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Original Article

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,

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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; Hoefeler *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 for cancer-related reasons (to treat or prevent bone lesions); the first two patients who had discontinued cancer-related treatment with bisphosphonates; and 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 underestimation 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 9303 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 ($n = 8768$) 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 ($n = 3559$)		Germany ($n = 4450$)		Italy ($n = 3272$)		Spain ($n = 2538$)		UK ($n = 3374$)	
	ST	HM	ST	HM	ST	HM	ST	HM	ST	HM	ST	HM
Male (%)	61	53	67	63	59	51	65	55	77	64	62	62
Median age (years)	67.7	67.5	69.6	67.5	62.6	67.3	70.3	68.3	66.8	64.3	69.6	68.2
Median age range (years)	15.1–100.3	10.5–99.6	26.7–100.3	20.4–94.2	24.8–100.3	29.8–89.2	19.6–100.3	10.5–89.1	16.8–99.8	20.4–99.6	15.1–99.9	20.0–97.6

HM, haematological malignancy; ST, solid tumour.

Table 2. Type of cancer in patients with bone metastases/lesions: data from the detailed questionnaire

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	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.

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 3, 13%; stage IV, 74%). Of the 1528 patients with multiple myeloma, most were diagnosed with stage III disease (stage I, 10%; stage 2, 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

Table 4. Circumstances of discovery of bone metastases and lesions, by malignancy type and by country: data from the detailed questionnaire

	Total (N = 8768)		France (n = 1665)		Germany (n = 2326)		Italy (n = 1680)		Spain (n = 1534)		UK (n = 1563)	
Response given (%)	ST	HM	ST	HM	ST	HM	ST	HM	ST	HM	ST	HM
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.

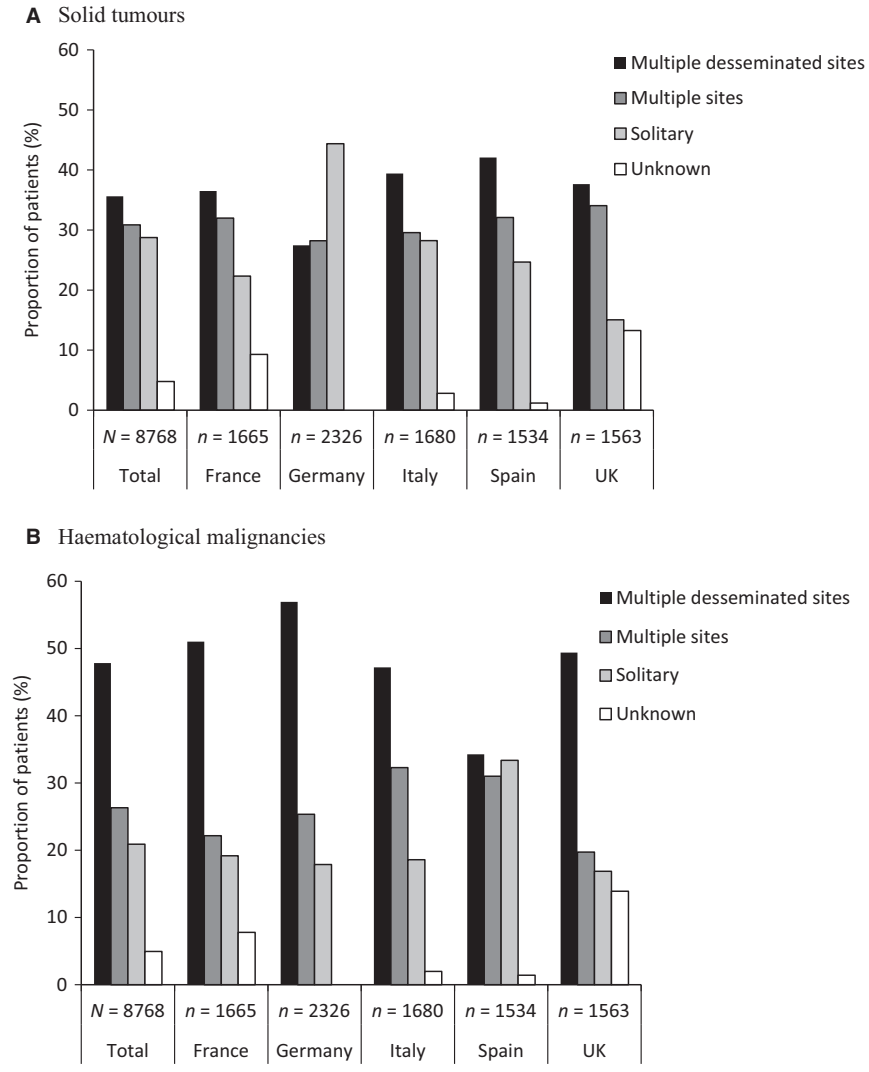

Figure 1. Description of bone metastases and lesions at discovery, by malignancy type and by country in patients with (A) solid tumours and (B) haematological malignancies: data from the detailed questionnaire. The difference between multiple disseminated sites and multiple sites was subjective and determined by the treating physician.

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

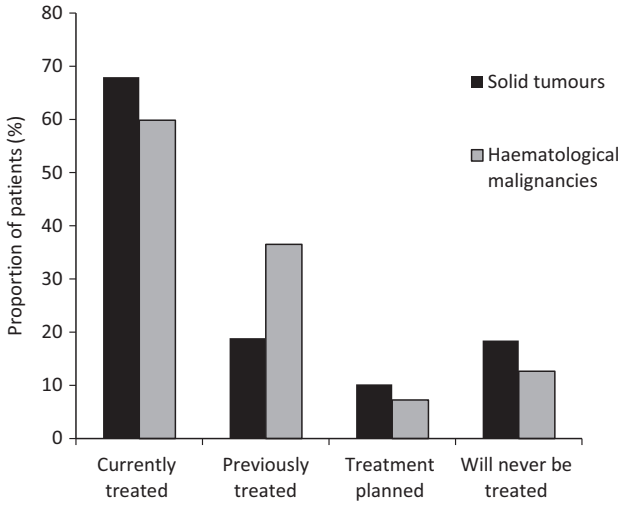

Figure 2. Bisphosphonate treatment rates in patients with bone metastases/lesions across all countries: data from the brief questionnaire (n = 14 871).

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

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

	Total (N = 7368)		France (n = 1483)		Germany (n = 1973)		Italy (n = 1427)		Spain (n = 1325)		UK (n = 1160)	
Response given (%)	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	1	0	0	1	2	3	3	1	2	0
Other	1	2	3	3	0	2	1	0	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

	Total (N = 1838)		France (n = 392)		Germany (n = 516)		Italy (n = 363)		Spain (n = 309)		UK (n = 258)	
Response given (%)	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	7	18	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

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

	Total (N = 947)		France (n = 220)		Germany (n = 329)		Italy (n = 167)		Spain (n = 155)		UK (n = 74)	
Treatment duration (%)	ST	HM	ST	HM	ST	HM	ST	HM	ST	HM	ST	HM
≤6 months	15	18	27	19	3	0	11	25	26	15	51	21
7–12 months	18	21	18	29	12	0	14	11	36	25	37	34
13–24 months	52	41	33	42	70	65	58	31	28	48	6	12
>24 months	14	17	20	5	15	35	18	30	10	11	4	33
Unknown	1	3	2	6	0	0	0	4	0	0	3	1

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

	Total (N = 1806)		France (n = 381)		Germany (n = 516)		Italy (n = 357)		Spain (n = 306)		UK (n = 246)	
Treatment duration (%)	ST	HM	ST	HM	ST	HM	ST	HM	ST	HM	ST	HM
≤6 months	28	20	37	23	14	4	24	23	33	20	50	20
7–12 months	21	22	19	29	17	7	19	16	30	28	26	16
13–24 months	37	38	29	39	55	51	36	31	28	43	9	33
>24 months	14	16	13	4	14	39	18	23	10	9	13	27
Unknown	1	4	2	4	0	0	2	7	0	0	2	4

HM, haematological malignancy; ST, solid tumour.

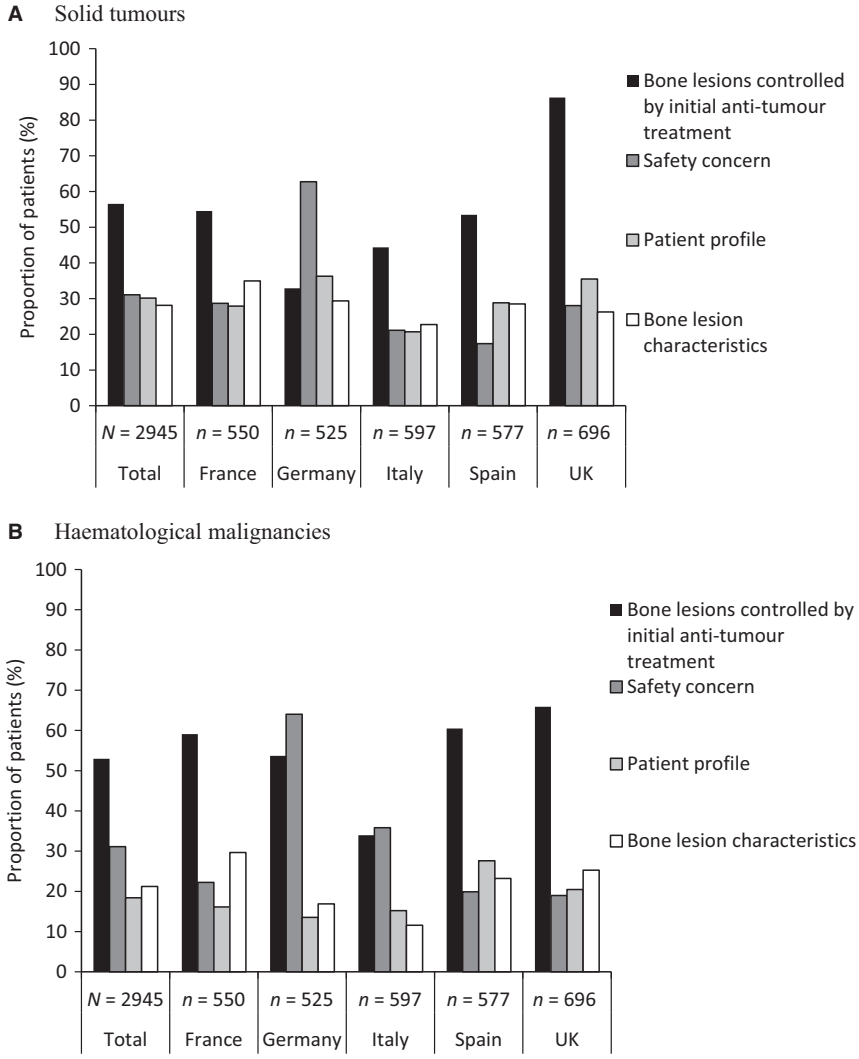

Figure 3. Reasons for delaying bisphosphonate treatment in patients with bone metastases/lesions, by malignancy type and by country in patients with (A) solid tumours and (B) haematological malignancies: data from the detailed questionnaire. Anti-tumour treatment included radiotherapy, hormonal therapy, 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

	Total (N = 1360)		France (n = 250)		Germany (n = 304)		Italy (n = 226)		Spain (n = 216)		UK (n = 364)	
Reason given (%)	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.

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

Table 10. Skeletal-related events in patients with bone metastases/lesions by malignancy type and by bisphosphonate treatment status: data from the detailed questionnaire

	All BM patients (N = 8768)		Currently treated (n = 5133)		Previously treated (n = 1699)		Treatment planned (n = 575)		Will never be treated (n = 1361)	
	ST	HM	ST	HM	ST	HM	ST	HM	ST	HM
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.
Some patients had multiple SREs.

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

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; Stopeck *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-

man *et al.* 2014b). Barriers still remain that prevent patients accessing bisphosphonates, including perceived short life expectancy and short treatment duration. Although recent guidelines published after this study was conducted have evolved, for instance, it is now recommend that patients expected to live for 3 months or longer should be considered for bone-targeted therapy (Coleman *et al.* 2014a), there are still gaps in the guidelines regarding optimal treatment duration. Improving screening and diagnostic practices for bone metastases and lesions throughout Europe to facilitate early detection (as seen in Germany) may allow earlier access to bone-targeted agents so that patients with cancer can receive the best standard of care.

CONCLUSION

The results from this study highlight some notable differences in treatment practices between countries as well as some unexpected findings when the data are considered in the context of international cancer treatment guidelines. It is likely that many of the patients who are expected not to receive bisphosphonates could benefit from this treatment. The number of patients discontinuing treatment after a short time is also of concern, particularly as these agents may prevent not only first SREs but also subsequent events. Therefore, improving access to treatment that reduces the risk of SREs could enhance the quality of life of patients with advanced cancer. This improved access could be achieved through increased awareness of both the overall burden of bone metastases and lesions, and the need to treat patients to prevent SREs, and improvements in cancer treatment guidelines. It is important to breakdown perceived treatment barriers, such as short life expectancy, and to ensure that guidelines provide appropriate advice on duration of treatment. The availability of new bone-targeted agents, with superior efficacy and no evidence of impact on renal function, may encourage physicians increase their focus on the management of bone involvement from ST and HM.

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)**

CENSUS

N°	Q.1. Consultation	Q.4. Cancer Type	Q.5. Date of initial diagnosis of this cancer	Q.7. Solid Tumour/NHL cases: Date of Re staging to Stage IV/ discovery of distant metastases	Q.9. Patient Status regarding Bisphosphonate treatment for cancer-related reasons:	Q.10. Date of next consultation
1	_____ _____ _____ DAY MONTH YEAR **Q.2. Sex** 1□ MALE 2□ FEMALE **Q.3. Date of birth** _____ Month Year	1□ Breast 2□ Prostate 3□ Lung 4□ Renal 5□ Colorectal 6□ Bladder 7□ Multiple Myeloma 8□ NHL 9□ Other (specify) :	_____ Month Year **Q.6. Stage at the diagnosis** 1□ Stage I 2□ Stage II 3□ Stage III 4□ Stage IV *(NA for multiple Myeloma)*	_____ Month Year **Q.8. Bone metastases/Lesions** **8a. Bone metastases/lesions?** 1□ Yes 2□ No **8b. *If yes*, Date of diagnosis of Bone Metastases/lesions** _____ Month Year	1□ Currently receiving bisphosphonate treatment, Start date of treatment: _____ Month Year 2□ Not currently treated but treatment with bisphosphonate planned 3□ Previously, but no longer treated with bisphosphonate, End date of treatment: _____ Month Year 4□ Will probably never be treated with bisphosphonate **Q9b.** If 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)	1□ In 1 week or less 2□ In 2 weeks 3□ In 3 weeks 4□ In 1 month 5□ In 2 - 3 months 6□ Over 3 months
N°	Q.1. Consultation	Q.4. Cancer Type	Q.5. Date of initial diagnosis of this cancer	Q.7. Solid Tumour/NHL cases: Date of Re staging to Stage IV/ discovery of distant metastases	Q.9. Patient Status regarding Bisphosphonate treatment for cancer-related reasons:	Q.10. Date of next consultation
2	_____ _____ _____ DAY MONTH YEAR **Q.2. Sex** 1□ MALE 2□ FEMALE **Q.3. Date of birth** _____ Month Year	1□ Breast 2□ Prostate 3□ Lung 4□ Renal 5□ Colorectal 6□ Bladder 7□ Multiple Myeloma 8□ NHL 9□ Other (specify) :	_____ Month Year **Q.6. Stage at the diagnosis** 1□ Stage I 2□ Stage II 3□ Stage III 4□ Stage IV *(NA for multiple Myeloma)*	_____ Month Year **Q.8. Bone metastases/Lesions** **8a. Bone metastases/lesions?** 1□ Yes 2□ No **8b. *If yes*, Date of diagnosis of Bone Metastases/lesions** _____ Month Year	1□ Currently receiving bisphosphonate treatment, Start date of treatment: _____ Month Year 2□ Not currently treated but treatment with bisphosphonate planned 3□ Previously, but no longer treated with bisphosphonate, End date of treatment: _____ Month Year 4□ Will probably never be treated with bisphosphonate **Q9b.** If 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)	1□ In 1 week or less 2□ In 2 weeks 3□ In 3 weeks 4□ In 1 month 5□ In 2 - 3 months 6□ Over 3 months
N°	Q.1. Consultation	Q.4. Cancer Type	Q.5. Date of initial diagnosis of this cancer	Q.7. Solid Tumour/NHL cases: Date of Re staging to Stage IV/ discovery of distant metastases	Q.9. Patient Status regarding Bisphosphonate treatment for cancer-related reasons:	Q.10. Date of next consultation
3	_____ _____ _____ DAY MONTH YEAR **Q.2. Sex** 1□ MALE 2□ FEMALE **Q.3. Date of birth** _____ Month Year	1□ Breast 2□ Prostate 3□ Lung 4□ Renal 5□ Colorectal 6□ Bladder 7□ Multiple Myeloma 8□ NHL 9□ Other (specify) :	_____ Month Year **Q.6. Stage at the diagnosis** 1□ Stage I 2□ Stage II 3□ Stage III 4□ Stage IV *(NA for multiple Myeloma)*	_____ Month Year **Q.8. Bone metastases/Lesions** **8a. Bone metastases/lesions?** 1□ Yes 2□ No **8b. *If yes*, Date of diagnosis of Bone Metastases/lesions** _____ Month Year	1□ Currently receiving bisphosphonate treatment, Start date of treatment: _____ Month Year 2□ Not currently treated but treatment with bisphosphonate planned 3□ Previously, but no longer treated with bisphosphonate, End date of treatment: _____ Month Year 4□ Will probably never be treated with bisphosphonate **Q9b.** If 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)	1□ In 1 week or less 2□ In 2 weeks 3□ In 3 weeks 4□ In 1 month 5□ In 2 - 3 months 6□ Over 3 months

APPENDIX 2

DETAILED QUESTIONNAIRE :

KANTAR HEALTH *Please insert contact here.*	Date of visit |__|__| |__|__| *Day Month* 2010	**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: 1☐ Male 2☐ 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):
1☐ None (>60mL/min) 2☐ Mild-Moderate (30-60 mL/min) 3☐ Severe (<30 mL/min) 4☐ Unknown

4.1 Other Significant co morbidity: 1☐ None 2☐ Diabetes 3☐ Cardio vascular 4☐ Other *(specify)*:……

5. Current patient management: 1☐ In-patient 2☐ Out-patient 3☐ Home hospitalisation 4☐ External consultation 5☐ Nursing home/hospice

6. Current anti-tumour treatment: 1☐ None 2☐ Conventional Chemotherapy 3☐ Targeted Therapy 4☐ Hormonal therapy 5☐ Radiotherapy 6☐ Other *(specify)*:……
6.1. Patient currently participating in clinical trials: 1☐ Yes 2☐ No
6.2. **If yes**, which treatments are they testing?: 1☐ Bisphosphonate 2☐ Chemotherapy 3☐ Other (*specify*):……

7. Current existence of distant metastases?
1☐ Yes *(specify)*: 1☐ Bone 2☐ Hepatic 3☐ Pulmonary 4☐ Suprarenal 5☐ Cerebral 6☐ Other(s)*(specify)*:……
2☐ No

8. Has the patient suffered skeletal related event(s)?
1☐ Yes ***If yes***: 8.1 What type of SRE? 1☐ Pathologic Fracture (vertebral, non-vertebral) 2☐ Spinal cord compression 3☐ Surgery to bone 4☐ Radiotherapy to bone
2☐ No 8.2 When did the first SRE occur? |___|___| |___|___| *Month Year*

***9. Prostate / Breast cancer only*:**
Current hormonal status 1☐ Hormone Sensitive 2☐ Hormone Resistant
9.1 ***If treated/ previously treated with hormone therapy***: Date start of first line hormone therapy: |___|___| |___|___| (mm/yy)
9.2 ***If applicable:*** Date of first line hormonal therapy failure: |___|___| |___|___| (mm/yy)

Description of the indication, diagnosis, and initial treatment

10. Initial site of cancer: 1☐ Breast 2☐ Prostate 3☐ Lung 4☐ Renal 5☐ Colorectal 6☐ Bladder 7☐ Multiple Myeloma 8☐ NHL 9☐ Other (specify):……

11. Date of initial diagnosis: |___|___| |___|___| *Month Year*

12. Stage at diagnosis (except in multiple myeloma cases): 1☐ Stage I 2☐ Stage II 3☐ Stage III 4☐ Stage IV
12.1. If stage IV, type of distant metastases: 1☐ Visceral 2☐ Bone metastasis 3☐ Other *(specify)*:……

13. Myeloma cases - Stage at diagnosis *(see Durie and Salmon classification in appendix)*:
1☐ Stage I 2☐ Stage II 3☐ Stage III

13.1. Bone lesions at diagnosis: 1☐ Yes 2☐ No
13.2. *If yes*, Number of bone lesions: |___| *or tick box (X) if* 1☐ Not assessed (multiple disseminated sites)

14. Initial treatments at diagnosis: 1☐ None 2☐ Surgery 3☐ Radiotherapy 4☐ Hormonal Therapy 5☐ Chemotherapy 6☐ Targeted therapy 7☐ Other *(specify)*:……

15. Date of 1st discovery of distant metastases |___|___||___|___| *Month Year* *or tick box (X) if* 1☐ Distant metastases/stage IV at diagnosis

16. Metastasis type at that time: 1☐ Visceral 2☐ Bone metastasis 3☐ Other *(specify)*:……

Description of bone metastases/lesions

17. Presence of bone metastases/bone lesions: 1☐ Yes 2☐ 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:
1☐ Staging at diagnosis 2☐ Routine metastases screening every |__| months 3☐ Accidental discovery
4☐ Investigation following an event (*specify*):

(18.1)	(18.2)
1☐ Pathologic Fracture (vertebral, non-vertebral) *specify*	1☐ Suspected or 2☐ Confirmed
2☐ Spinal cord compression *specify*	1☐ Suspected or 2☐ Confirmed

5☐ Bone pain 6☐ Hypercalcaemia 7☐ Other *(specify)*:……

19. Type of bone metastases/lesions at discovery: 1☐ Osteolytic 2☐ Osteoblastic 3☐ Mixed
19.1. 1☐ Solitary bone metastasis/lesion 2☐ Multiple sites *(specify number)*: |___| 3☐ Multiple disseminated sites *(n° not assessed)*

20. Location of bone metastases/lesions at discovery:
1☐ Long bone 2☐ Vertebrae 3☐ Pelvis/hip 4☐ Ribs 5☐ Head 6☐ Other *(specify)*: ……

21. Estimation of risk of SRE (or new SRE) at bone metastases/lesions diagnosis: 1☐ Low 2☐ Moderate 3☐ High

22. Life expectancy prognosis at bone metastases/lesions diagnosis: 1☐ <1 year 2☐ 1-3 years 3☐ > 3 years

23. Was bisphosphonate treatment initiated immediately at bone metastases/lesions discovery [or in the first month following discovery]
1☐ Yes ➞ ***If Yes**, go directly to question 25.1.* 2☐ No ➞ ***If no, go to question 24***

24. Reasons for **not** prescribing a bisphosphonate treatment **at bone metastases/lesions discovery**?
1☐ Bone metastases/lesions controlled by initial anti-tumour treatment
24.1. Specify: 1☐ Radiotherapy 2☐ Hormonal therapy 3☐ Chemotherapy 4☐ Targeted therapy 5 ☐ Other (specify):……
2☐ Safety concern
24.2. *Specify:* 1☐ Existing Renal impairment 2☐ To avoid renal deterioration 3☐ Dental health issue 4☐ Other (*specify)*:….
3☐ Bone metastases/lesions characteristics
24.3. *Specify:* 1☐ Low risk of fracture/compression 2☐ No pain from bone metastases
3☐ Pain from bone metastases controlled by analgesics 4☐ Other (*specify)*:……..
4☐ Patient profile
24.4. *Specify:* 1☐ Poor performance status 2☐ Bad life expectancy prognosis 3☐ Other (*specify)*:……
4☐ To reduce overall treatment duration with bisphosphonates

Patient bisphosphonate treatment status:

25.1. ☐ This patient is currently receiving bisphosphonate treatment
25.2. ☐ This patient is not currently treated with bisphosphonate but a treatment with bisphosphonate is planned
25.3. ☐ This patient was previously treated with a bisphosphonate, but is no longer treated*: Specify reason for ending treatment*
25.3b.1☐ Toxicity *(specify)*:……..…… 2☐ Risk of toxicity *(specify)*:…… 3☐ Lack of efficacy
4☐ End of treatment as planned 5☐ Contraindication due to concomitant treatment
6☐ Other *(specify)*:……
25.4. ☐ This patient will probably never receive a bisphosphonate: *Specify reason(s):*
25.4b. 1☐ Renal issue 2☐ Dental health issue 3☐ Poor benefit/risk ratio for this patient 4☐ Patient refusal
5☐ Short life expectancy 6☐ Pain from bone metastases controlled by analgesics/opioids 7☐ Other *(specify)*:……..

26.*(If treated/previously treated with bisphosponates)*Reasons for initiating 1st prescription of a bisphosphonate treatment for this patient:
1☐ Prevent SREs (Fracture/ spinal cord compression/ surgery or radiotherapy to bone) 2☐ to treat/prevent pain
3☐ End of anti-tumour treatment 4☐ Patient's disease has high risk factors
5☐ To treat bone metastases/lesions at original site(s) *specify factors motivaing bisphosphonates prescription:* ……..
6☐ to prevent new bone metastases/lesions 7☐ Other reason(s) *(specify)*: ……

If bone metastasis/bone lesion at the 1st prescription of a bisphosphonate treatment :
27. Location of bone metastasis/lesion at initiation of treatment with bisphosphonates:
1☐ Long bone 2☐ Vertebrae 3☐ Pelvis/hip 4☐ Ribs 5☐ Head 6☐ Other *(specify)*:…….

28. Estimation of risk of SRE (or new SRE) at Bisphosphonate initiation : 1☐ Low 2☐ Moderate 3☐ High

Description of current treatment with bisphosphonate
(or last treatment if this patient has previously received a bisphosphonate, but is no longer treated)

29. Start date of the current treatment: |___|___||___|___|
Month *Year*

29.1 Treatment duration planned for:
A maximum of |___| months, or *(tick if applicable)* 2 ☐ indefinitely

30. Initial prescriber: 1☐ Yourself 2☐ Another physician (*please specify the speciality)*: …….

31. Name of current/last bisphosphonate prescribed *(specify)*:……

32. Method of administration: 1☐ Injection *(go to question 33)* 2☐ Oral *(go to question 34.1)*

33. Administration: 1☐ Hospital /hospice 2☐ At home 3☐ GP/Private office 4☐ Other *(specify)*:……

Dosage (dose and injection timing) at treatment initiation and new dose if changed since initiation (complete tables below):

34. Prescribed dosage at start of treatment (complete table)			**35.** Modified dosage *if changed since initiation*		
a. Bisphosphonate dose at treatment initiation (injection)	**b.**Timing of injections	**c.**Total n° of injections at this dosage received since initiation (same dose; same timing of injections)	**a.** New Bisphosphonate dose (injection)	**b.**Timing of injections	**c.**Total n° of injections at this dosage received since modification (same dose; same timing of injections)
|__|__| mg	1 injection every |__| weeks	|___|___|	|__|__| mg	1 injection every |__| weeks	|___|___|
34.1. (If administered **orally**) Total dosage per day ……			**35.1.** (If administered **orally**) Total dosage per day ……		
			35.2. Reasons for change of dosage (injection/oral) ……		

36. During this treatment (still ongoing or ended) was your bisphosphonate treatment continuous? *(regular, without drug holidays)*
1☐ Yes *(go to question 37 if applicable)* 2☐ No
36.1. If no, for what reasons was it interrupted?
1☐ Drug holiday 2☐ Tolerance problem *(specify)*:……3☐ Other *(specify)*: ……
36.2. Duration of interruption : |___|___| day(s)

37. How frequently do you currently measure kidney function for this patient?
1☐ Approx every month 2☐ Approx every 3 months 3☐ Approx every 6 months 4☐ Every year 5☐ Never

38. Is this treatment still ongoing? 1☐ Yes 2☐ No ➞ **38.1.** If no, what was the end date? |___|___||___|___|
Month *Year*

39.Prior to the current [or last] bisphosphonate treatment, did the patient received an alternative bisphosphonate ?
1☐ Yes ➞ If yes, name of alternative bisphosphonate prescribed *(specify)*:……
2☐ No

40. Method of administration: 1☐ Injection 2☐ Oral

41. Reason for switch to the current [or last] bisphosphonate :
1☐ Oral formulation 2☐ Toxicity 3☐ Risk of toxicity 4☐ Cost 5☐ 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.