Support Care Cancer (2005) 13: 975–986
DOI 10.1007/s00520-005-0828-1

ORIGINAL ARTICLE

E. De Cock
J. Hutton
P. Canney
J. J. Body
P. Barrett-Lee
M. P. Neary
G. Lewis

Cost-effectiveness of oral ibandronate compared with intravenous (i.v.) zoledronic acid or i.v. generic pamidronate in breast cancer patients with metastatic bone disease undergoing i.v. chemotherapy

Received: 30 September 2004
Accepted: 14 April 2005
Published online: 4 May 2005

E. De Cock (✉) · J. Hutton
The MEDTAP Institute at UBC,
20 Bloomsbury Square,
London, WC1A 2NS, UK
e-mail: Decock@unitedbiosource.com
Tel.: +44-207-2994560
Fax: +44-207-2994555

P. Canney
Western Hospital,
Glasgow, UK

J. J. Body
Institut Jules Bordet,
Université Libre de Bruxelles,
Brussels, Belgium

P. Barrett-Lee
Velindre Cancer Centre,
Cardiff, UK

M. P. Neary
Hoffmann-La Roche Inc.,
Nutley, NJ, USA

G. Lewis
Roche Pharmaceuticals UK,
Welwyn, UK

Abstract *Background:* Ibandronate is the first third-generation bisphosphonate to have both oral and intravenous (i.v.) efficacy. An incremental cost-effectiveness model compared oral ibandronate with i.v. zoledronic acid and i.v. generic pamidronate in female breast cancer patients with metastatic bone disease, undergoing i.v. chemotherapy. *Methods:* A global economic model was adapted to the UK National Health Service (NHS), with primary outcomes of direct healthcare costs and quality-adjusted life years (QALYs). Efficacy, measured as relative risk reduction of skeletal-related events (SREs), was obtained from clinical trials. Resource use data for i.v. bisphosphonates and the cost of managing SREs were obtained from published studies. Hospital management and SRE treatment costs were taken from unit cost databases. Monthly drug acquisition costs were obtained from the British National Formulary. Utility scores were applied to time with/without an SRE to adjust survival for quality of life. Model design and inputs were validated through expert UK clinician review. *Results:* Total cost, including drug acquisition, was £386 less per patient with oral ibandronate vs. i.v. zoledronic acid and £224 less vs. i.v. generic pamidronate. Oral ibandronate gained 0.019 and 0.02 QALYs vs. i.v. zoledronic acid and i.v. pamidronate, respectively, making it the economically dominant option. At a threshold of £30,000 per QALY, oral ibandronate was cost-effective vs. zoledronic acid in 85% of simulations and vs. pamidronate in 79%. *Conclusions:* Oral ibandronate is a cost-effective treatment for metastatic bone disease from breast cancer due to reduced SREs, bone pain, and cost savings from avoidance of resource use commonly associated with bisphosphonate infusions.

Keywords Ibandronate · Metastatic bone disease · Cost-effectiveness · Zoledronic acid · Skeletal-related events

Introduction

Metastatic bone disease is a common and debilitating complication of cancer [1]. Bone metastases and their complications cause significant morbidity from severe bone pain, pathological fractures, spinal cord compression (associated with paralysis), and hypercalcaemia of malignancy, all of which can significantly impair a patient's functional status and quality of life (QoL) [1–3]. Bone metastases are particularly common in patients with multiple myeloma, prostate cancer, lung cancer, and breast cancer [1, 2, 4]. Over 40,000 women are newly diagnosed with breast cancer in the UK each year (2,000 figures [5]), and ~80% with advanced breast cancer will develop bone metastases at some point in their illness [6]. This represents a sigtnificant disease burden in the UK.

Skeletal complications, in particular, impose a significant economic burden on the healthcare system, largely from hospital stays, prophylactic bone surgery, and treatment for bone pain [7]. It is estimated that each year, 25–40% of patients with breast cancer will need radiotherapy for bone pain, whilst 17–50% will have vertebral fractures [7]. In a retrospective observational costing study of US patients with bone metastases from breast cancer, total medical care costs were more than US $52,000 higher in patients with skeletal-related events (SREs) than in patients with no SREs (US $119,798 vs. US $67,699, respectively, $P<0.001$). Total medical care costs directly attributable to SREs was reported to be US $14,580 per patient [8].

Current bisphosphonate therapy guidelines recommend ongoing treatment in patients with metastatic bone disease, from diagnosis of symptomatic bone metastases until death [9]. With an increased incidence in breast cancer cases and a simultaneous decline in mortality rates from this cause [5], it is expected that many more patients will undergo bisphosphonate therapies and for longer durations, often following the completion of chemotherapy regimens. Further, it is increasingly important to manage bone metastases effectively in order to minimise long-term skeletal morbidity, relieve pain, and improve quality of life.

Metastatic bone disease disturbs the normal metabolic balance between new bone formation by osteoblasts and resorption of old bone by osteoclasts. Bisphosphonates potently inhibit osteoclasts and bone resorption, interrupting bone destruction and decreasing the risk of skeletal complications. They are currently the standard treatment for metastatic bone disease [2, 10, 11].

Bisphosphonates have been shown to reduce the cost of treating SREs, such as vertebral fractures, and improve patient quality of life through relief of bone pain. However, long-term bisphosphonate therapy in malignancy is commonly regarded as expensive. Several cost-effectiveness analyses of bisphosphonates in metastatic bone disease have been performed using differing methodologies and assumptions.

DesHarnais Castel et al. [12] conducted a time and motion study as part of a clinical trial performed in the US to calculate resource use in intravenous (i.v.) zoledronic acid treatment compared with i.v. pamidronate in patients with metastatic bone disease. This microcosting analysis found that total direct administration costs were US $728 per patient per visit for zoledronic acid and US $776 for pamidronate. The average visit duration was 1 h 6 min for zoledronic acid, compared with 2 h 52 min for pamidronate. Infusion time accounted for most of the difference in visit time.

A post hoc cost-effectiveness analysis by Hillner et al. [13] was based on a hypothetical group of women meeting the entry criteria of two 24-month randomised clinical trials of pamidronate vs. placebo [14–16]. The authors concluded that whilst pamidronate was effective in reducing SREs, the incremental cost-effectiveness ratio (ICER) vs. placebo was very high [US $108,000 per quality-adjusted life year (QALY) gained] primarily due to drug-acquisition costs. Dranitsaris and Hsu [17] performed a cost–utility analysis of prophylactic pamidronate in metastatic breast cancer in Canada and found that i.v. pamidronate gave an incremental cost of Canadian $18,700 (US $14,025) per QALY gained. Although the authors compared this incremental cost favourably with that of other therapies [17], it showed that the high drug-acquisition costs of pamidronate were not totally offset by cost savings resulting from effective SRE management.

A more recent evaluation of the impact of pamidronate on medical resources used a retrospective chart review of breast cancer patients diagnosed with metastatic bone disease in usual clinical practice [18]. This study demonstrated that i.v. pamidronate may reduce the burden of metastatic bone disease on hospital resources by shortening inpatient stays, although the associated cost savings were not calculated.

In patients with multiple myeloma, Laakso et al. [19] reported that compared with placebo, oral clodronate significantly reduced the progression of osteolytic bone lesions, but did not significantly increase treatment costs. However, a more rigorous analysis suggested that clodronate therapy increased the cost of treatment by 17% (£3,400 over 4 years) [20]. The authors estimated that the extra cost would be offset by a 50% reduction in patients with severe hypercalcaemia, a 48% decrease in patients who developed nonvertebral fractures, an estimated 31% decrease in patients sustaining incident vertebral fractures, and a 45% reduction in the frequency of back pain at 24 months. However, the cost savings of these were not calculated.

In summary, the results of cost-effectiveness evaluations of bisphosphonates to date suggest that the benefits of therapy are only achieved at considerable cost to healthcare systems. The present paper is the first to report on the results of a cost-effectiveness analysis of oral ibandronate (Bondronat, also known as ibandronic acid), a third-generation aminobisphosphonate recently approved in the EU for the prevention of skeletal events in patients with breast cancer and bone metastases. In the UK, ibandronate is available in both i.v. and oral formulations that showed equivalent efficacy in preventing bone complications and reducing bone pain in 96-week clinical trials [21, 22]. We used a pharmacoeconomic model adapted to the perspective of the UK to assess the cost-effectiveness of oral ibandronate compared with i.v. zoledronic acid and i.v. pamidronate, in patients with metastatic bone disease from breast cancer receiving i.v. chemotherapy. The cost-effectiveness of oral ibandronate in patients with breast cancer receiving oral hormonal therapy is reported elsewhere [48].

Materials and methods

Model scope and perspective

The model estimated costs and benefits per patient over expected average survival, following an intent-to-treat approach, and produced a cost–utility analysis, with incremental cost per QALY as the primary outcome. The model is globally applicable, but for this analysis it was adapted to the perspective of the UK National Health Service (NHS). Only direct healthcare costs were considered, assuming a single funding source for all costs at the hospital level.

Average survival

Due to the absence of direct comparative survival data from the three bisphosphonates assessed in the model, the mean average survival for patients with metastatic breast cancer was assumed at 14.3 months, as used in a previous cost-effectiveness model of pamidronate vs. placebo [13–15]. As alternative survival times are likely to be of interest and relevant to the specific population under study, the effect of a longer survival period on cost-effectiveness was tested using sensitivity analysis.

Patient population

The analysis was undertaken for a cohort of women with breast cancer and metastatic bone disease, receiving i.v. chemxotherapy. Population characteristics were aligned with those of phase III trials of oral ibandronate in metastatic bone disease from breast cancer [22].

Key assumptions

– All patients will receive bisphosphonates for metastatic bone disease along with i.v. chemotherapy for breast cancer.
– Patients will receive 4 months of i.v. chemotherapy in six 3-weekly cycles, as is typical for patients with advanced metastatic breast cancer in the UK (expert UK clinician opinion).
– Since no cost differences are expected amongst i.v. chemotherapies, costs for these therapies are excluded.
– During and subsequent to the completion of i.v. chemotherapy (4 months onwards), i.v. bisphosphonate therapy requires hospital visits every month for infusion and monitoring (totalling 12 visits a year) vs. every 3 months (four visits a year) for the monitoring of patients receiving oral ibandronate.

Model inputs

Skeletal-related events

The key effectiveness driver in the model was the number of SREs for each treatment (Table 1). The mean numbers of SREs for each drug were not directly comparable because of differences in patient populations, time horizons, and efficacy measures (e.g. skeletal morbidity rate in zoledronic acid trials, which counts SREs occurring within a 21-day event window, vs. the skeletal-morbidity period rate for ibandronate, which calculates the rate of SREs as the number of bone complications occurring within a single 12-week period, divided by the number of 12-week periods on study) [21, 23–26]. Therefore, a baseline (placebo) level of 3.23 months with an SRE per patient was assumed, as used in a previous cost-effectiveness analysis [13]. Each drug's relative risk reduction for SREs was applied to this placebo value. The reduction rates for oral ibandronate 50 mg and i.v. pamidronate 90 mg were taken from published literature [22, 27]. As there is no comparative trial of i.v. zoledronic acid and placebo in metastatic bone disease from breast cancer, we assumed the same SRE relative risk reduction as used for oral ibandronate (Table 1). The time spent with/without an SRE over 14.3 months of survival was calculated for each treatment and the associated costs and quality of life weights applied. The duration of a single SRE was assumed to be 1 month [13].

Bone pain management

Bone pain is the main outcome of metastatic bone disease, and it is usually managed until the end of life. Reducing bone pain in patients with metastatic bone disease means that less money is spent on therapies for pain, such as palliative radiotherapy and analgesics. Radiotherapy cost was not included in the cost of pain management, as it was included in the SRE treatment cost.

Table 1 Model inputs: skeletal-related events

Drug	SRE relative risk reduction	Expected number of SREs	Months per patient with/without an SRE[a]
Placebo	NA	3.23 [13]	NA
Oral ibandronate	38% [21]	2.00	2.00/12.30
I.v. zoledronic acid	38%[b]	2.00	2.00/12.30
I.v. pamidronate	35% [27]	2.49	2.45/11.85

NA Not applicable
[a]Assuming 14.3-month survival
[b]Assuming same SRE efficacy as oral ibandronate, based on expert opinion

Table 2 Model inputs: utilities

Parameter	Value	Reference
Baseline utility for patient with metastatic bone disease	0.4	[44]
Reduction in baseline utility due to SRE	30%	[13]
Utility for a month with an SRE	0.28	NA (calculated)
Estimated increase in baseline utility when using oral ibandronate	0.02	NA (estimate)
Utility for an SRE-free month when receiving oral ibandronate	0.42	NA (calculated)
Utility for an SRE-free month when receiving i.v. pamidronate or i.v. zoledronic acid	0.40	[44]

The base case values for the proportion of patients with placebo receiving each type of medication and dosing/duration over a period of 12 months came from expert clinician opinion. A monthly cost was calculated and multiplied by the survival time to yield the total cost of analgesic use for patients not receiving treatment. For each bisphosphonate, the reduction in analgesic score was estimated from published literature [23, 27–30] and was assumed to reflect the reduction in analgesic use. These reductions were applied to placebo data to calculate reduced analgesic consumption over the assumed survival period. Pain from SREs was not considered, as this was covered by the SRE episode cost.

The average percentage point reduction in analgesic use scores for oral ibandronate (vs placebo) was assumed to be 7%, as estimated from the change in analgesic scores from baseline to 96 weeks in a phase III trial [22, 28]. As comparable data were not available for other bisphosphonates, a 3% reduction in analgesic consumption was estimated from published literature and supported by expert clinician opinion [23, 27, 29, 30].

Quality of life values

Bisphosphonates have incremental benefits that might be reflected in maintained quality of life (QoL) related to avoidance of SREs and/or reduction in bone pain. In order to reflect these benefits in the economic model, we used the QALY, an outcomes measure that involves a weighting of years of life by QoL (in utilities) [31]. To calculate QALYs, the amount of time spent in a health state is weighted by its utility score on a continuum between 0 (death) and 1 (best possible health state). One year of perfect health (utility score=1) equals one QALY.

The time with and without SREs was adjusted for QoL using the utility estimates presented in Table 2, resulting in a total QALY value. van Hout et al. [32] reported a baseline average utility value of 0.40 for a month without an SRE for patients with metastatic bone disease who are not receiving a bisphosphonate. As no utility score was given for an SRE, we assumed a 30% reduction in QoL (as in Hillner et al. [13]), generating a utility score of 0.28.

As no published data were available on how a reduction in bone pain affects overall utility in metastatic bone disease patients, we assumed a utility value of 0.42 with oral ibandronate due to bone pain relief (significantly reduced below baseline for 2 years in phase III trials) [28]. We consider a 0.02 (5%) increase in utility over placebo to be a conservative estimate, given the overall impact of pain on QoL in these patients [2, 3]. Although pamidronate and zoledronic acid reduced bone pain below baseline for 1 year in metastatic breast cancer patients [23], these reductions were not statistically significant or reported during the 2-year follow-up [24]. Bone pain levels increased from baseline in other pamidronate trials over time [27]. We therefore assumed no improved utility due to bone pain relief with these bisphosphonates, and this assumption was further supported by expert clinician opinion.

Drug safety: effect on continuation/discontinuation and costs

Discontinuation can occur because of a drug-related adverse event or noncompliance. The termination of effective treatment will likely be followed by an increase in incidence of SREs. The discontinuation rate of 3.2% (nine out of 286 reported adverse events) for oral ibandronate was taken from phase III trials [33]. According to Li and Davis [34], ~6 to 7% of patients on i.v. zoledronic acid discontinued treatment due to treatment-related adverse events, but based on expert physician opinion, this was lowered to 4%. In the absence of published data, the discontinuation rate for i.v. pamidronate was assumed at 2%, as reported for i.v. ibandronate [21]. We assumed discontinuation for drug-related adverse events to occur at 1 month.

Base case values for early discontinuation due to noncompliance were obtained from expert UK clinician opinion. We assumed that after 6 months of bisphosphonates, 25% of patients would decline further i.v. treatment because of the inconvenience of monthly hospital visits. Of those who discontinued, an estimated 50% of patients would switch to oral ibandronate, with the rest stopping all bisphosphonate treatment. We assumed that there would be no early discontinuation with oral ibandronate, as it does not have the inconvenience of i.v. bisphosphonates (monthly infusion). The probabilities for treatment discontinuation used in the base case cost-effectiveness analysis are shown in Table 3.

The model took into account the potential impact of renal impairment on treatment-related costs. Only drug-related renal toxicity was considered. Renal toxicity was the only

Table 3 Probabilities of treatment continuation used in base case cost-effectiveness analysis

	Probabilities of continuation (%)			Time point
	Oral ibandronate	I.v. zoledronic acid	I.v. pamidronate	
Patient continued	96.9	71.0	73.0	Over survival
Switching to oral ibandronate after failed compliance	0.0	12.5	12.5	At 6 months
Discontinuation after adverse events	3.2	4.0	2.0	At 1 month
Discontinuation after failed compliance	0.0	12.5	12.5	At 6 months
Total	100	100	100	

serious adverse event with zoledronic acid in phase III trials of patients with breast cancer, multiple myeloma, prostate cancer or other solid tumours [35], affecting 8.8–15.2% of patients compared with 6.7–11.5% of those given placebo. Due to the absence of a placebo-controlled trial for zoledronic acid in breast cancer, we applied the 9% risk of renal impairment over 1 year of treatment from the breast cancer and multiple myeloma trial [23] to the placebo rate of renal impairment from the i.v. and oral ibandronate breast cancer trials (4%) at 1 year [36], resulting in an estimated 5% incidence for zoledronic acid. The same definition of renal impairment was used in each study (serum creatinine increases to 0.5 mg/dl from baseline, if baseline serum creatinine was <1.4 mg/dl; 1.0 mg/dl from baseline, if baseline serum creatinine was ≥1.4 mg/dl, or twice the baseline value). The model also incorporated a probability of renal failure (0.015%) with zoledronic acid to assess its impact on treatment-related costs. This probability was based on the incidence of renal failure in a recent review of the Food and Drug Administration Adverse Event Reporting system over an 18-month period [37].

No additional risk of drug-related renal impairment or failure was assumed for oral ibandronate. This was based on phase III trial data showing an incidence comparable with placebo in patients with breast cancer and bone metastases [33]. Additionally, there have been no reports of renal failure with the recommended doses for metastatic bone disease in clinical practice.

The incidence of renal impairment with i.v. pamidronate was 8% in the noninferiority trial of zoledronic acid and pamidronate for patients with bone metastases from breast cancer or multiple myeloma [23]. However, the prescribing information for i.v. pamidronate only reports a risk of renal deterioration in patients with multiple myeloma, rather than breast cancer (the target population of the model) (Aredia SmPC). Renal dysfunction was not reported as an adverse event in the placebo-controlled breast cancer trials [27]. Therefore, the model conservatively assumed no additional risk of renal toxicity with i.v. pamidronate, as for ibandronate. This was supported by expert clinician opinion.

Resource use

Total resource use and resource time (staff time) for bisphosphonate administration was obtained from a US micro-costing study [12]. A UK clinician validated the resource time for the UK setting. Healthcare professional (e.g. nurse) time for bisphosphonate infusions was assumed to be the same for each patient (22 min and 30 s), irrespective of the drug received. Although recommended infusion times differ between bisphosphonates (e.g. 1 h for ibandronate, 15 min for zoledronic acid and 90 min for pamidronate), it was assumed that nurses can treat multiple patients at the same time and are free to carry out other tasks once i.v. lines have been inserted. The choice of 22 min 30 s was based on an infusion time for pamidronate of 90 min and expert opinion suggesting that nurses administering lengthy infusions can treat up to four patients in a clinic suite at any one time.

Unit costs

Tables 4 and 5 show the unit costs of the healthcare resources. These came from a variety of sources, including the Unit Costs of Health and Social Care [28], and the UK section of an international unit cost database [39]. Unit costs were applied to SRE management, i.v. bisphosphonate administration, laboratory tests, renal impairment or failure, and drug acquisition.

Clinical trials of ibandronate, zoledronic acid, and pamidronate defined SREs as pathological fracture, spinal cord compression, radiation therapy, and surgery to bone. For the model, we estimated a total cost of SRE management from NHS average costs for pathological fracture due to

Table 4 Unit costs used in the model

	Unit cost	Source
SRE management		
Pathological fracture and radiotherapy	£2,351	NHS reference costs 2003 [45]
I.v. administration costs		
Personnel		
Physician	£90	PSSRU [38]
Pharmacy technician	£11	http://www.yahoo.workthing.com
Nurse	£18	PSSRU [38]
Auxiliary nurse	£10	PSSRU [38]
Supplies		
Needle	£0.07	http://www.medisave.co.uk
Gauze	£0.05	http://www.medisave.co.uk
Alcohol swab	£0.02	http://www.medisave.co.uk
Syringe	£0.08	http://www.medisave.co.uk
Set of gloves	£0.05	http://www.medisave.co.uk
Medical tape	£0.03	http://www.medisave.co.uk
Sample tubes	£0.05	http://www.medisave.co.uk
Disposable i.v. set	£2.50	UK hospital
Piggyback connector	£0.24	http://www.medisave.co.uk
250 ml of 5% dextrose solution	£8.15	BNF 46 [46]
Laboratory tests		
Biochemistry plus haemogram test	£25.66	MEDTAP unit cost database [39]
Renal failure		
Home dialysis (per year)	£19,985	NICE appraisal guidance 48 [47]
Hospital dialysis (per year)	£22,781	NICE appraisal guidance 48 [47]
Home dialysis (per session)	£128	NICE appraisal guidance 48 [47]
Hospital dialysis (per session)	£146	NICE appraisal guidance 48 [47]
Renal impairment (per week)	£57	BNF 46 [46]

malignancy of bone and connective tissue using 2003 NHS reference costs for both inpatient and outpatient care combined. This included elective and nonelective care, and patients either with or without complications for pathological fracture codes, for diagnosis codes H53 and H54. These costs include all services provided to patients in these two diagnostic groups including the management of fractures with surgery and radiotherapy. It should be noted that the radiotherapy cost excluded transport to attend the radiotherapy department.

Sensitivity analyses

One-way sensitivity analyses

We conducted one-way sensitivity analyses to vary key assumptions that might reduce the QALY and cost-effectiveness advantage of oral ibandronate over the other i.v. bisphosphonates, compared with the base case. The following scenarios were included:

Table 5 Medication costs

	Cost per package[a] (£)	Package size	Dose per unit	28-day cost per unit (£)
Oral ibandronate 50 mg/day			50 mg	195
I.v. zoledronic acid (4 mg q3–4 weeks)			4 mg	195
I.v. generic pamidronate (90 mg q3–4 weeks)			90 mg	165
rHuEPO (Eprex)	50	Six syringes	0.5 ml	8.38
ACE inhibitors (Captopril)	3	56	12.5 mg	0.06
Morphine (MST continua)	15	60	30 mg	0.24
Oxycodone (Oxycontin)	21	56	30 mg	0.38
Paracetamol (Remedeine)	12	112	500 mg	0.11
Ibuprofen (Brufen)	12	100	600 mg	0.12

[a]BNF 46 [46]

- prolonged survival of 24 months (base case 14.3 months);
- no QoL advantage for ibandronate (base case assumes a 0.02 increase in baseline utility for a month without an SRE and no advantage for the alternative drugs);
- same QoL advantage of 0.02 increase in baseline utility for all options;
- 100% compliance/no discontinuation (base case assumes that some patients will stop i.v. bisphosphonates due to drug-related adverse events or noncompliance);
- similar 2% rate of discontinuation due to treatment-related adverse events for all bisphosphonates, and no renal impairment (rather than renal impairment assumed to be related to zoledronic acid only);
- nursing cost directly correlated to length of infusion (rather than a nurse time of 22 min and 30 s per patient); and
- 50% decrease in SRE treatment cost vs. the base case.

Probabilistic analysis

A probabilistic sensitivity analysis was performed to account for uncertainty in the model parameters. This method handles uncertainly in the cost-effectiveness results by assigning each parameter a distribution and undertaking repeated Monte Carlo simulations of the cost-effectiveness analysis. Five thousand simulations were undertaken, and for each threshold value of a QALY gained, the probability of the results being cost-effective was calculated [32].

Results

Base case analysis

Table 6 and Fig. 1 show this model's simulated results for a patient receiving a bisphosphonate and i.v. chemotherapy for metastatic bone disease from breast cancer. With a survival period of 14.3 months, the model projected that the total cost of treatment (including drug acquisition), renal failure, SREs, and pain management was £386 less per patient with oral ibandronate than with zoledronic acid and £224 less than with i.v. generic pamidronate.

Taking a reduction in utility due to SREs into account and an increase in baseline utility with ibandronate if without an SRE, oral ibandronate led to a gain of 0.019 and 0.020 QALYs compared with zoledronic acid and generic pamidronate, respectively (corresponding to an additional 6.9 and 7.2 quality-adjusted life days, respectively;

Table 6 Base case cost-effectiveness results

	Oral ibandronate	I.v. zoledronic acid	I.v. pamidronate
Cost per patient			
Drug acquisition (if drug continued)	£2,701	£1,980	£1,722
Personnel and supply (if drug continued)	£0	£310	£318
Monitoring (if drug continued)	£29	£206	£173
Bisphosphonate treatment (switch to oral ibandronate)	£0	£388	£363
Bisphosphonate (discontinued)	£6	£194	£163
Renal impairment and failure	£0	£34	£0
SREs	£4,708	£4,708	£4,919
Pain management	£249	£259	£259
TOTAL cost per patient	£7,693	£8,079	£7,917
Saving vs. zoledronic acid	£386		
Saving vs. pamidronate	£224		
SRE events			
Months per patient with an SRE	2.00	2.00	2.09
Months per patient without SRE	12.30	12.30	12.21
Additional SRE-free months vs. zoledronic acid	0.00		
Additional SRE-free months vs. pamidronate	0.09		
Quality-adjusted end points			
QALYs with SREs (months)	0.56	0.56	0.59
QALYs without SREs (months)	5.16	4.94	4.90
Total quality-adjusted life months	5.73	5.50	5.49
Total QALYs	0.477	0.458	0.457
Additional QALYs vs. zoledronic acid	0.019 (6.9 days)		
Additional QALYs vs. pamidronate	0.020 (7.2 days)		

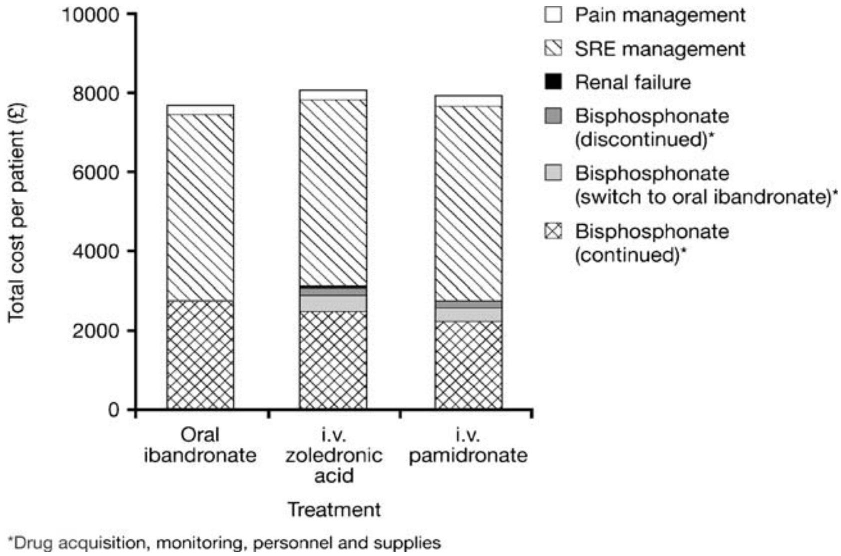

Fig. 1 Direct cost of treatment with oral ibandronate vs. i.v. zoledronic acid and i.v. generic pamidronate

Table 6). Based on these data, the incremental cost-effectiveness ratio (ICER) showed oral ibandronate to be the dominant treatment option.

Sensitivity analyses

One-way analysis

Table 7 provides a summary of the results of the one-way sensitivity analyses, which showed that:

– 24-month survival (rather than 14.3 months) increases the time in which a patient is not having chemotherapy, so the incremental cost advantage of an oral ibandronate over zoledronic acid rose from £386 per patient in the base case to £493 per patient;
– with an equal utility score of 0.40 when no SRE for all treatments, oral ibandronate still gave a higher number of QALYs in the timeframe of the model vs. pamidronate, due to a slightly greater risk reduction for SREs;
– oral ibandronate remained dominant when 100% compliance/no discontinuation was assumed;
– with a 2% rate of discontinuation due to treatment-related adverse events for all bisphosphonates, and no renal toxicity (rather than renal toxicity assumed for zoledronic acid only), results for oral ibandronate vs. zoledronic acid were similar to the base case results, as the absence of renal toxicity would mean patients would receive i.v. zoledronic acid for longer, increasing treatment costs;
– if the nurse was assumed to stay with the patient throughout the whole infusion (rather than for 22 min

Table 7 Sensitivity analysis of oral ibandronate compared with i.v. zoledronic acid and i.v. pamidronate (INB, ∆cost, ∆benefit)

Base case	Oral ibandronate vs. i.v. zoledronic acid £951 (£−386, 0.019)	Oral ibandronate vs. i.v. pamidronate £816 (£−224, 0.020)
Prolonged survival of 24 months	£1,413 (£−493, 0.031)	£1,216 (£−248, 0.032)
No QOL advantage for oral ibandronate	£386 (£−386, 0.000)	£250 (£−223, 0.001)
Similar 2% adverse event discontinuation rate and no renal toxicity	£953 (£−387, 0.019)	£787 (£−194, 0.020)
100% compliance	£1,308 (£−693, 0.020)	£1,121 (£−477, 0.021)
Nursing cost correlated with licensed infusion time[a]	£925 (£−360, 0.019)	£1,059 (£−466, 0.020)
50% reduction in SRE treatment cost	£951 (£−386, 0.019)	£711 (£−118, 0.020)

[a] 1 h for ibandronate, 1.5 h for pamidronate, 15 min for zoledronic acid

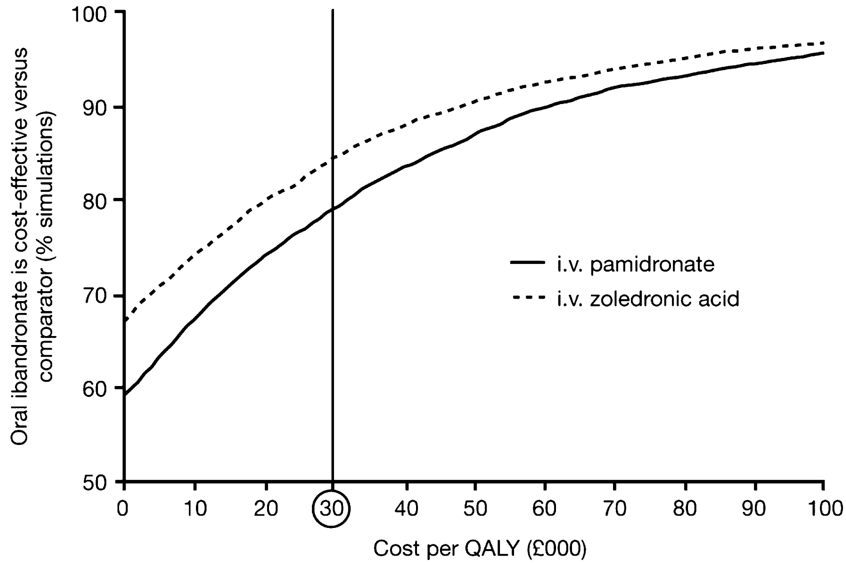

Fig. 2 Cost-effectiveness acceptability curve for oral ibandronate vs. i.v. zoledronic acid and generic pamidronate

30 s with each bisphosphonate), staff cost increased with i.v. generic pamidronate, making oral ibandronate more dominant. A zoledronic acid infusion time of 15 min reduced staff costs, but the cost-effectiveness of oral ibandronate remained dominant; and

– assuming a 50% decrease in SRE treatment cost vs. base case, results were less dominant for oral ibandronate vs. pamidronate, as cost savings decreased by ~50% compared with the base case. There was no drop in cost savings vs. zoledronic acid, because of the similar number of expected SREs for ibandronate and zoledronic acid.

All one-way sensitivity analyses showed a positive incremental net benefit (INB), which implies that our results remained cost-effective versus the comparators given a cost-effectiveness threshold of £30,000 per QALY.

Probabilistic analysis

Using pairwise comparisons, the cost-effectiveness acceptability curves showed that at a cost per QALY of £30,000, oral ibandronate was the cost-effective strategy in 85% of simulations vs. zoledronic acid and 79% of simulations vs. i.v. pamidronate (Fig. 2).

Discussion

The model projects that the total costs per patient of oral ibandronate treatment are less than for i.v. bisphosphonates for metastatic bone disease due to breast cancer. As the benefits in QALYs gained are greater for oral ibandronate than for other i.v. bisphosphonates, it is the dominant treatment option in this indication.

The model assumed that patients would receive six 3-weekly cycles of i.v. chemotherapy (during a 4-month period), as is typical in the UK for patients with advanced breast cancer and bone metastases (expert clinician opinion). It might be expected that i.v. bisphosphonate infusions would be cost-effective in these patients, as they can be given at the chemotherapy visit. However, as the modelling results show, oral ibandronate is cost-effective compared with i.v. bisphosphonates over the assumed duration of survival (14.3 months). This result occurs since we assume that bisphosphonate therapy will be continued beyond the time when the patient would receive chemotherapy (e.g. from diagnosis until the end of life), requiring additional hospital visits for the infusional bisphosphonate patients. These patients would use considerable healthcare personnel time and resources (particularly for safety monitoring), increasing the overall cost of care and reducing capacity for alternative treatments and activities compared to an oral bisphosphonate. Consequently, the cost savings of oral ibandronate increased further when the assumed survival duration was extended to 2 years, as patients would continue to visit hospital for i.v. bisphosphonate infusions in the 20 months following the completion of chemotherapy.

The drug acquisition costs for all bisphosphonates in the model were taken from the British National Formulary. As more generic supplies become available, it is likely that the cost of pamidronate in the UK will fall in the future. Using the current model, the cost of generic pamidronate would have to decrease below £146 per month before ibandronate stops being cost-saving. However, the outcomes would remain slightly better for oral ibandronate vs. i.v. pamidronate.

Another key driver in the model was the cost of managing SREs (£2,351 per patient). This was estimated from NHS reference costs for the management of pathological fractures, with or without complications, incorporating interventions such as bone surgery and radiotherapy. Whilst the cost of radiotherapy alone may have been a suitable choice (as the most common form of treatment), no standard probabilities for the use of radiotherapy in patients with bone metastases (and associated costs) were available from a published source. For completeness and to ensure face validity, the pathological fracture cost included patient-elective surgery, although the majority of procedures are likely to be nonelective. Therefore, to account for the possibility that the management cost chosen for SREs was high, a sensitivity analysis was conducted to reduce it by 50%. This halved the overall cost advantage of oral ibandronate vs. i.v. pamidronate, although oral ibandronate remained dominant.

The model assumed that zoledronic acid had a risk of renal impairment, with extra costs for patient safety monitoring (serum creatinine) and managing adverse events. In the absence of placebo-controlled trial data for zoledronic acid, the rate of impairment in the trial of patients with breast cancer and multiple myeloma [23] was applied to a placebo rate from ibandronate trials, using identical serum creatinine increase criteria. It is possible that the rate for zoledronic acid was subsequently overestimated, as the patients who had multiple myeloma might be expected to be at greater risk of renal function deterioration than those with breast cancer. However, myeloma patients made up less than one third of the study population [23] and given the higher incidence of renal dysfunction in other zoledronic acid trials [38] and in clinical practice [40, 41], the 5% risk was deemed to be fairly conservative.

The assumption that i.v. zoledronic acid is linked (albeit rarely) to a risk of drug-related renal failure came from a published study superseding the clinical trials [37]. The 0.015% incidence of renal failure from this paper was used in the model, and unit costs for the management of this condition were applied. The base case analysis showed that the costs of renal toxicity management were relatively low (£34 per patient). However, we examined the impact of a similar incidence of renal failure for oral ibandronate, zoledronic acid, and pamidronate (set at 0%) on the cost-effectiveness results, using one-way sensitivity analysis. This analysis was deemed relevant because precautions for the use of i.v. zoledronic acid (e.g. serum creatinine monitoring prior to each dose) (Zometa SmPC) are recommended to reduce the renal toxicity risk. The results of the sensitivity analysis suggested that oral ibandronate would still be the economically dominant option, primarily due to the avoidance of healthcare professional, supply, and monitoring costs associated with zoledronic acid infusion. Assuming that the absence of renal impairment increased the rate of continuation in the zoledronic acid group, the overall cost of treatment increased and more than offset the costs saved by avoiding renal failure management.

The model did not assume a rate of discontinuation due to noncompliance with oral ibandronate, due to the convenience of once-daily dosing of a single tablet at home. Whilst noncompliance can be an issue with oral therapy due to occasional missed doses, preclinical models of the bone exposure of ibandronate suggest that this will not significantly affect clinical outcome (Hoffmann-La Roche, data on file).

Most of the extra costs of generic pamidronate were from SRE management, as the model assumed that oral ibandronate would give more SRE-free months. The model was unavoidably limited by its reliance on post hoc analysis of SRE data from published clinical trials of bisphosphonates in metastatic bone disease. Because there were no direct comparative data, and no placebo-controlled trials for zoledronic acid in metastatic breast cancer, we applied the risk reduction of SREs with each bisphosphonate to a placebo rate of SREs in patients receiving chemotherapy for breast cancer in a randomised trial [14, 15]; as applied by Hillner et al. [13]). In an attempt to overcome the limitations of this methodology, we used SRE risk reduction rates from a pooled analysis of randomised, placebo-controlled trials of i.v. pamidronate 90 mg [27] and assumed comparable SRE efficacy for i.v. zoledronic acid and oral ibandronate.

Estimates for analgesic use and bone pain reductions also had to be taken from separate clinical studies. Other assumptions in the model were based on local expert opinion and therefore subjective. However, the one-way and probabilistic sensitivity analyses suggested that oral ibandronate would remain cost-effective when several parameters, such as adverse event discontinuation rates and QOL, were varied.

Although the recommended infusion times for i.v. zoledronic acid and i.v. pamidronate differ (15 vs. 90 min, respectively), the model assumed that nurses would spend an equal amount of time with patients receiving either bisphosphonate, as they would be able to conduct other tasks whilst pamidronate infusions are ongoing (based on expert clinician opinion). Sensitivity analysis showed that oral ibandronate remained cost-effective, due to lower hospital resource use (no bisphosphonate administration, and three monthly visits rather than monthly visits for infusions).

The cost-effectiveness of ibandronate has also been examined in patients with bone metastases and breast cancer receiving oral hormonal therapy, using a second economic model [42]. The results show that oral ibandronate is cost-effective in this clinical setting. The availability of two ibandronate formulations improves choice for healthcare payers and gives clinicians the flexibility to adjust treatment regimens to patients' individual circumstances (e.g. i.v. bisphosphonates whilst in hospital for chemotherapy, and oral bisphosphonates with oral hormonal therapy at home). The cost-effectiveness of oral ibandronate might be expected to increase for patients who have completed i.v. chemotherapy due to the avoidance of hospital visits for bisphosphonate infusions (reducing the burden of bisphosphonate treatment on nurses and available resources). For patients, this formulation also offers once-daily dosing, gastrointestinal tolerability, and a small tablet that is easy to take. Unlike in clodronate trials, no patients receiving oral ibandronate in phase III studies withdrew due to difficulty in swallowing the tablets [22, 43].

The model we have described includes only the direct healthcare cost of bisphosphonates, assuming a single funding source for all costs at the hospital level. It would be interesting to investigate the impact of oral ibandronate on indirect costs, such as lost productivity for patients and caregivers due to SREs and significant disability from metastatic bone pain. Other indirect costs exclusive to i.v. bisphosphonates include out-of-pocket expenses (such as travel costs) and leisure time for patients travelling for bisphosphonate infusions. As the model was constructed from a global perspective and applied to the UK NHS, it also remains to be evaluated whether oral ibandronate would be cost-effective in other countries, where treatment practices for metastatic bone disease may be different from those in the UK. For example, the cost-effectiveness of oral ibandronate vs. i.v. bisphosphonates would be reduced if a longer duration of i.v. chemotherapy was assumed, as is typical in some other European countries. Between-country variations in management approaches to vertebral fractures are also likely. Further international analysis of the cost-effectiveness of bisphosphonates using this model is warranted.

Conclusion

From the perspective of the UK NHS, oral ibandronate has been shown in this study to be a highly cost-effective treatment option when compared with i.v. zoledronic acid or i.v. generic pamidronate for treating bone metastases in breast cancer patients receiving i.v. chemotherapy. Oral ibandronate effectively prevents fractures, relieves bone pain, and has a favourable safety profile with minimal discontinuation, and avoidance of renal impairment that has been reported for i.v. zoledronic acid. Use of oral ibandronate also avoids the cost and resource burden of the administration and monitoring, and clinic visits associated with bisphosphonate infusions.

In particular, the oral therapy should provide further resource advantages once the patient has completed i.v. chemotherapy, with respect to a reduction in the number of required clinic visits and resource use related to infusions. The availability of both oral and i.v. regimens of ibandronate allows for the switching of patients to the oral regimen upon completion of i.v. chemotherapy. Indirect advantages, with respect to a reduction in patient and caregiver burden, should also be expected.

References

1. Coleman RE (1997) Skeletal complications of malignancy. Cancer 80(8 Suppl):1588–1594
2. Coleman RE (2001) Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 27(3):165–176
3. Diel IJ, Solomayer EF, Bastert G (2000) Treatment of metastatic bone disease in breast cancer: bisphosphonates. Clin Breast Cancer 1(1):43–51
4. Janjan N (2001) Bone metastases: approaches to management. Semin Oncol 28(4 Suppl 11):28–34
5. Cancer Research UK. http://www.cancerresearchuk.org/
6. Scheid V, Buzdar AU, Smith TL et al (1986) Clinical course of breast cancer patients with osseous metastasis treated with combination chemotherapy. Cancer 58:2589–2593
7. Body J-J (2003) Effectiveness and cost of bisphosphonate therapy in tumor bone disease. Cancer 97(3 Suppl):859–865
8. Delea T, McKiernan J, Liss M et al (2004) Effects of skeletal complications on total medical care costs in women with bone metastases of breast cancer. Bone 34(Suppl 1):S86 (abstract 68)
9. Hillner BE, Ingle JN, Chlebowski RT et al (2003) American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol 21:4042–4057
10. Van Poznak CH (2002) The use of bisphosphonates in patients with breast cancer. Cancer Control 9(6):480–489
11. Body JJ, Bartl R, Burckhardt P, For the International Bone and Cancer Study Group et al (1998) Current use of bisphosphonates in oncology. J Clin Oncol 16:3890–3899
12. DesHarnais Castel L, Bajwa K, Markle JP, Timbie JW, Zacker C, Schulman KA (2001) A microcosting analysis of zoledronic acid and pamidronate therapy in patients with metastatic bone disease. Support Care Cancer 9(7):545–551
13. Hillner BE, Weeks JC, Desch CE, Smith TJ (2000) Pamidronate in prevention of bone complications in metastatic breast cancer: a cost-effectiveness analysis. J Clin Oncol 18 (1):72–79
14. Hortobagyi GN, Theriault RL, Porter L et al (1996) Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. N Engl J Med 335(24):1785–1791
15. Hortobagyi G, Theriault R, Lipton A et al (1998) Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. J Clin Oncol 16:2038–2044
16. Theriault RL, Lipton A, Hortobagyi GN et al (1999) Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. J Clin Oncol 17 (3):846–854

17. Dranitsaris G, Hsu T (1999) Cost utility analysis of prophylactic pamidronate for the prevention of skeletal related events in patients with advanced breast cancer. Support Care Cancer 7(4):271–279
18. Beusterien KM, Hill MC, Ackerman SJ, Zacker C (2001) The impact of pamidronate on inpatient and outpatient services among metastatic breast cancer patients. Support Care Cancer 9 (3):169–176
19. Laakso M, Lahtinen R, Virkkunen P, Elomaa I (1994) Subgroup and cost-benefit analysis of the Finnish multicentre trial of clodronate in multiple myeloma. Finnish Leukaemia Group. Br J Haematol 87(4):725–729
20. Bruce NJ, McCloskey EV, Kanis JA, Guest JF (1999) Economic impact of using clodronate in the management of patients with multiple myeloma. Br J Haematol 104(2):358–364
21. Body J-J, Kanis J, Diel I, Bergstrom B (2003) Risk reductions in metastatic breast cancer: multivariate Poisson regression analyses of oral and i.v. ibandronate. Proc Am Soc Clin Oncol 22:46 (abstract 184)
22. Body J-J, Diel IJ, Lichinitzer M et al (2004a) Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomised, placebo-controlled phase III studies. Br J Cancer 90(6):1133–1137
23. Rosen LS, Gordon D, Kaminski M et al (2001) Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. Cancer J 7(5):377–387
24. Rosen LS, Gordon D, Kaminski M et al (2003a) Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. Cancer 98:1735–1744
25. Rosen LS, Gordon D, Tchekmedyian S et al (2003b) Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial—the Zoledronic Acid Lung Cancer and other solid tumors study group. J Clin Oncol 21:3150–3157
26. Saad F (2002) Zoledronic acid significantly reduces pathologic fractures in patients with advanced-stage prostate cancer metastatic to bone. Clin Prostate Cancer 1:145–152
27. Lipton A, Theriault RL, Hortobagyi GN et al (2000) Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. Cancer 88(5):1082–1090
28. Tripathy D, Body J-J, Diel IJ, Bergstrom B (2003) Intravenous and oral ibandronate alleviate pain in patients with skeletal metastases from breast cancer. Breast Cancer Res Treat 82(Suppl 1):S133–S134 (abstract 548)
29. Fulfaro F, Casuccio A, Ticozzi C, Ripamonti C (1998) The role of bisphosphonates in the treatment of painful metastatic bone disease: a review of phase III trials. Pain 78(3): 157–169
30. Berenson JR (2001) Zoledronic acid in cancer patients with bone metastases: results of phase I and II trials. Semin Oncol 28(2 Suppl 6):25–34
31. Drummond MF, O'Brien BJ, Stoddart GL, Torrance GW (1997) Methods for the economic evaluation of health care programmes, 2nd edn. Oxford University Press, Oxford
32. van Hout BA, Al MJ, Gordon GS, Rutten FF (1994) Costs, effects and C/E-ratios alongside a clinical trial. Health Econ 3:309–319
33. Diel I, Bell R, Tripathy D, Body J-J, Bergstrom B (2003) Renal safety of oral and intravenous ibandronate in metastatic bone disease: phase III clinical trial results. Support Care Cancer 11:415 (abstract A-106)
34. Li EC, Davis LE (2003) Zoledronic acid: a new parenteral bisphosphonate. Clin Ther 25(11):2669–2708
35. Ibrahim A, Scher N, Williams G et al (2003) Approval summary for zoledronic acid for treatment of multiple myeloma and cancer bone metastases. Clin Cancer Res 9(7):2394–2399
36. Body J, Diel I, Bergström B (2004b) Intravenous ibandronate does not affect time to renal function deterioration in patients with metastatic bone disease from breast cancer. Support Care Cancer 12:405 (A-120)
37. Chang JT, Green L, Beitz J (2003) Renal failure with the use of zoledronic acid. N Engl J Med 349:1676–1679
38. PSSRU (2003) Unit costs of health and social care 2003. University of Kent at Canterbury, Canterbury
39. MEDTAP International (2003) MEDTAP Unit Cost Database
40. Johnson KB, Gable P, Kaime EM, Luiken G, Castillos T, Hu J (2003) Significant deterioration in renal function with the new bisphosphonate, zoledronic acid. Proc Am Soc Clin Oncol 22:738 (abstract 2968)
41. Mazj S, Lichtman SMI (2004) Renal dysfunction associated with bisphosphonate use: retrospective analysis of 293 patients with respect to age and other clinical characteristics. Proc Am Soc Clin Oncol 23:735 (abstract 8039)
42. De Cock E, Hutton J, Barrett-Lee P et al (2004) Cost-effectiveness analysis of oral ibandronate versus i.v. zoledronic acid or i.v. generic pamidronate for bone metastases from breast cancer in patients receiving oral hormonal therapy in the UK. EU ISPOR 2004 (submitted for publication)
43. Powles T, Paterson S, Kanis JA et al (2002) Randomized placebo-controlled trial of clodronate in patients with primary operable breast cancer. J Clin Oncol 20:3219–3224
44. van den Hout WB, van der Linden YM, Steenland E et al (2003) Single- versus multiple-fraction radiotherapy in patients with painful bone metastases: cost-utility analysis based on a randomized trial. J Natl Cancer Inst 95(3):222–229
45. NHS Reference Costs 2003 and National Tariff 2004. Appendix 4—National schedule of reference costs: NHS trusts and primary care trusts combined. http://www.dh.gov.uk/
46. British National Formulary 46. http://www.bnf.org/bnf/. March 2004
47. NICE Appraisal Guidance 48
48. Verrill M, De Cock E, Hutton J, Body JJ, Canney P, Neary M, Lewis G (2004) Medical resource use and costs for oral ibandronic acid compared to i.v. zoledronic acid or i.v. pamidronate for metastatic bone disease from breast cancer. Ann Oncol 15(Suppl. 3): iii51: (Abstract 192P)