) | France ($n = 4,430$) | Germany ($n = 3,559$) | Italy ($n = 4,272$) | Spain ($n = 2,538$) | UK ($n = 3,374$) |
|------------------|----------------------|----------------------|----------------------|---------------------|---------------------|------------------|
|                  |                     |                      |                      |                     |                     |                  |
| Male (%)         |                     |                      |                      |                     |                     |                  |
| ST               | 61                   | 53                   | 59                   | 62                  | 60                  | 61               |
| HM               | 53                   | 67                   | 59                   | 68                  | 60                  | 59               |
| Median age (years) | 67.5               | 67.5                 | 67.5                 | 67.5                | 67.5                | 67.5             |
| Median age range (years) | 20.4–94.2 | 20.4–94.2 | 20.4–94.2 | 20.4–94.2 | 20.4–94.2 | 20.4–94.2 |

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Data from the detailed questionnaire showed that disease staging at initial diagnosis was consistent across countries (data not shown). Almost half of the 7558 patients with ST were diagnosed with stage IV disease (stage I, 5%; stage II, 23%; stage III, 25%; stage IV, 46%). Similarly, for patients with NHL (n = 227), most patients were diagnosed with the latest stage disease (stage I, 3%; stage II, 10%; stage III, 13%; stage IV, 74%). Of the 1528 patients with multiple myeloma, most were diagnosed with stage III disease (stage I, 10%; stage II, 18%, stage III, 71%).

Detection of bone metastases/lesions

From the detailed questionnaire, almost all patients had bone metastases or bone lesions (94%; n = 8768). Of these patients, 82% had ST and 17% had HM (Table 2). The largest proportion of patients with bone involvement had their metastases or lesions identified during staging at diagnosis of the primary cancer (ST, 38%; HM, 65%) or as a result of bone pain (ST, 35%; HM, 36%) (Table 4). Germany was an exception because routine screening during follow-up was the main method of detection of bone metastases and lesions in patients with ST (41%). Furthermore, metastases or lesions were less frequently identified in patients with ST as a result of bone pain in Germany (20%) than in other countries (range, 34–48%) (Table 4). Across most countries, patients were most likely to have bone metastases or lesions identified at multiple disseminated sites (ST, 36%; HM, 48%; Fig. 1). Again, Germany was the exception because patients with ST were more likely to have solitary bone metastasis at diagnosis (44%) than to have metastases at multiple disseminated sites (27%). The circumstances of diagnosis of bone lesions in patients with HM in Germany were similar to those in other countries.

Treatment of bone metastases/lesions

In the first part of the audit (brief questionnaire), most patients had bone metastases or lesions at the time of consultation (86%). Although a large proportion of these patients were currently receiving bisphosphonate treatment (ST, 68%; HM, 60%), many had their treatment

| Cancer type (%) | Total [N = 8768] | France [n = 1665] | Germany [n = 2326] | Italy [n = 1680] | Spain [n = 1534] | UK [n = 1563] |
|-----------------|------------------|-------------------|-------------------|-----------------|-----------------|--------------|
| Prostate cancer | 31               | 33                | 20                | 35              | 37              | 34           |
| Breast cancer   | 22               | 22                | 21                | 21              | 19              | 27           |
| Lung cancer     | 13               | 12                | 20                | 9               | 13              | 8            |
| Renal cell carcinoma | 7     | 6                 | 10                | 5               | 5               | 7            |
| Bladder cancer  | 4                | 2                 | 9                 | 3               | 4               | 2            |
| Colorectal cancer| 3                | 1                 | 7                 | 2               | 2               | 2            |
| Other solid tumour | 2            | 3                 | 3                 | 2               | 2               | 1            |
| Multiple myeloma | 15              | 18                | 9                 | 20              | 16              | 16           |
| Non-Hodgkin lymphoma | 2       | 3                 | 3                 | 2               | 1               |              |

HM, haematological malignancy; ST, solid tumour.

| Table 3. ECOG performance status and life expectancy (according to treating physician’s opinion) in patients with bone metastases/lesions: data from the detailed questionnaire |
|---------------------------------------------------------------|
| Total (N = 8768) | France (n = 1665) | Germany (n = 2326) | Italy (n = 1680) | Spain (n = 1534) | UK (n = 1563) |
| ST HM | ST HM | ST HM | ST HM | ST HM | ST HM |
| Performance status (%) |  |  |  |  |  |  |  |  |  |  |  |  |
| ECOG 0 | 16 | 31 | 16 | 38 | 9 | 9 | 25 | 42 | 18 | 20 | 15 | 40 |
| ECOG 1 | 47 | 38 | 48 | 36 | 52 | 54 | 40 | 33 | 47 | 31 | 45 | 40 |
| ECOG 2 | 27 | 22 | 28 | 18 | 29 | 34 | 25 | 19 | 26 | 30 | 26 | 14 |
| ECOG 3 | 9 | 6 | 7 | 6 | 9 | 2 | 8 | 5 | 7 | 15 | 12 | 4 |
| ECOG 4 | 1 | 1 | 1 | 3 | 1 | 0 | 1 | 1 | 2 | 1 | 1 | 2 |
| Life expectancy (%) |  |  |  |  |  |  |  |  |  |  |  |  |
| <1 year | 17 | 4 | 15 | 3 | 10 | 6 | 20 | 5 | 24 | 3 | 22 | 4 |
| 1–3 years | 46 | 34 | 42 | 25 | 43 | 41 | 47 | 33 | 48 | 50 | 53 | 26 |
| >3 years | 36 | 60 | 42 | 69 | 47 | 52 | 33 | 62 | 27 | 47 | 26 | 69 |

ECOG, Eastern Cooperative Oncology Group; HM, haematological malignancy; ST, solid tumour.
stopped (ST, 19%; HM, 36%) or would never receive bisphosphonates (ST, 18%; HM, 13%). Treatment with bisphosphonates was planned in a small proportion of patients (ST, 10%; HM, 7%) (Fig. 2).

Almost one-fifth of patients with ST and bone metastases or lesions were expected never to receive bisphosphonates (ST, 18%; HM, 13%) although most patients in this group had a moderate-to-high estimated risk of

| Response given [%] | Total [N = 8768] | France [n = 1665] | Germany [n = 2326] | Italy [n = 1680] | Spain [n = 1534] | UK [n = 1563] |
|-------------------|-----------------|------------------|-------------------|-----------------|-----------------|--------------|
| Staging at diagnosis | 38 65 | 41 74 | 31 75 | 39 57 | 37 52 | 45 68 |
| Bone pain | 35 36 | 48 52 | 20 7 | 34 37 | 37 46 | 42 34 |
| Routine metastases screening | 25 5 | 14 2 | 41 12 | 30 6 | 21 7 | 6 1 |
| Investigation following an event* | 7 18 | 9 20 | 5 10 | 6 23 | 5 20 | 9 13 |
| Hypercalcaemia | 5 9 | 6 15 | 3 1 | 4 7 | 5 9 | 6 13 |
| Accidental discovery | 5 3 | 5 1 | 5 1 | 5 3 | 6 9 | 4 1 |
| Other† | 3 0 | 6 0 | 0 0 | 3 0 | 4 0 | 3 0 |

HM, haematological malignancy; PSA, prostate-specific antigen; ST, solid tumour.
*Events included confirmed or suspected pathologic fracture or spinal compression.
†Including increase in tumour markers (e.g. PSA), check on spread of metastases/restaging for any metastases, extensive examination after finding lumps, worsening of general condition and pain. Investigators could give more than one response.

Figure 1. Description of bone metastases and lesions at discovery, by malignancy type and by country in patients with [A] solid tumours and [B] haematological malignancies: data from the detailed questionnaire. The difference between multiple disseminated sites and multiple sites was subjective and determined by the treating physician.
developing an SRE (evaluated by the physician) [data not shown]. The proportions of patients with ST who were expected never to receive bisphosphonates were reasonably consistent across countries with the exception of the UK, where almost twice as many patients were expected never to receive bisphosphonates (26%) as in other countries (range, 13–14%). Zoledronic acid was the most commonly used bisphosphonate in both malignancy types [ST, 75%; HM, 66%]. Pamidronate, clodronate and ibandronate were the next most common bisphosphonates and their use ranged from 5% to 9% in patients with ST, and from 4% to 14% in those with HM.

The main rationales for bisphosphonate treatment were: to prevent SREs (ST, 71%; HM, 66%), to treat or prevent pain (ST, 55%; HM, 42%), to prevent the development of new bone metastases or lesions (ST, 38%; HM, 47%) and to treat bone metastases or lesions at the original site (ST, 38%; HM, 36%) [Table 5]. Compared with other countries, Germany reported more frequently that the rationale for bisphosphonate use was based on the assumption that they prevent new metastases or lesions [ST, 69%; HM, 67%], whereas in France, this reason was given infrequently [ST, 15%; HM, 33%] [Table 5].

The most common reason for discontinuing bisphosphonate treatment was the ‘end of treatment as planned’ [ST, 51%; HM, 72%, Table 6]. Overall, patients were most often treated with bisphosphonates for a duration of 13–24 months [ST, 37%; HM, 38%] [Table 7]. In Germany, a larger proportion of patients were treated with

![Figure 2. Bisphosphonate treatment rates in patients with bone metastases/lesions across all countries: data from the brief questionnaire (n = 14 871).](image)

Table 5. Reason for initial treatment with bisphosphonates in patients with bone metastases/lesions, by malignancy type and by country: data from the detailed questionnaire

| Response given (%) | Total (N = 7368) | France (n = 1483) | Germany (n = 1973) | Italy (n = 1427) | Spain (n = 1325) | UK (n = 1160) |
|--------------------|------------------|------------------|-------------------|-----------------|-----------------|--------------|
|                    | ST   | HM   | ST   | HM   | ST   | HM   | ST   | HM   | ST   | HM   | ST   | HM   |
| Prevent SREs       | 71   | 66   | 66   | 67   | 84   | 87   | 64   | 62   | 65   | 57   | 67   | 61   |
| Treat/prevent pain | 55   | 42   | 57   | 44   | 68   | 72   | 43   | 32   | 49   | 42   | 48   | 29   |
| Prevent new bone metastases/bone lesions | 38   | 47   | 15   | 33   | 69   | 67   | 32   | 47   | 26   | 42   | 26   | 49   |
| Treat bone metastases/lesion at original site[s] | 38   | 36   | 30   | 26   | 59   | 47   | 36   | 38   | 19   | 43   | 33   | 31   |
| Patient’s disease has high risk factors | 5    | 7    | 9    | 20   | 1    | 0    | 5    | 6    | 4    | 3    | 10   | 4    |
| End of anti-tumour treatment | 1    | 1    | 0    | 1    | 0    | 1    | 2    | 3    | 3    | 1    | 2    | 0    |
| Other              | 1    | 2    | 3    | 3    | 0    | 2    | 1    | 0    | 0    | 2    | 4    |

HM, haematological malignancy; ST, solid tumour. Investigators could give more than one response.

Table 6. Reasons for discontinuation of bisphosphonates in patients with bone metastases/lesions, by malignancy type and by country: data from the detailed questionnaire

| Response given (%) | Total (N = 1838) | France (n = 392) | Germany (n = 516) | Italy (n = 363) | Spain (n = 309) | UK (n = 258) |
|--------------------|------------------|------------------|-------------------|-----------------|-----------------|--------------|
|                    | ST   | HM   | ST   | HM   | ST   | HM   | ST   | HM   | ST   | HM   | ST   | HM   |
| End of treatment as planned* | 51   | 72   | 48   | 77   | 67   | 60   | 38   | 68   | 44   | 85   | 36   | 56   |
| Toxicity           | 16   | 11   | 25   | 7    | 18   | 7    | 20   | 15   | 34   | 9    | 3    | 5    |
| Risk of toxicity   | 7    | 6    | 10   | 3    | 9    | 17   | 5    | 9    | 5    | 1    | 6    | 9    |
| Lack of efficacy†  | 12   | 4    | 7    | 7    | 13   | 9    | 20   | 1    | 7    | 1    | 10   | 3    |
| Contraindication due to concomitant treatment | 3    | 1    | 1    | 1    | 3    | 8    | 0    | 0    | 3    | 1    | 1    | 0    |
| Other              | 9    | 7    | 18   | 11   | 4    | 10   | 16   | 6    | 5    | 0    | 7    | 8    |

HM, haematological malignancy; ST, solid tumour. Investigators could give more than one response.

*Planned duration of treatment was determined by treating physician.
†As determined by treating physician.
Bisphosphonates for 13–24 months (ST, 55%; HM, 51%) than in the other countries [range, 9–37% (ST), 33–43% (HM)] (Table 7). Some patients who had their treatment stopped as planned were treated for only 6 months or less (ST, 15%; HM, 18%) (Table 8). Of those who had their treatment stopped owing to reaching the end of their planned treatment period, there was considerable variation between the countries: only 3% of patients with ST in Germany received bisphosphonates for 6 months or less, in contrast to 51% in the UK (Table 8).

Bisphosphonate treatment was often delayed in all countries except Germany (data not shown). The main justification for delaying bisphosphonate treatment was that bone metastases and lesions were controlled by initial anti-tumour therapy (ST, 57%; HM, 53%) (Fig. 3). This reason was particularly common in the UK (ST, 86%; HM, 66%). This justification was used fairly consistently in the other countries for patients with ST or multiple myeloma, but was used more frequently for patients with NHL (71%). Across all countries, the most common cancer treatments at diagnosis for patients with ST were hormone therapy (42%), surgery (40%), and chemotherapy (37%). Most patients with HM (77%) received chemotherapy as an initial treatment for their cancer (Table S1).

Owing to the risk of side effects associated with bisphosphonates, it is perhaps unsurprising that concern over safety was frequently given as a reason for treatment delay (ST, 31%; HM, 31%). This was the most common reason given in Germany (ST, 63%; HM, 64%). The next most common reasons for treatment delay were patient profile [e.g. poor performance status or short life expectancy] (ST, 30%; HM, 18%) and bone lesion characteristics (e.g. pain controlled with analgesics and the risk of SREs) (ST, 28%; HM, 21%) (Fig. 3). Patient profile was more commonly used as a justification for delaying treatment in patients with lung cancer (50%), bladder cancer (48%) and other ST (47%) than for patients with other types of malignancy.

The most common reasons given by physicians predicting that patients would never receive bisphosphonate treatment were: short life expectancy (ST, 41%; HM, 21%), renal issues (ST, 36%; HM, 39%) and poor benefit–risk ratio (ST, 34%; HM, 31%) (Table 9). These reasons were commonly given in all the countries studied, although their relative frequencies varied. For example, renal complications were the most common reason for not administering bisphosphonates in Germany (ST, 55%; HM, 66%), whereas this reason was recorded much less frequently in the UK (ST, 18%; HM, 22%). More than one-third of patients who took part in the second part of the audit had renal complications (ST, 31%; HM, 32%) and these proportions were consistent with observations in both Germany and the UK.

**Skeletal-related events**

At the timepoint of this survey, many patients had experienced at least one SRE, irrespective of the time of their

| Table 7. Duration of treatment with bisphosphonates for those patients with bone metastases/lesions who had treatment stopped, by malignancy type and by country: data from the detailed questionnaire |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment duration (%) | Total | France | Germany | Italy | Spain | UK |
| | | (N = 947) | (n = 220) | (n = 329) | (n = 167) | (n = 155) | (n = 74) |
| ≤6 months | | | | | | | |
| HM | 15 | 18 | 3 | 0 | 11 | 25 |
| ST | 18 | 21 | 12 | 0 | 14 | 25 |
| | 13–24 months | | | | | | |
| HM | 52 | 41 | 15 | 35 | 18 | 10 |
| ST | 47 | 35 | 12 | 16 | 30 | 43 |
| | >24 months | | | | | | |
| HM | 14 | 17 | 15 | 35 | 18 | 10 |
| ST | 17 | 20 | 12 | 20 | 30 | 43 |
| Unknown | 1 | 3 | 2 | 6 | 0 | 0 |

| Table 8. Duration of treatment with bisphosphonates for those patients with bone metastases/lesions who had treatment stopped owing to end of planned treatment, by malignancy type and by country: data from the detailed questionnaire |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment duration (%) | Total | France | Germany | Italy | Spain | UK |
| | | (N = 1806) | (n = 381) | (n = 516) | (n = 357) | (n = 306) | (n = 246) |
| ≤6 months | | | | | | | |
| HM | 28 | 20 | 37 | 23 | 14 | 4 |
| ST | 21 | 22 | 19 | 29 | 17 | 7 |
| | 7–12 months | | | | | | |
| HM | 21 | 22 | 19 | 29 | 17 | 7 |
| ST | 19 | 16 | 17 | 7 |
| | >24 months | | | | | | |
| HM | 14 | 16 | 13 | 4 | 14 | 39 |
| ST | 17 | 20 | 12 | 20 | 30 | 43 |
| Unknown | 1 | 4 | 2 | 4 | 0 | 0 |

HM, haematological malignancy; ST, solid tumour.
cancer diagnosis (ST, 22%; HM, 41%) (Table 10). The most common SRE in patients with ST was radiation to bone, and for those with HM it was pathological fracture. Patients who were currently treated or had previously been treated with bisphosphonates were most likely to have experienced an SRE. In those who were expected to receive bisphosphonates in the future, the prevalence of SREs was 10% and 32% among patients with ST and HM respectively. Of those patients who were expected never to receive bisphosphonate treatment (12% of patients

![Figure 3](image-url)  
Figure 3. Reasons for delaying bisphosphonate treatment in patients with bone metastases/lesions, by malignancy type and by country in patients with [A] solid tumours and [B] haematological malignancies: data from the detailed questionnaire. Anti-tumour treatment included radiotherapy, hormonal therapy, chemotherapy and targeted therapy. Safety concerns included existing renal impairment, to avoid renal deterioration and dental health issues. Patient profile included poor performance status and short life expectancy prognosis. Bone lesion characteristics included low risk of fracture/compression, no pain and pain controlled by analgesics. Investigators could give more than one response.

Table 9. Reasons why patients with bone metastases/lesions would never receive bisphosphonates, by malignancy type and by country: data from the detailed questionnaire

| Reason given (%) | Total N = 1360 | France n = 250 | Germany n = 304 | Italy n = 226 | Spain n = 216 | UK n = 364 |
|------------------|---------------|---------------|----------------|--------------|--------------|------------|
|                  | ST HM ST HM ST HM ST HM ST HM ST HM ST HM |
| Renal issue      | 36 39 46 21 55 66 34 59 33 32 18 22 |
| Dental health issue | 9 10 9 8 20 12 9 15 3 12 2 1 |
| Poor benefit-risk ratio | 34 31 43 40 29 23 38 21 25 28 36 42 |
| Patient refusal  | 6 3 7 2 10 2 6 8 4 0 5 5 |
| Short life expectancy | 41 21 38 13 41 14 32 17 52 42 41 22 |
| Pain from BM controlled by analgesics/opioids | 14 11 19 21 14 12 8 4 9 5 18 4 |
| Other            | 5 17 7 35 3 17 5 18 9 10 4 0 |

BM, bone metastases/lesions; HM, haematological malignancy; ST, solid tumour. Investigators could give more than one response.
with ST and 7% of those with HM), a large proportion had received radiation to bone and/or experienced a pathological fracture.

**DISCUSSION**

This large-scale chart audit with a robust methodology provides insight into the real-life management of patients with bone metastases or bone lesions in five European countries. These data suggest that approximately 80% of patients with bone metastases or lesions receive treatment with bisphosphonates during the course of their disease, and although most of these patients were receiving treatment at the time of this survey, there were patients who may benefit from initiating, or continuing treatment.

In general, the findings for patients with ST were consistent with those for patients with HM. Bone metastases and lesions were most likely to be discovered during disease staging at diagnosis, and most patients had multiple metastases or lesions. The major difference between malignancy types was that fewer patients with ST than those with HM were currently being treated, or had treatment planned, with bisphosphonates. This may be due to a combination of patient characteristics, such as poor performance status or life expectancy prognosis, and a lack of consensus in guideline recommendations. Bone pathology is one of the defining features of multiple myeloma (Raje et al. 2014). One study found that 79% of patients with multiple myeloma had bone abnormalities and 67% of patients had lytic bone lesions. In addition, more than half of patients experienced bone pain (Kyle et al. 2003; Raje et al. 2014). Bisphosphonates are therefore recommended in several guidelines to manage pain and control SREs in patients with multiple myeloma (Berenson et al. 2002; Harrouseau et al. 2005). This appears to be reflected in our study where more patients with HM than with ST were receiving bisphosphonate treatment. Bone involvement in breast cancer and prostate cancer is also common, with the reported incidence being as high as 75–90% (Coleman 2001; Parker et al. 2013). Therefore, it was surprising that over one-third of patients with ST were not receiving bisphosphonate treatment. Bone-targeted agents are recommended by several guidelines for patients with ST, therefore these results highlight differences between guidelines and real-life use of bisphosphonates. This also suggests that there are patients who could benefit from, but are not receiving, bisphosphonates.

Approximately, half of the patients in our study received bisphosphonate treatment for 1 year or more. The majority of patients had their bisphosphonate therapy stopped owing to the end of planned treatment and approximately one-fifth of those individuals received treatment for only 6 months or less. This was more common in the UK, with the majority of patients with ST receiving bisphosphonate treatment for 6 months or less. The optimum duration of bone-targeted therapy is unknown although pivotal studies for the bisphosphonates were generally conducted over 2 years and clinical benefit was observed throughout this time-frame (Berenson et al. 2002). Continued treatment for at least 2 years could be beneficial because bone-targeted therapy delays not only first but also subsequent SREs (Saad et al. 2007a; Stopeck et al. 2010; Fizazi et al. 2011; Henry et al. 2011). A placebo-controlled study of patients with prostate cancer showed that in the second year of bisphosphonate treatment, the risk of SREs continued to be substantially reduced, with a risk reduction of 53% compared with placebo (Saad et al. 2007a). The same study also demonstrated that treatment significantly reduced the risk of further SREs in patients who have already experienced one event. Furthermore, a significantly reduced risk of SREs has been reported in patients with breast cancer during the second year of bisphosphonate treatment (Aapro et al. 2010).

Perhaps, owing to the lack of information and consensus in the guidelines regarding optimal duration of treatment, effective medication for patients with bone metastases or

| Table 10. Skeletal-related events in patients with bone metastases/lesions by malignancy type and by bisphosphonate treatment status: data from the detailed questionnaire |
|-----------------------------------------------|
|                                | ST | HM    | ST | HM    | ST | HM    | ST | HM    | ST | HM    |
|-----------------------------------------------|
| All BM patients                             |    |       |    |       |    |       |    |       |    |       |
| (N = 8768)                                  |    |       |    |       |    |       |    |       |    |       |
| Currently treated                           |    |       |    |       |    |       |    |       |    |       |
| (n = 5133)                                  |    |       |    |       |    |       |    |       |    |       |
| Previously treated                          |    |       |    |       |    |       |    |       |    |       |
| (n = 1699)                                  |    |       |    |       |    |       |    |       |    |       |
| Treatment planned                           |    |       |    |       |    |       |    |       |    |       |
| (n = 575)                                   |    |       |    |       |    |       |    |       |    |       |
| Will never be treated                       |    |       |    |       |    |       |    |       |    |       |
| (n = 1361)                                  |    |       |    |       |    |       |    |       |    |       |
| All SREs (%)                                | 22 | 41    | 21 | 45    | 25 | 40    | 10 | 32    | 16 | 25    |
| n                                            | 1592 | 646  | 1043 | 386  | 303 | 188  | 51 | 19    | 189 | 47    |
| Radiotherapy to bone                        | 62 | 28    | 63 | 27    | 63 | 28    | 57 | 20    | 55 | 47    |
| Pathologic fracture                         | 30 | 62    | 31 | 63    | 29 | 62    | 31 | 74    | 30 | 53    |
| Spinal cord compression                     | 15 | 19    | 14 | 18    | 16 | 24    | 12 | 16    | 20 | 9     |
| Surgery to bone                             | 7  | 8     | 6  | 9     | 6  | 7     | 4  | 16    | 12 | 0     |

BM, bone metastases/bone lesions, HM, haematological malignancy; SRE, skeletal-related event; ST, solid tumour.
bone lesions may be being stopped at a point at which benefit could still be derived. At the time of this study, only one guideline recommended continuing bone-targeted therapy for more than 2 years because of the continued risk of SREs [Aapro et al. 2008]. Other guidelines did not advise on optimal treatment duration [Aapro et al. 2008; Cardoso et al. 2010; Mohler et al. 2010], therefore it may be difficult for physicians to make decisions on planned bisphosphonate treatment schedules. More recently, the International Myeloma Network has recommended zoledronic acid should be given continuously to patients with active multiple myeloma until disease progression or until a very good or complete response is achieved [Terpos et al. 2013]. Similarly, the European Myeloma Network has recommended continuous treatment with zoledronic acid, and treatment with pamidronate for up to 2 years [Terpos et al. 2015]. There is still a need for clarification regarding the optimal duration of bone-targeted therapy in general for patients with bone metastases resulting from ST because more recently published guidelines have not reached a consensus [Van Poznak et al. 2011; European Association of Urology 2016; European Society for Medical Oncology 2015; National Comprehensive Cancer Network 2016].

In this study, many patients with bone disease secondary to malignancies were expected never to receive bisphosphonate treatment. Short life expectancy was the most common reason cited for not treating patients with bisphosphonates, although over two-thirds of patients with bone metastases or lesions had a life expectancy of more than 1 year. Therefore, benefit could be derived from treatment with bone-targeted agents which can reduce the risk of SREs and therefore improve the quality of life of patients [Lipton 2010]. More recent guidelines suggest that patients expected to live for 3 months or longer should be considered for bone-targeted therapy [Coleman et al. 2014a]. It remains unknown whether bisphosphonate treatment in patients with asymptomatic multiple myeloma offers any advantage in the prevention of SREs [Terpos et al. 2013, 2014, 2015].

In this survey, it was noted that treatment with bisphosphonates was frequently delayed owing to safety concerns in patients with bone metastases or lesions secondary to ST of HM. These concerns included side effects such as osteonecrosis of the jaw and renal toxicity (Conte & Guarneri 2004; Woo et al. 2006). Osteonecrosis of the jaw has since been identified as being associated with all bone-targeted agents and while the risk remains low, the European Medicines Agency has recommended the implementation of updates to product information and the introduction of patient reminder cards [EMA 2015a]. Interestingly, however, historical data suggest that for most patients, the benefits of treatment outweigh the associated risks [Coleman 2008]. In our survey, renal complications were given as a common reason to avoid administering bisphosphonates. Renal morbidity was prevalent in our study, affecting one-third of patients to some degree. The EU approval in 2010 of the RANK Ligand inhibitor, denosumab, which has no effect on renal function as its metabolism and elimination follow the immunoglobulin clearance pathways [von Moos et al. 2013; EMA 2015b], may lead to more patients receiving and benefiting from bone-targeted therapies given that renal impairment is particularly relevant in elderly cancer patients [Body et al. 2010; Fizazi et al. 2011]. Furthermore, denosumab treatment resulted in a superior reduction in the risk of SREs compared with zoledronic acid in patients with ST and therefore is a more efficacious treatment choice [Henry et al. 2010, 2014; Stopec et al. 2010; Fizazi et al. 2011].

Although the results of the present study were generally consistent across countries, and across malignancy type, the German data stood out for a number of reasons. First, patients with ST were younger than in the other countries. This could be owing to more widespread cancer screening, leading to diagnosis at a younger age, rather than to differences in the epidemiology of the cancers. This is supported by the finding that bone metastases and lesions were discovered more frequently in German patients through routine screening during follow-up than during staging at diagnosis. Furthermore, more patients were diagnosed with a solitary bone metastasis or lesion and fewer patients were diagnosed owing to development of pain in Germany than in the other countries, which suggest that these bone metastases and lesions were being detected at an earlier stage. At the time of this study, the German National Health Service had approved the reimbursement of positron emission tomography for disease staging and tumour characterisation in patients with non-small cell lung cancer [Buck et al. 2010], which may have promoted a different approach to cancer diagnosis in general. Routine bone scanning in asymptomatic patients [not currently recommended by treatment guidelines] could lead to earlier detection of bone metastases and lesions, which is a more proactive attitude to diagnosis and preventive treatment of SREs in Germany than in other countries.

Although we were unable to collect data on denosumab use because the survey was conducted before the agent received marketing authorisation, the results of this patient chart audit are still relevant to current clinical practice because disagreements still exist between guideline recommendations and physicians’ opinions relating to optimal bone care for patients with cancer [Payne et al. 2013;Cole-
CONFLICTS OF INTEREST

Thierry Lebret has participated in advisory boards for Novartis and Amgen. Michele Cavo has received honoraria from Amgen. Penella J. Woll has participated in advisory boards for Novartis and Amgen. Caroline Kennedy is an employee of Takeda Global Research & Development Centre (Europe) Ltd, has been an employee of Amgen Limited and holds Amgen Limited Stock. Paul Schoen is an employee of Amgen (Europe) GmbH and holds stock. Christian Jackisch is a member of the Amgen speakers bureau and has received honoraria. Ana Casas and Catherine Deleplace declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Catherine Deleplace, Paul Schoen and Thierry Lebret contributed to the design of this study. Catherine Deleplace and Paul Schoen contributed to the collection of data. Thierry Lebret, Ana Casas, Michele Cavo, Penella J. Woll, Catherine Deleplace, Caroline Kennedy, Paul Schoen and Christian Jackisch critically analysed the data, contributed to the drafting and review of the manuscript, and approved the final version for submission.

COMPLIANCE WITH ETHICS GUIDELINES

No patient information was collected prospectively; all data were collected through chart survey and anonymised. Therefore, ethics approval and patient consent were not required for this study.

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**APPENDIX 1**

**SIMPLE QUESTIONNAIRE:**

Please report on all cancer patients (solid tumour, NHL, multiple myeloma) meeting the following criteria:

- Patients with bone metastases / bone lesions
- Patients without bone metastases / bone lesions (BM/BL) but treated with bisphosphonates (to delay progression to Bone metastases/Bone lesions or to treat for Cancer Treatment Induced Bone Loss (CTIBL))

| N° | Q.1. Consultation | Q.4. Cancer Type | Q.5. Date of initial diagnosis of this cancer | Q.6. Date of Re staging to Stage IV / discovery of distant metastases | Q.7. Solid Tumour/NHL cases: Date of Re staging to Stage IV / discovery of distant metastases | Q.8. Patient Status regarding Bisphosphonate treatment for cancer-related reasons: | Q.10. Date of next consultation |
|----|------------------|-----------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|-----------------------|
| 1  | Breast           | 1               | Breast                          | 1                               | 1                               | 1                               | In 1 week or less         |
|    |                  | 2               | Prostate                        | 2                               | 2                               | 2                               | In 2 weeks               |
|    |                  | 3               | Lung                            | 3                               | 3                               | 3                               | In 3 weeks               |
|    |                  | 4               | Renal                           | 4                               | 4                               | 4                               | In 1 month               |
|    |                  | 5               | Colorectal                      | 5                               | 5                               | 5                               | In 2 - 3 months          |
|    |                  | 6               | Bladder                         | 6                               | 6                               | 6                               | Over 3 months            |
|    |                  | 7               | Multiple Myeloma                | 7                               | 7                               | 7                               |                        |
|    |                  | 8               | NHL                             | 8                               | 8                               | 8                               |                        |
|    |                  | 9               | Other (specify)                 | 9                               | 9                               | 9                               |                        |
|    |                  |                  |                                 |                                 |                                 |                                 |                        |
| 2  | Male             | 1               | Stage I                         | 1                               | 1                               | 1                               |                        |
|    |                  | 2               | Stage II                        | 2                               | 2                               | 2                               |                        |
|    |                  | 3               | Stage III                       | 3                               | 3                               | 3                               |                        |
|    |                  |                  |                                 |                                 |                                 |                                 |                        |
| 3  | Female           | 1               | Stage I                         | 1                               | 1                               | 1                               |                        |
|    |                  | 2               | Stage II                        | 2                               | 2                               | 2                               |                        |
|    |                  | 3               | Stage III                       | 3                               | 3                               | 3                               |                        |
|    |                  |                  |                                 |                                 |                                 |                                 |                        |

Q1b. If the patient is currently receiving bisphosphonates and does not have bone metastases / bone lesions, why is s/he treated with bisphosphonates?

1. To delay progression to Bone metastases / Bone lesions
2. To treat bone loss due to hormonal cancer treatments (CTIBL = cancer treatment induced bone loss)
APPENDIX 2

DETAILED QUESTIONNAIRE:

| Date of visit | Patient with bone metastases/lesions; or treated with Bisphosphonate to delay progression to bone metastases/lesions | Patient N°1 Patient initials | Patient number in census |
|---------------|--------------------------------------------------------------------------------------------------------------------------|----------------------------|--------------------------|

**Patient characteristics**

1. Sex: ☐ Male ☐ Female

2. Year of Birth: ________

**CURRENT PATIENT STATUS:**

3. Current ECOG performance status score: (see appendix) ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

4. Current renal morbidity (creatinine clearance):
   - ☐ None (>60 mL/min)
   - ☐ Mild-Moderate (30-60 mL/min)
   - ☐ Severe (<30 mL/min)
   - ☐ Unknown

4.1 Other significant co morbidity: ☐ None ☐ Diabetes ☐ Cardiovascular ☐ Other (specify): …

5. Current patient management:
   - ☐ In-patient
   - ☐ Out-patient
   - ☐ Home hospitalisation
   - ☐ External consultation
   - ☐ Nursing home/hospital

6. Current anti-tumour treatment:
   - ☐ None
   - ☐ Conventional Chemotherapy
   - ☐ Targeted Therapy
   - ☐ Hormonal therapy
   - ☐ Radiotherapy
   - ☐ Other (specify): …

   6.1. Patient currently participating in clinical trials: ☐ Yes ☐ No

   6.2. If yes, which treatments are they testing?: ☐ Bisphosphonate ☐ Chemotherapy ☐ Other (specify): …

7. Current existence of distant metastases?
   - ☐ Yes (specify) ☐ Bone ☐ Hepatic ☐ Pulmonary ☐ Suprarenal ☐ Cerebral ☐ Other(s) (specify): …

   ☐ No

8. Has the patient suffered skeletal related event(s)?
   - ☐ Yes ☐ No
   - ☐ 8.1 What type of SRE? ☐ Pathologic Fracture ☐ Spinal cord compression ☐ Surgery to bone ☐ Radiotherapy to bone

   ☐ No ☐ 8.2 When did the first SRE occur?: [Month Year]

9. Prostate / Breast cancer only:
   - ☐ Hormone Sensitive ☐ Hormone Resistant

   9.1 If treated/ previously treated with hormone therapy: Date start of first line hormone therapy: [Month Year]

   9.2 If applicable: Date of first line hormone therapy failure: [Month Year]

**Description of the indication, diagnosis, and initial treatment**

10. Initial site of cancer: ☐ Breast ☐ Prostate ☐ Lung ☐ Renal ☐ Colorectal ☐ Bladder

   ☐ Multiple Myeloma ☐ NHL ☐ Other (specify): …

11. Date of initial diagnosis: [Month Year]

12. Stage at diagnosis (except in multiple myeloma cases):
   - ☐ Stage I ☐ Stage II ☐ Stage III ☐ Stage IV

   12.1. If stage IV, type of distant metastases:
   - ☐ Visceral ☐ Bone metastasis ☐ Other (specify): …

13. Myeloma cases - Stage at diagnosis (see Durie and Salmon classification in appendix):
   - ☐ Stage I ☐ Stage II ☐ Stage III

13.1. Bone lesions at diagnosis:
   - ☐ Yes ☐ No

   ☐ 13.2. If yes, Number of bone lesions: __________

14. Initial treatments at diagnosis:
   - ☐ None
   - ☐ Surgery
   - ☐ Radiotherapy
   - ☐ Hormonal Therapy
   - ☐ Chemotherapy
   - ☐ Targeted therapy
   - ☐ Other (specify): …

15. Date of 1st discovery of distant metastases [Month Year]

   ☐ 15.1. if tick box (X) if ☐ Distant Metastases/Stage IV at diagnosis

16. Metastasis type at that time:
   - ☐ Visceral ☐ Bone metastasis ☐ Other (specify): …

**Description of bone metastases/lesions**

17. Presence of bone metastases/bone lesions:
   - ☐ Yes ☐ No ☐ If no, go directly to question 25.1.

   17.1. Discovery date of the bone metastases/lesions: [Month Year]

18. Circumstances of bone metastases/lesions discovery:
   - ☐ Staging at diagnosis ☐ Routine metastases screening every ____ months ☐ Accidental discovery

   ☐ Investigation following an event (specify):
   - ☐ Pathologic Fracture (vertebral, non-vertebral) ☐ Spinal cord compression

   ☐ Suspected or ☐ Confirmed

   ☐ Bone pain ☐ Hypercalcaemia ☐ Other (specify): …

19. Type of bone metastases/lesions at discovery:
   - ☐ Osteolytic ☐ Osteoblastic ☐ Mixed

   19.1. ☐ Solitary bone metastases/lesion ☐ Multiple sites (specify number): __________

   ☐ Multiple disseminated sites (not assessed)

20. Location of bone metastases/lesions at discovery:
   - ☐ Long bone ☐ Vertebral ☐ Pelvis/hip ☐ Ribs ☐ Head ☐ Other (specify): …
### Supporting Information

Additional Supporting Information may be found online in the Supporting Information tab for this article:

**Table S1.** Current cancer treatments at diagnosis, by malignancy type and by country: data from the detailed questionnaire.

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### SUPPORTING INFORMATION

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**Table S1.** Current cancer treatments at diagnosis, by malignancy type and by country: data from the detailed questionnaire.