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Extended Safety Profile of Oral Clodronate After Long-Term Use in Primary Breast Cancer Patients

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Abstract

Introduction: Long-term safety and tolerance is paramount when treating women who are otherwise healthy after the primary adjuvant therapy of breast cancer. Efficacy and limited safety results of a large-scale clinical trial, using adjuvant oral clodronate to prevent bone metastases in primary breast cancer patients, have been reported previously, demonstrating a reduction in the rate of bone metastases during treatment. Here we present expanded safety and tolerability results for clodronate treatment from this trial (cut-off date extended from June 1997 to June 2000).

Study Design and Methods: For this randomised, double-blind, placebo-controlled, multicentre study, patients were enrolled and randomised to receive oral clodronate (Bonefos®) 1600 mg/day or placebo for 2 years. The total median treatment period plus follow-up was 5.5 years. Adverse events (AEs) and laboratory parameters were followed up regularly for the total study period. The 95% CIs were estimated for the difference in the rate of AEs between the treatment groups.

Patients: A total of 1079 women with primary operable breast cancer were enrolled to the study; 538 received clodronate and 541 received placebo.

Results: Overall incidence of AEs (96.5% of the patients) was the same in both treatment groups, although gastrointestinal disorders were significantly more frequent in the clodronate group during the total study period (66% vs 56.2%; 95% CI 4.0–15.6; $p < 0.05$). This was mainly due to an increase in non-severe diarrhoea beginning 3–4 months after treatment start. Serious AEs (SAEs) were reported for 39.4% of the patients receiving clodronate and 44.5% of those receiving placebo; no drug-related (clodronate or placebo) SAEs were identified. Clodronate significantly lowered mortality (98 deaths vs 129 deaths; hazard ratio 0.77; 95% CI 0.59–1.00; $p = 0.047$) reducing the risk of death over the total study period by 23%. AEs caused 58 early discontinuations (five drug-related events) in the clodronate group and 43 discontinuations (three drug-related events) in the placebo group.

Conclusion: These results indicate that in women with early breast cancer receiving adjuvant systemic therapy, oral clodronate for 2 years is generally well tolerated with no serious long-term sequelae, providing a safe, long-term therapy in the adjuvant setting.

Background

The occurrence of metastatic bone disease is a landmark during the progression of breast cancer and bears an adverse prognostic impact for the patient. Skeletal metastases are typically complicated by bone pain, fractures, and hypercalcaemia causing severe impairment in the patients' quality of life. The treatment modalities currently applied in the treatment of primary breast cancer reduce the overall rate of relapses but do not totally eradicate the problem of developing osteolytic metastases. An optimal new therapy would be effective in improving survival by inhibiting the development of both visceral and skeletal metastases as well as being safe and well tolerated during long-term treatment of women who are otherwise healthy after the primary adjuvant therapy of breast cancer.

It has recently been demonstrated that the long-term (24 months) administration of oral clodronate, a non-nitrogen containing bisphosphonate, significantly reduces the incidence of bone metastases during the treatment period in patients with primary operable breast cancer.[1] Clodronate, as other oral bisphosphonates, has a low absorption rate, at about 2%, from the gastrointestinal (GI) tract. From the circulation, clodronate goes to the skeleton and is tightly bound by bone, which makes the elimination phase slow. Any clodronate that is not bound to bone is excreted unchanged through the kidneys.[2] The current therapeutic use of clodronate includes the management of metastatic bone disease by a symptomatic control of osteolytic lesions, including a reduction in bone pain and hypercalcaemia, pathological fractures and other skeletal morbidity.[3,4] The mechanism of action appears to be due to the inhibition of osteoclast-mediated bone resorption.[5] Lately, more emphasis has been given to clodronate use in the earlier phases of malignancy instead of late palliative usage, since in the light of recent results, the earlier the clodronate treatment is started, the more benefit is obtainable for the patients.[1]

The efficacy of oral clodronate and intravenous pamidronate in malignant bone disease are similar.[6] Oral administration provides a flexible alternative to intravenous usage, which is important in the management of patients on long-term therapy. The intravenous route is ideal for patients in the postoperative period, who often receive concomitant drugs administered by intravenous infusion. Also, in some cases, intravenous drug administration is necessary to reduce patient morbidity from the adverse effects of nausea and vomiting caused by chemotherapeutic agents. However, following discharge of patients from hospital, the oral form of clodronate provides a more convenient alternative to the intravenous formulation, especially for those who require long-term therapy. Nevertheless, any possible risk associated with use of the oral route, such as the potentially increased likelihood of GI adverse effects, should not outweigh the convenience benefit for the patient.

The objective of the current study is to assess safety and tolerability of oral clodronate using data from a large scale, multicentre adjuvant study.

Patients and Methods

Study Design and Follow-Up

A multicentre, double-blind, randomised, placebo-controlled study involving 1079 patients assessed the efficacy of oral clodronate treatment on the development of bone metastases and other cancer relapses together with its safety during long-term use in patients receiving therapy for primary breast cancer.[1] The study was started in 1989 and the medication period was 2 years. Results from the study presented only limited safety data acquired before a cut-off point of June 1997. To assess the

long-term safety of oral clodronate in this study, the results from a longer follow-up period are presented here, extending to June 30, 2000 (median of 3.5 years of follow-up after completion of medication giving a total median study period of 5.5 years).

The trial centres were the Royal Marsden Hospital, London and Sutton, UK; the Tom Baker Cancer Center, Calgary, Canada; the Hôpital St Luc, Montreal, Canada; the Norwegian Radium Hospital, Oslo (acting as the main co-ordinator for the 21 satellite hospitals in Norway); and Jyväskylä Central Hospital, Finland. The study protocol was sent to the local ethics committees for approval before the start of the study.

Study data were subject to annual review under the scrutiny of an external data-monitoring committee. Rules governing study cessation were defined in the protocol and the study is now closed.

Patient Selection and Treatment Regimen

Patients had histologically or cytologically confirmed operable primary breast cancer with no evidence of metastases, significant renal or hepatic impairment, or non-malignant bone disease. They were psychologically suitable for the study treatment, gave written informed consent and had no previous history of cancer (except basal cell or *in situ* cervical cancer) or use of bisphosphonates. The patients received the normal therapy regimen for the primary breast cancer including local (surgery, either resection or mastectomy, and radiotherapy) and systemic (chemotherapy, endocrine therapy) treatments. Additionally, the patients were randomised to receive either oral clodronate (Bonefos®[1], Leiras Oy, Finland) 1600mg daily or placebo for 2 years. The study medication was taken as four 400mg capsules in the morning without food or two 400mg capsules twice daily without food depending on the tolerability, which was clinically defined and predominantly associated with GI symptoms. The study medication was started within 6 months of randomisation. The patients were followed up for relapses irrespective of the type of first relapse until the end of study or death.

Between November 1989 and July 1995, 1079 patients were randomised to receive clodronate (n = 538) or placebo (n = 541) in six centres in the UK, Canada and Scandinavia. Ten of these patients were randomised (eight to clodronate; two to placebo) but withdrew their consent before the initial assessment prior to starting medication. However, to compile all safety data on an intention-to-treat basis, all 1079 patients were included in baseline and follow-up data on AEs and are therefore also included in these results. The demographic data have been compiled for 1069 patients.

Adverse Event Assessments

Pre-randomisation safety assessments included physical examination, full blood cell count and biochemical parameters. The physical examination paid special attention to assessments of back pain, both breasts, arm oedema, lymph nodes, skin nodules, shortness of breath and liver size. Haematological and biochemical tests as well as physical examination were repeated at 3-month intervals in the first year, 6-month intervals until the 5-year timepoint, and thereafter annually. Calcium assessments were part of the efficacy evaluations in this study.

AEs, also including adverse effects of possible concomitant chemotherapy, and compliance were evaluated after 6 weeks, at 3-monthly intervals for the first year, at 6-monthly intervals until 5 years, and thereafter annually. All AEs, whether drug-related or not, were recorded on the case report forms (CRF) by the investigator throughout the study. The severity of the AE, its duration, frequency, and any possible causal relationship to the study drug as defined by the investigator were documented together with any subsequent changes to the study medication. Severity was graded by the investigator. AEs were classified according to the WHO's Adverse Reaction Dictionary (ARD) including the system organ class (SOC) and preferred term (e.g. 'back pain').

1 Use of tradenames is for product identification only and does not imply endorsement.

An AE was considered a serious adverse event (SAE) in case of death, life-threatening AE, permanently disabling event, event leading to hospitalisation or secondary neoplasm. All SAEs were reported immediately to the sponsor, Leiras Oy, and appropriate health authorities. SAEs were also classified according to SOC and preferred term (WHO-ARD).

Events not recorded as AEs or SAEs were: progression of the underlying malignancy (except severe impairment of organ functions or death due to disease progression); low white blood cell count caused by chemotherapy (except in the case of infection due to leucopenia) and hospitalisation for the basic treatment of the underlying malignancy or for non-medical reasons (e.g. if hospitalisation was necessary to avoid long-distance travel for radiotherapy).

In the case of premature discontinuation, documentation of the reason, whether related to an AE (also including SAEs) or to another cause, was required on the CRF. Deaths were also documented as SAEs and documented on the CRF, with details on the cause of death.

Concomitant medication was recorded at 3 months and then identically to the reporting of AEs throughout the study, collected on the CRFs and coded with WHO's anatomical therapeutic chemical classification.

All centres were monitored regularly on-site and CRFs were verified with the appropriate source documents in accordance with standards for Good Clinical Practice.

Statistical Analysis

The 95% CIs were estimated for the difference in the rate of adverse events (AEs) between the treatment groups. Safety laboratory measurements were analysed by analysis of variance for repeated measurements. Survival was analysed using the Cox regression model.

Results

Patients

As previously described,[1] the clodronate and placebo groups were well matched for demographic and clinical characteristics, as well as for choice of primary surgical treatment, axillary surgery, use of radiation therapy and systemic endocrine and chemotherapy. Such characteristics were also evenly matched within different trial centres. The mean time from primary treatment (surgery or preoperative chemotherapy) to the beginning of study treatment was similar for both groups (clodronate 49.1 days ± 74.0 days vs placebo 47.3 days ± 81.1 days). Also, the median time on the study medication (clodronate 2.0 years [range 0–3.75 years] vs placebo 2.0 years [range 0–3.75 years]), and the median time in the study (clodronate 5.6 years [range 0.05–10.5 years] vs placebo 5.5. years [range 0.05–10.6 years]) were similar between the groups. Compliance with study medication, as evaluated by capsule intake, was well balanced between the treatment groups during the medication period.

Adverse Events

A total of 1041 patients (96.5%) experienced AEs with a similar overall incidence in both treatment groups: AEs were reported for 519 patients (96.5%) in the clodronate group and 522 patients (96.5%) in the placebo group. Of those patients with reported AEs, severe AEs were reported for 248 patients (47.8%) in the clodronate group and 262 patients (50.2%) in the placebo group. Moderate AEs were reported for 225 patients (43.4%) in the clodronate group and for 215 patients (41.2%) in the placebo group. For the rest of the patients, AEs were either mild or their nature was not recorded (five patients).

When the occurrence of AEs by SOC was assessed, GI system disorders were significantly more common in the clodronate group, particularly during the medication period. In contrast, skin and appendage disorders and red blood cell disorders were significantly more frequent in the placebo group, the

Table I. The system organ class (SOC) for adverse events (AEs) during the medication and follow-up periods

SOC	Clodronate group		Placebo group	
	no. of patients with AE (%) during the medication period (n = 538)	no. of patients with AE (%) during the follow-up period (n = 509)	no. of patients with AE (%) during the medication period (n = 541)	no. of patients with AE (%) during the follow-up period (n = 518)
Body as whole – general disorders	292 (54.3)	234 (49.2)	308 (56.9)	230 (47.9)
GI system disorders[a] (95% CI 4.0–15.6)	307 (57.1)	151 (31.7)	245 (45.3)	131 (27.3)
Musculo-skeletal system disorders	178 (33.1)	225 (47.3)	216 (39.9)	220 (45.8)
Skin and appendages disorders[a] (95% CI –12.0 to –0.1)	194 (36.1)	83 (17.4)	231 (42.7)	97 (20.2)
Reproductive disorders, female	135 (25.1)	132 (27.7)	151 (27.9)	137 (28.5)
Psychiatric disorders	145 (27.0)	87 (18.3)	160 (29.6)	109 (22.7)
Respiratory system disorders	93 (17.3)	102 (21.4)	113 (20.9)	116 (24.2)
Central and peripheral nervous system disorders	73 (13.6)	87 (18.3)	81 (15.0)	71 (14.8)
Neoplasm	47 (8.7)	82 (17.2)	54 (10.0)	102 (21.3)
Urinary system disorders	47 (8.7)	89 (18.7)	62 (11.5)	77 (16.0)
Metabolic and nutritional disorders	47 (8.7)	84 (17.6)	45 (8.3)	90 (18.8)
Resistance mechanism disorders	56 (10.4)	56 (11.8)	70 (12.9)	41 (8.5)
Liver and biliary system disorders	49 (9.1)	78 (16.4)	54 (10.0)	81 (16.9)
White cell and reticuloendothelial system disorders	55 (10.2)	43 (9.0)	55 (10.2)	38 (7.9)
Cardiovascular disorders, general	35 (6.5)	55 (11.6)	18 (3.3)	50 (10.4)
Vision disorders	47 (8.7)	26 (5.5)	46 (8.5)	31 (6.5)
Red blood cell disorders[a] (95% CI –7.9 to –0.1)	34 (6.3)	27 (5.7)	44 (8.1)	40 (8.3)

a Statistically significant difference between the groups during the total follow-up ($p < 0.05$).

AE = adverse event; **CI** = confidence interval for the proportion of patients reporting AEs during the total study period.

difference was seen both on and off medication (table I). There were no significant differences between the treatment groups as regards any other SOCs. Interestingly, no renal toxicity was observed for clodronate based on the equal distribution of urinary tract disorders for the treatment groups during both the medication period and the off medication period. It should be noted that SOC 'neoplasm' includes all deaths due to the underlying malignancy, in addition to several types of metastases, therefore increasing the total number of these AEs.

Diarrhoea was the only significantly more frequent AE in the clodronate group (table II), reported twice as often among the clodronate group patients during both the medication and follow-up periods, the difference during the study period being statistically significant ($p < 0.05$). Within the study groups, the distribution of diarrhoea by severity was similar among the patients reporting diarrhoea during the study (clodronate, mild vs moderate vs severe; 50.5% vs 42.1% vs 6.5%; placebo, mild vs moderate vs severe 44.4% vs 44% vs 9.3% of patients). In both groups, diarrhoea frequency was similar during the first 2 study months. During the third and fourth study months, diarrhoea was reported more frequently in the clodronate group, reaching a plateau by the fifth month; the difference between the treatment groups in the reporting of diarrhoea was seen until the end of the study.

There were no prominent differences between the treatment groups in the occurrence of nausea, dyspepsia, vomiting or abdominal pain either on medication or off medication (table II, which also shows severe events). There were 36 patients with reports of either oesophagitis or gastritis during the study,

12 patients on clodronate and 24 patients on placebo. Oesophageal ulcers were not reported; gastric ulcer was reported for six patients in the clodronate and two patients in the placebo group. Despite the small numbers, the results suggest that clodronate is not associated with mucosal irritation in the upper GI tract.

A causal relationship (yes or uncertain) between the study treatment and AE was reported for a total of 44 patients, 25 of whom received clodronate. Diarrhoea and dyspepsia were the only AEs for which a causal relationship to the study drug was reported more frequently for the clodronate group, as diarrhoea was reported to have causal relationship with the study medication for seven patients on clodronate and one patient on placebo; the figures for dyspepsia were ten and two patients for clodronate and placebo groups, respectively. Nausea was reported as treatment related for three patients in both study groups; abnormal hepatic function was reported as treatment related for two patients in the clodronate group. Various AEs, reported for one patient each, were reported as related to the study treatment in eight events in the clodronate group and in 16 events on placebo. Of the various related AEs, three were GI disorders in both the clodronate and placebo groups.

There were no differences between the treatment groups with regard to the overall distribution of the timepoints at which AEs were reported, either by SOC or preferred term. The reporting rate for AEs was highest during the first study year, reaching almost 90% of the patients, probably due to the other cancer therapies applied after the primary diagnosis. The reporting rate decreased slightly up to the fourth years, when approximately 70% of the patients reported an AE. After the fourth year about 80% of the patients reported an AE. At all timepoints, patients who received chemotherapy as a primary treatment reported AEs more frequently than those who received none.

Serious Adverse Events

A total of 747 SAEs (clodronate group 355 vs placebo group 392) were reported for 453 patients during the study (clodronate group 212 [39.4%] vs placebo group 241 [44.5%]). The number of patients with SAE was equally distributed between the treatment groups when evaluated by SOCs (table III), nor was an imbalance evident when SAEs affecting the GI system were compared. Moreover, there were no statistically significant differences between the treatment groups as shown by the 95% CIs for the most frequent preferred terms. Furthermore, the occurrence of secondary neoplasms was similar in the

Table II. The most frequent gastrointestinal (GI) system disorders during the medication and follow-up

Most frequent preferred terms for GI disorders	Clodronate group		Placebo group	
	no. of patients with AE (%) during the medication period (n = 538)	no. of patients with AE (%) during the follow-up period (n = 509)	no. of patients with AE (%) during the medication period (n = 541)	no. of patients with AE (%) during the follow-up period (n = 518)
Nausea	120 (22.3)	33 (6.9)	126 (23.3)	50 (10.4)
severe nausea	6 (1.1)	2 (0.4)	15 (2.8)	3 (0.6)
Diarrhoea[a] (95% CI 5.7–14.1)	81 (15.1)	38 (8.0)	37 (6.8)	19 (4.0)
severe diarrhoea	7 (1.3)	0 (0)	3 (0.6)	2 (0.4)
Dyspepsia	56 (10.4)	32 (6.7)	49 (9.1)	28 (5.8)
severe dyspepsia	7 (1.3)	0 (0)	2 (0.4)	0 (0)
Vomiting	60 (11.2)	28 (5.9)	53 (9.8)	25 (5.2)
severe vomiting	8 (1.5)	4 (0.8)	5 (0.9)	4 (0.8)
Abdominal pain	39 (7.2)	39 (8.2)	27 (5.0)	32 (6.7)
severe abdominal pain	4 (0.7)	2 (0.4)	3 (0.6)	5 (1.0)

a Statistically significant difference between the groups during the total follow-up ($p < 0.05$).

AE = adverse event; **CI** = confidence interval for the proportion of patients reporting adverse events during the total study period.

Table III. The most common system organ classes (SOC) for serious adverse events (SAE)

SOC	No. of patients with SAE (%) in the clodronate group (n = 538)	No. of patients with SAE (%) in the placebo group (n = 541)
Neoplasm	112 (20.8)	136 (25.1)
Resistance mechanism disorders	21 (3.9)	26 (4.8)
Vascular (extracardiac) disorders	24 (4.5)	22 (4.1)
Reproductive disorders, female	23 (4.3)	23 (4.3)
Respiratory system disorders	18 (3.3)	21 (3.9)
Musculoskeletal system disorders	22 (4.1)	15 (2.8)
Gastrointestinal system disorders	16 (3.0)	14 (2.6)

two groups (clodronate group 36 vs placebo group 35). There were a total of 12 new different malignancy types, the most common being breast cancer (clodronate group 13 vs placebo group 10) followed by endometrial cancer (clodronate group 5 vs placebo group 7). A causal relationship to the study drug was not reported for any of the SAEs in either of the treatment groups.

The reporting rate for SAEs was highest during the first year of the study, with SAEs reported for 129 patients (clodronate group 57 vs placebo group 72). Thereafter, the number of patients reporting an SAE decreased steadily, reaching 78 during the fourth year. After that, 152 patients experienced SAEs. The higher number of SAEs during the first year of the study was probably due to the numerous cancer treatments, including chemotherapy, administered to the patients, which may have caused many of these SAEs.

Mortality

A total of 227 patients died during the study (medication period 10 vs follow-up period 217): 98 (18.5%) in the clodronate group and 129 (23.9%) in the placebo group, including 188 deaths due to the underlying malignancy (clodronate group 83 vs placebo group 105). As regards non-breast cancer deaths (clodronate group 15 vs placebo group 24), pneumonia, secondary neoplasms and vascular events were the most common causes, five of them occurring during the medication period (clodronate group 3 vs placebo group 2). The mortality rate was significantly lower in the clodronate group ($p = 0.047$), with a hazard ratio of 0.77 (95% CI 0.59–1.00) indicating a 23% reduction in the overall risk of death during the total study time.

Premature Discontinuations

Premature discontinuation of study treatment due to AEs, also including the patients with SAEs, was reported for a total of 101 patients, 58 receiving clodronate and 43 receiving placebo. GI disorders were the most frequent reason for discontinuation (table IV). Discontinuation due to AEs was considered related to the study drug in five patients in the clodronate group, (GI disorders [diarrhoea, dyspepsia, nausea and change in bowel habits] for four patients, and metabolic disorder [hypophosphataemia] for one patient) and in three patients in the placebo group, (GI disorders: abdominal pain, diarrhoea and dyspepsia). Table III shows the ten most common SOCs of the AEs with suspected causality (yes or uncertain) to the study drug, leading to premature discontinuation.

Laboratory Parameters

At baseline, patients who received clodronate had a statistically significantly higher median serum AST level compared with the placebo group (22.0 U/L vs 21.0 U/L; $p < 0.0001$), although the difference was of no clinical relevance. All other safety laboratory parameters and serum calcium levels were well balanced at baseline. During the medication period, the following significant differences in changes in the median values, when compared with baseline, were evident between the treatment groups at the 2-year timepoint, i.e. at the end of the study medication period, although they were all within the predefined reference limits: serum AST, (clodronate group 22.0–25.0 U/L vs placebo group 21.0–21.0 U/L; $p < 0.0001$); serum ALT (clodronate group 20.0–29.0 U/L vs placebo group 19.0–21.0 U/

Table IV. The most common system organ class (SOC) with reported causality (yes or uncertain) for adverse events leading to premature discontinuation

SOC	Reported causality	Clodronate group (n = 538)	Placebo group (n = 541)
Gastrointestinal system disorders	Yes	4	3
	Uncertain	30	18
Skin and appendages disorders	Yes	0	0
	Uncertain	3	6
General disorders	Yes	0	0
	Uncertain	5	2
Musculo-skeletal system disorders	Yes	0	0
	Uncertain	5	2
Psychiatric disorders	Yes	0	0
	Uncertain	3	0
Neoplasm	Yes	0	0
	Uncertain	0	0
Resistance mechanism disorders	Yes	0	0
	Uncertain	0	0
White cell and reticuloendothelial system disorders	Yes	0	0
	Uncertain	1	2
Urinary system disorders	Yes	0	0
	Uncertain	0	1
Metabolic and nutritional disorders	Yes	1	0
	Uncertain	2	0

L; $p < 0.0001$) [ALT was only measured in the Canadian study centres]; and for serum phosphate (clodronate group 1.08–1.02 mmol/L vs placebo group 1.09–1.05 mmol/L; $p = 0.011$). After 5 years, the differences in these parameters between the treatment groups were no longer significant. Altogether, these findings were of little clinical significance.

There were no significant differences between the treatment groups with regard to the changes in other haematological or biochemical parameters measured during or after the medication period. Clodronate had no effect on serum calcium levels as there were no significant changes in the mean serum calcium in either of the treatment groups during the medication or follow-up periods. Additionally, no renal effect of clodronate was noted when assessed by mean serum creatinine level, which was similar in both treatment groups after the medication period (77 μmol/L).

Physical Examination

Physical examinations aimed to evaluate the long-term effects of breast surgery in patients and to detect possible recurrence of the disease by means of assessing arm oedema, shortness of breath, status of both operated and healthy breast, presence of skin nodules and lymph nodes and liver size. No differences were seen between the clodronate and placebo groups at individual timepoints. The finding was expected, since these evaluations aim to diagnose postoperative complications and possible metastases rather than seeking differences between the treatment groups.

Concomitant Medications

Nearly all patients used concomitant medication during the study (clodronate: 529 patients, placebo: 536 patients). The treatment groups were well balanced with respect to the frequency of use of concomitant medication both during the medication and follow-up periods. Interestingly, there was no differ-

ence between the groups in the use of medication for alimentary tract and metabolism (clodronate group 44.7% vs placebo group 50.5%), indicating that reported GI problems were of no serious concern for the patients.

Discussion

The safety profile of a pharmaceutical compound must be balanced with the benefits predicted for patients. Malignancies are typically diseases where even severe therapy-related adverse effects may be acceptable in order to be able to effectively fight or totally eradicate the cancer. This is particularly the case with cancers at high risk of recurrence or at advanced stage. However, when treating primary breast cancer in otherwise healthy women using adjuvant therapy, any unwanted adverse effects need to be carefully balanced against beneficial effects. Also, the therapeutic efficacy might be compromised if patients fail to comply with long-term treatment because of adverse effects. Therefore all new drugs, including those aiming at malignant indications, should be as safe and well tolerated as possible especially in the adjuvant setting, when indicated for a long-term use.

Oral clodronate is typically associated with GI reactions such as nausea, vomiting and diarrhoea, reported in 2–10% of patients with bone disease treated with clodronate,[7,8] and also seen in studies of primary and metastatic breast cancer.[9,10] The results of the safety analysis in this study were in line with those previous studies: there was a greater incidence of GI AEs, particularly mild diarrhoea, among the patients in the clodronate group. However, these disorders seem to have had no limiting effect on the therapy for the majority of patients receiving clodronate, with regard to either treatment discontinuation or treatment compliance. In addition, the use of medication for alimentary tract disorders did not increase in patients receiving clodronate compared with those taking placebo, reinforcing the conclusion that, while apparently more frequently associated with clodronate use, GI disorders were not the cause of significant morbidity.

The most common AE for clodronate in long-term use seems to be diarrhoea. This makes the safety profile of oral clodronate different from that of oral aminobisphosphonates, since it mostly affects the lower GI tract, whereas aminobisphosphonates have the most prominent impact in the upper GI tract.[11] The effect in the lower GI tract began after approximately three months use of clodronate in this study; the reason for this is open to question. Interestingly, patients reporting diarrhoea continued to report this event until the end of the study so that the difference between the study groups persisted in the absence of exposure to oral clodronate. It is difficult to provide a mechanism by which clodronate could cause bowel irritation several years after stopping the medication, as it is bound exclusively to bone and only secreted by renal function. The increased incidence did not have a high impact on patients' daily life, since severe diarrhoea was rare in both treatment arms.

Analysis of the incidence of upper GI AEs confirms that therapy with oral clodronate does not increase the frequency of upper GI diseases. In particular, there appears to be no increase in the frequency of more serious upper GI AEs such as oesophagitis, reported for oral pamidronate and alendronate.[12,13] As a consequence of oesophagitis, pamidronate is marketed only for intravenous use and there are some precautions for the use of oral alendronate. Direct contact between pill and oesophageal mucosa has been suggested as a possible reason for oesophageal damage.[14] Also, aminobisphosphonates have been shown to inhibit the growth or induce apoptosis in human epithelial cells, whereas non-aminobisphosphonates have no such effect,[15] possibly giving another explanation for the biological background of these differences.

When assessing SAEs, the important alarm signals of safety problems in clinical studies, no unexpected issues were raised in this study. The overall rate of SAEs was expected and acceptable considering the patient group and length of the study. The imbalance between the two groups in the occurrence of GI AEs was not evident in the case of the SAEs, further confirming the mild nature of the GI prob-

lems associated with clodronate. Moreover, there was no causal relationship to the study drug reported for any of the SAEs, an interesting finding taking into account the number of patients in the study.

The laboratory findings confirm the mild and transient effect of oral clodronate on liver enzymes AST and ALT as reported also in other studies.[16] However, the median values for patients receiving clodronate were well within the normal laboratory reference range during the medication period and returned to the baseline level by the 5-year time-point. Therefore, the increase in the activity of liver transaminases derives rather from the induction of enzyme activity than from the impaired liver function and is reversed on stopping treatment.

When evaluating the serum creatinine measurements, clodronate seems to have no adverse effect on renal function, confirmed also by urinary tract related AEs, which were as frequent in both groups. This finding is somewhat contradictory to the results presented for aminobisphosphonates.[17]

A statistically significant difference in survival between the treatment groups was seen during the entire study period, indicating a 23% decrease in the risk of death in the clodronate group. In the light of these results, clodronate had a significant beneficial effect on survival, which is obviously the most important safety-related finding for the patients. The possible mechanisms behind the survival benefit include the overall decrease in tumour cell burden by decreasing the rate of skeletal metastases and the clodronate-induced suppression of tumour cells in the bone marrow, seen in the studies using breast cancer cell lines,[18] thereby preventing the subsequent tumour cell spread to viscera. Visceral metastases are associated with a remarkably poor prognosis, therefore by inhibiting their development it is possible to have an effect on survival. Previously, Diel et al.[19] demonstrated that when patients received clodronate, there was a significant decrease in visceral metastases after 3 years' follow-up associated with a survival benefit, even though the beneficial effect on visceral metastases was diminished after 5 years' follow-up.[20] Results opposing these have also been published, where an increased rate of visceral metastases and a subsequent adverse effect on survival were associated with clodronate.[10] The mechanism of this finding, if one assumes it to be true, is unclear and remains open to debate. That the observation may have more likely represented a simple randomisation bias, is a possibility that is supported by unbalanced hormone receptor status at baseline, when there were more patients with receptor-negative breast cancer in the clodronate group. Moreover, more of these patients with poor prognosis in the clodronate group were treated with only endocrine therapy as compared with the control group, further deteriorating their prognosis. An ongoing National Surgical Adjuvant Breast and Bowel (NSABP) trial will give new information on efficacy and safety of clodronate using a medication period of 3 years.

Conclusion

The results of this long-term randomised placebo-controlled trial of 1079 breast cancer patients, spanning a total time-period of 11 years confirm the favourable tolerability and safety profile of oral clodronate when given as a dose of 1600mg daily for 2 years. Particularly, oral clodronate is gastrointestinally well tolerated and not associated with serious upper GI adverse reactions or renal problems reported for some aminobisphosphonates.These results lend further support to previously reported findings of a good tolerability and safety profile for clodronate from many studies in both malignant and non-malignant indications.[21,22]

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