Results: Treatment with intravenous ibandronate 6 mg or oral ibandronate 50 mg rapidly reduced bone-pain scores and maintained them below baseline levels until the 2-year study endpoint. These reductions were statistically significant compared with placebo (intravenous ibandronate 6 mg, −0.28 versus +0.21, p<0.001; oral ibandronate 50 mg, −0.10 versus +0.20, p=0.001). Analgesic use was also significantly lower with oral ibandronate 50 mg versus placebo (p=0.019). Alleviation of bone pain with intravenous and oral ibandronate was accompanied by significant improvements in global QoL (p=0.004 and p=0.03 versus placebo, respectively). Compared with placebo, intravenous ibandronate also significantly improved physical functioning (p=0.034), emotional functioning (p=0.025) and social functioning (p=0.008), while oral ibandronate 50 mg significantly improved physical functioning (p<0.05) and role functioning (p<0.01).

Conclusions: Treatment with intravenous ibandronate 6 mg or oral ibandronate 50 mg significantly relieved bone pain in patients with bone metastases from breast cancer over 2 years of treatment. Sustained relief of bone pain allowed improved quality of life and mobility. Such benefits have not previously been reported with other bisphosphonates for metastatic bone disease.

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Long-term safety of oral ibandronate in patients with skeletal metastases from breast cancer: 4-year follow-up data

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Background: Long-term tolerability is an important consideration in the selection of bisphosphonates for metastatic bone disease, due to the lengthy duration of exposure needed to prevent bone events and help alleviate bone pain. Ibandronate is a newly approved bisphosphonate for the prevention of skeletal events in patients with breast cancer and bone metastases. The pooled results of phase III clinical trials have shown that oral ibandronate 50 mg once daily for 2 years has a safety profile comparable to placebo in metastatic breast cancer [1]. This abstract reports the results of non-controlled, follow-up studies that were conducted to examine the 4-year safety of oral ibandronate.

Methods: On completion of the 2-year placebo-controlled study period, patients received oral ibandronate 50 mg once daily for a further 2 years (n=115). Adverse events (AEs) and laboratory parameters were recorded.

Results: As might be expected with advanced cancer, 18% of patients did not complete the follow-up period due to AEs, and the majority of patients (83%) experienced at least one AE. Malignancy progression was the most commonly reported AE (52%), leading to the withdrawal of 11% of patients. AEs leading to withdrawal are summarized in Table 1.

Table 1.

	% patients (N)
Any AE	18.3 (21)
Malignancy progression	11.3 (13)
Esophagitis	1.7 (2)
Cerebral infarction	1.7 (2)
Bone pain	0.8 (1)
Back pain	0.8 (1)
Asthenia	0.8 (1)
Ascites	0.8 (1)
Renal AEs	0.0 (0)

Hypocalcemia (n=3), dyspepsia (n=3) and esophagitis (n=2) were the only AEs considered possibly related to oral ibandronate treatment by the study investigators. None of these AEs were serious or led to withdrawal from treatment. Oral ibandronate was not associated with any renal AEs or laboratory/vital sign abnormalities.

Conclusions: Oral ibandronate 50 mg is well tolerated for up to 4 years of treatment, with very few drug-related AEs and no renal AEs reported. These results suggest that oral ibandronate is particularly suitable for long-term administration at home, without the need for close AE monitoring.

References

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Local relapse and systemic recurrence in breast cancer patients. Are they related?

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Introduction: The main problem that still remains unresolved is to define a group of patients for whom local recurrence is a marker or a cause of systemic disease.

Materials and Methods: In order to examine the above mentioned issue we analysed data of 3110 operable breast cancer cases coming from Breast Oncology's Unit registry of IASO Women's Hospital, in Athens. Median follow up period was 52 months (1–344 months). The recorded characteristics are patients age, the type of surgery, the tumor's size and grade, the lymph nodes status, the estrogen and progesterone status, the presence of a lymphatic infiltration and Extended Intraductal Component. To account a systemic recurrence as a consequence of the local recurrence this should have followed in a time period shorter than 12 months. During the follow period we have observed 30 such cases (group 1). On the other hand, 94 patients did not present a systemic recurrence within 12 months after the local relapse (group 2).

Results: The two groups do not differ statistically significant for any of the recorded risk factors. More specifically, mean age was 53.55 and 52.33 years old in the two groups respectively (p-value=0.615). Two (6.7%) and 17 (18.1%) have lymphatic infiltration (p-value=0.157), 11 (36.7%) and 25 (26.60%) patients have EIC (p-value=0.365) in the two groups respectively. The tumor's size in 9 (30%) and 41 (43.6%) cases was 1–20 mm, in 19 (63.3%) and 47 (50.0%) it was 21–50 mm and in 2 (6.7%) and 5 (5.3%) the tumor's size was greater than 50 mm in the two groups respectively (p-value= 0.548). As the lymph nodes status is concerned, no statistically significant difference was found between the two groups (p-value= 0.770). Three patients in group 1 (10%) and 5 (5.3%) in group 2 had a grade I tumor, 17 (56.7%) patients in group 1 and 54 (57.4%) in group 2 had a grade II tumor while 10 patients (33.3%) in group 1 and 32 patients (34.0%) in group 2 had a grade III tumor (p-value= 0.7101). As far as the hormone receptors status is concerned, no significant difference was found (p-values= 0.444, 0.602).

Conclusion: Comparing the two groups with respect to the known risk factors we did not find any significant differences between them. The issue of the relation between local and systemic recurrence remain unsolved and further research is required.

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Zometa® (zoledronic acid) in patients with skeletal metastases secondary to breast cancer – a study of home versus hospital administration

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In patients with breast carcinoma zoledronic acid 4-mg (Z, Zometa®) has been shown to be significantly more effective than pamidronate 90-mg, reducing the risk of skeletal-related events by an additional 30% in patients receiving hormonal therapy (P=0.009) (Rosen et al. Cancer: 2003, 98(8)). It has the further advantage of being administered over only 15 minutes (every 3–4 weeks), allowing the possibility for home administration.

Aim: to compare quality of life (QoL) and pain scores in breast cancer patients receiving Z when administered either at home or in hospital, and to assess the safety of Z by performing serial evaluations of serum creatinine.

Design: breast cancer patients with at least one bone metastasis and receiving hormone therapy were recruited to the study. After a lead-in phase of 3 infusions of Z 4-mg in hospital (to ensure disease stabilisation on hormone therapy), 100 patients were randomised to receive 3 open-label infusions at home or in hospital, to be followed by a further 3 infusions at the opposite venue.

Method: the EORTC QoL scale (QLQ-C30) and brief pain inventory (BPI) were used to assess the potential benefits of Z treatment.

Results: 84 patients completed the study, with 79 available for analysis. Overall global health status, as measured by the QLQ-C30, showed a significant median improvement of 8.3% over the 9 infusions (P=0.0127). According to the BPI, there were significant reductions over the 9 infusions

in worst pain (P=0.008), and average pain in the last 7 days (P=0.04), interference with general activity (P=0.01) and interference with walking ability (P=0.001). In every case there were significant improvements on treatment in the home setting (P=0.04, P=0.008, P=0.0004, and P=0.003 respectively). Serum creatinine was normal throughout for the majority of participants, with only 4 patients (3%) experiencing an increase in serum creatinine of greater than 44 μmol/l above baseline.

Conclusion: this study demonstrates that Z 4-mg significantly improves QoL and pain scores, particularly when administered to patients at home, and can be given safely in this setting.

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Dose-finding study of the combination of oral idarubicin and oral capecitabine in the treatment of locally advanced or advanced breast cancer

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Introduction: Anthracyclines and 5FU are amongst the most widely used and effective drugs for the treatment of breast cancer. In locally recurrent and metastatic breast cancer response rates of over 70% can be achieved using a schedule of weekly bolus adriamycin and continuous infusional 5FU (Gabra et al. 1996). Many patients however prefer oral chemotherapy, so we have developed an all oral regimen using idarubicin and the oral 5FU pro drug capecitabine.

Materials and Methods: Between June 1999 and July 2003, 30 post menopausal patients were recruited, 17 in the dose finding phase and 13 in the expansion phase. The starting doses were 10 mg/m^2 idarubicin days 1–3 and capecitabine 750 mg/m$^{2\ bd}$ days 1–14, repeated every 21 days.

Doses were escalated as follows; 10/750 (n=6), 10/1000 (n=3), 10/1250 (n=5), 12.5/1000 (n=3), with the expansion phase at 10/1000 (n=13). Patients were evaluated for toxicity with each cycle and for response at cycles 3 and 6. 4 patients remain on treatment. Dose limiting toxicity was defined as either 2 of 6 patients or 2 of 3 patients having the same grade 3 toxicity at a particular dose level.

Results: The median age of patients was 66 (54–76), and the mean number of cycles dispensed was 4.9 (1–12). Two patients were treated for primary breast carcinoma, and the remainder received this regimen as first line chemotherapy for metastatic or locally recurrent disease. All patients had adequate cardiac function assessed by MUGA scanning at entry to the study.

	10/750 (n=6)	10/1000 (n=3)	10/1250 (n=5)	12.5/1000 (n=3)	10/1000 (expansion, n=12)
Episodes of grade 3 or 4 toxicity (neutropenia)	5 (0)	2(1)	5(2)	8(5)	9(5)
Number of dose reductions	0	2	2	1	5
Delays due to toxicity	1	2	7	1	11
Withdrawn for toxicity	2	0	1	1	0

There were three deaths within 4 weeks of receiving trial medication. Two were attributable to progressive disease and one was related to haematological and other treatment related toxicity at the highest dose level. The dose limiting toxicity was neutropenia. Within the dose finding phase there was one complete and 6 partial physician reported responses with a further 3 patients achieving stable disease, giving an objective response rate of 41%. Four patients remain on treatment in the expansion phase, but to date there have been 4 objective responses observed and 4 patients with stable disease within 10 evaluable patients. These were physician reported and will be subject to independent radiological review.

Conclusions: We believe that we have developed a feasible oral cytotoxic regimen for the treatment of primary and advanced breast carcinoma, which shows encouraging evidence of disease activity. The 10/1000 combination requires further evaluation in the phase 2 setting.

References

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Oral Vinorelbine in metastatic breast cancer: Long-term results of 2 multicenter phase II studies

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Navelbine® (NVB) oral is a soft-gelatin capsule for which reliable-dose-equivalence with Navelbine® intravenous (IV) has been demonstrated. Two multicenter, phase II studies (S1 and S2) were conducted to evaluate the activity of NVB oral in the first-line treatment of advanced breast cancer (ABC) using the same inclusion criteria. NVB oral was given at 60 mg/m^2/week for the first 3 administrations and then increased to 80 mg/m^2 in absence of severe neutropenia defined as one episode of grade 4 or 2 episodes of grade 3. Between November 1997 and August 2000, 64 and 72 patients (pts) were enrolled in S1 and S2, respectively. For both studies median age was 63 years; 61% of pts in S1 and 47% in S2 had visceral lesions. The majority of pts underwent dose increase from 60 to 80 mg/m^2 (95% for S1, 86% for S2). Median number of administrations were 9 and 10, respectively. Main efficacy results are displayed in table 1.

Table 1

	RR* all pts	RR* evaluable pts	Median PFS**	Median survival
S1	30%	31%	4.2 mo	24 mo
S2	27%	30%	4.6 mo	21 mo

* RR, Response Rate; **Progression-free survival.

Safety results from the 2 studies were pooled. Main dose-limiting toxicity was neutropenia with 42% of pts with grade 3–4 and 4% with febrile neutropenia. Non haematologic toxicities included nausea (8% of pts with grade 3–4), vomiting (8% with grade 3–4), diarrhea (7% with grade 3) and constipation (1% with grade 3). Nausea and vomiting are easily controlled by prophylactic use of antiemetics, preferably oral setrons. No toxic death was reported.

In conclusion, NVB oral gave consistent results in two independent studies. It has shown the same efficacy and safety profile as NVB IV with the advantages of convenience and lack of venous toxicity of oral chemotherapy.

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Weekly docetaxel and trastuzumab for her-2-overexpressing metastatic breast cancer: efficacy and correlation with biological markers in a phase II, multicenter study

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Purpose: 1) To evaluate the efficacy and safety of weekly docetaxel and trastuzumab for patients with HER-2 overexpressing metastatic breast cancer. 2) To analyze correlations between response and the expression of biological markers.

Patients and Methods: Thirty-five women with HER-2 overexpressing metastatic breast cancer were enrolled in the study. Eligible patients received Trastuzumab 4 mg/kg day 1 before the start of the first cycle followed by docetaxel (40 mg/m^2) and trastuzumab (2 mg/kg) weekly for three weeks. The pretreatment expression of p53, Bcl-2, Caspase-3, MAP Kinase, and R-ras in 18 cases were evaluated by immuno- histochemical staining.

Results: 1) The overall response rate was 61.8% (95% CI: 44–79) [complete and partial response, 6 (18%) and 15 (44%), respectively]. The median time to failure was 154 days (range, 28 to 616 days). 2) The median number of cycles administered was four (range, 1 to 8). The median delivered dose-intensity for docetaxel was 27 mg/m^2 (range, 19 to 30), which is equal to a median relative dose-intensity of 90%. 3) Grade 3/4 toxicities (NCI-CTCver.2) were neutropenia 9 pts (26%), anorexia 1 pts (3%), fatigue 1 pts (3%), diarrhea 1 pts (3%), stomatitis 1 pts (3%). 17 pts (49%) showed Grade 2 nail changes and 7 pts stopped treatment by this adverse events. 4) The pretreatment expression of p53, Bcl-2, Caspase-3, MAP kinase, and R-ras was unlikely to predict