exposed to A. The low toxicity of the FuFolNav regimen allowed safe administration in the outpatient setting.

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Bisphosphonates in metastatic breast cancer

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Background: The use of bisphosphonates is an essential in the treatment of patients with osteolytic bone metastasis of breast cancer. The guidelines of the American Society of Clinical Oncology recommends the administration of bisphosphonates each 3–4 weeks continuously until impairment in the performance status.

We analyze the therapeutic results and adverse effects of bisphosphonates in breast cancer patients with bone metastases.

Material and Methods: from October 1997 until February 2002 we studied 178 patients treated with Pamidronate 90 mg IV given in 60 minutes each 3–4 weeks. After that date, we administered Zoledronic Acid 4 mg IV in 15 minutes, to all the patients, but this is not the endpoint on this report. We analyzed the age, metastatic location, number of administrations, adverse effects and the number of skeletal complications along the time that the drug was given. All the patients received concurrently chemotherapy, hormonal therapy and/or radiotherapy if it was needed. Bisphosphonates were given until it was an important decreased in performance status.

Results: All the patients were diagnosed of breast cancer with bone metastases. The median age was 55.6 years old (range 29–81). A total of 17.4% of patients had only one metastatic lesion. The average of administered cycles were 10 (range 3–62), and the average accumulated dose was 900 mg (270–5580 mg). A 48.3% (86) of the patients received treatment continuously at least for 2 years. We analyzed the calcium and creatinine serum levels. A total of 2.5% of the patients developed an analytic hypocaliemia (Ca<8 mg/dl) without symptoms. We had no events of renal failure or creatinine levels >2 mg/dl. The percentage of skeletal-related events is 20.8% and a total of 33.1% need radiotherapy treatment simultaneously. Pain, evaluated by a visual analogic scale (VAS) is decreased in these patients but there are many factors that contribute to these results. Breakthrough pain was reported only in 12% of the patients with a level of VAS superior to 5. A total of 6.18% (11) related an increase of pain after the first cycle of bisphosphonates and a total of 14.6% (26) referred an acute phase reaction of bone pain fever arthralgias and myalgias.

Conclusion: Bisphosphonates improve the intensity of pain in patients with breast cancer and bone metastases, and decrease the episodes of breakthrough pain. The adverse effects are presented in a small proportion and are slight and transitory. In our series we have no events of renal failure. The skeletal-related events are small when compared with historical controls. It can be administered simultaneously with chemotherapy hormonal therapy and radiotherapy without relevant clinical problems.

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Results of a phase II study of liposomal doxorubicin (Myocet®) in combination with weekly paclitaxel and trastuzumab (Herceptin®) in patients with HER2-positive locally advanced or metastatic breast cancer (LA/MBC)

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Background: The pivotal trial (H0648g) in patients with HER2-positive MBC demonstrated that first-line trastuzumab (Herceptin®) plus doxorubicin was efficacious, but associated with an increased risk of cardiotoxicity compared with doxorubicin alone. Myocet®, a liposome-encapsulated form of doxorubicin, is as effective as doxorubicin in MBC, but is associated with less cardiac toxicity. Following promising results from a phase I dose-finding study (n=21), in which the combination of Myocet®, Herceptin® and paclitaxel produced a high response rate with very low cardiac toxicity, this combination was investigated further in this phase II study.

Materials and methods: Patients with HER2-positive (IHC 3+/FISH+) LA/MBC (previously untreated) were eligible for this study. Treatment consisted of Myocet® 50 mg/m^2 every 3 weeks $\times$6, weekly paclitaxel 80 mg/m^2 and Herceptin® 2 mg/kg, given for 52 weeks for LA and until disease progression for MBC. Cardiac function was assessed every 3 weeks and tumour response every 6 weeks during therapy. The primary endpoint was response rate.

Results: A total of 54 patients were included; 30 patients had LA and 24 MBC. Of these, 52 patients have been evaluated for response (29 with LA and 23 with MBC). The ORR is 92.3% (CR 25, PR 23), a further 4 patients had stable disease. The response rate in patients with LA was 93.1% (CR 20, PR 7) and in patients with MBC 91.3% (CR 5, PR 16). Neutropenia was the most common grade 3–4 event, with 12 episodes of febrile neutropenia. Other toxicities included alopecia, nausea, vomiting, hand–foot syndrome and ungueal toxicity. Three patients had decreases in LVEF to below 50%, with no cases of symptomatic heart failure.

Conclusions: In women with HER2-positive LA/MBC, the combination of Myocet® with paclitaxel and Herceptin® is highly active and well tolerated, with no unexpected toxicity.

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Renal safety of ibandronate in patients with bone metastases from breast cancer: phase III trial results

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Background: Increasing awareness of the nephrotoxic potential of certain intravenous bisphosphonates that are used to manage metastatic bone disease has led to recent publications [1–4] and modification of the prescribing information. Patient management would be simplified by availability of a bisphosphonate that does not have significant renal safety issues. Ibandronate is a highly-potent aminobisphosphonate that has recently been approved for the prevention of skeletal events in patients with breast cancer and bone metastases. In this context, the renal safety of ibandronate given intravenously and orally has been examined in multicenter, randomized, double-blind phase III trials over 96 weeks of treatment, supporting a difference versus other intravenous aminobisophosphonates.

Methods: In a trial of intravenous ibandronate, patients were randomized to a 6 mg dose (n=154) or placebo (n=158) infused over 1–2 hours every 3–4 weeks. In two oral studies (data pooled), patients received ibandronate 50 mg (n=287) or placebo (n=277) once daily. Renal adverse events (AEs) and serum creatinine levels were monitored throughout the study period.

Results: The percentage of patients with renal AEs or increased creatinine levels was low and similar between the intravenous ibandronate 6 mg and placebo groups (4.0% versus 4.5%; 2.6% versus 1.3%, respectively). None of the renal AEs with intravenous ibandronate were graded serious, or led to withdrawal from treatment. The incidence of renal AEs with oral ibandronate 50 mg was also comparable to placebo (5.2% versus 4.7%). Elevated serum creatinine levels were observed in 1.4% of patients in the oral ibandronate group and 2.2% of patients in the placebo group.

Conclusions: Intravenous and oral ibandronate have renal safety profiles that are comparable to placebo in patients with metastatic bone disease from breast cancer. As stated in the product labelling, ibandronate may be used in patients with existing renal function impairment and patients taking nephrotoxic medications; and serum creatinine monitoring is at the clinician's discretion (not required prior to each dose).

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Fulvestrant in postmenopausal women with metastatic breast cancer progressing on prior endocrine therapy – results from an expanded access programme

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Background: Fulvestrant ('Faslodex') is an estrogen receptor (ER) antagonist with no agonist effects. Fulvestrant downregulates the ER, which leads to reduced cellular levels of progesterone receptor (PgR). This abstract reports the results of an expanded access programme (supported by AstraZeneca) in which postmenopausal women with metastatic breast cancer whose disease had progressed on prior endocrine therapy were treated with fulvestrant 250 mg.

Methods: Fulvestrant 250 mg was given as a single 5 mL intramuscular injection, once every 28 days until disease progression or

other event necessitating withdrawal. Tumour response was assessed monthly using Union Internationale Contre le Cancer criteria. Time to progression (TTP) was defined from start of treatment until objective disease progression. Duration of response (DOR) was defined, for responding patients only, as the time from treatment initiation to disease progression.

Results: Between 8/2001 and 10/2003 a total of 44 patients (median age 63 years [range 39–91 years]) were treated in our centre and the median follow-up was 28 weeks (range 12–104 weeks). 86% of patients had ER-positive and/or PgR-positive disease. All had received prior endocrine treatment for advanced disease and 50% had received adjuvant endocrine treatment. Thirty patients (68%) had also received prior chemotherapy. Most patients (75%) were receiving fulvestrant as their 3rd- or 4th-line endocrine treatment for advanced disease. Three patients (7%) had a partial response (PR); all responses were ongoing at the time of analysis (currently of 40, 76 and 104 weeks duration). Twenty patients (45%) had stable disease (SD) ⩾24 weeks giving a clinical benefit rate (PR + SD ⩾ 24 weeks) of 52%. The median TTP was 22 weeks. Fulvestrant 250 mg was well tolerated and no WHO grade III/IV toxicities were observed.

Conclusion: Fulvestrant 250 mg is a promising endocrine agent with demonstrable efficacy and a very favourable tolerability profile in patients with advanced, breast cancer. The monthly injection schedule supports both close patient monitoring and good compliance. Fulvestrant offers clinicians a new option for the treatment of postmenopausal women with advanced breast cancer progressing on prior endocrine therapy.

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Intensive intravenous ibandronate treatment significantly relieves opioid-resistant bone pain and improves quality of life in patients with skeletal metastases

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Background: Bone metastases are associated with severe and sometimes intractable pain, leading to poor quality of life. A phase III placebo-controlled trial demonstrated that treatment with intravenous (i.v.) ibandronate 6 mg every 3–4 weeks significantly reduced the risk of bone events ($p=0.003$) and reduced bone pain below baseline for 2 years of treatment in metastatic breast cancer ($p<0.001$) [1]. Ibandronate has a renal event profile similar to placebo, supporting the use of higher doses to achieve bone pain relief. This open-label pilot study investigated the effects of intensive "loading dose" treatment with i.v. ibandronate for opioid-resistant bone pain.

Patients and methods: Eighteen patients with resistant pain from bone metastases due to various advanced tumor types (10 breast, 8 miscellaneous) received ibandronate 4 mg by 2-hour infusion for 4 consecutive days (16 mg total dose). Mean baseline opioid analgesic-use was equivalent to 400 mg/day morphine. Patients were assessed for 6 weeks or until death. Study assessments included bone pain (visual analog scale [VAS] from 0=no pain to 10=maximum pain), opioid consumption (morphine equivalent daily dose [MEDD]), patient functioning (EFAT scale), quality of life (VAS from 0=good to 10=poor), and performance status (ECOG scale). Renal function was assessed by serum urea and creatinine measurement.

Results: Intensive "loading dose" ibandronate treatment significantly reduced mean bone pain scores within 7 days ($p<0.001$) and maintained them below baseline levels throughout the study. Ibandronate significantly improved quality of life, patient functioning and performance status ($p<0.05$). Bone-pain relief was not due to increased use of opioids: mean MEDD was unchanged from baseline to endpoint. Ibandronate was well tolerated, with no changes in renal functioning.

Conclusions: Intensive "loading dose" treatment with i.v. ibandronate had a marked analgesic effect in patients with opioid-resistant bone pain, with benefits for patient quality of life and functioning. Despite the high dosing schedule, ibandronate did not lead to dose-limiting renal toxicity. Ibandronate may therefore provide a useful adjuvant to more commonly-used palliative treatments for bone pain, such as opioids, non-opioid analgesics and radiotherapy. The positive effects of intensive ibandronate treatment in this pilot study warrant further investigation in controlled clinical trials.

References

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Phase I intrapatient dose escalation study of weekly epirubicin and docetaxel as first line chemotherapy in metastatic breast cancer

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Anthracyclines in combination with docetaxel are amongst the most active combination therapies for the treatment of advanced breast cancer but are associated with high incidence of myelotoxicity. Weekly combination with these agents has the potential to produce less haematological toxicity than standard 3-weekly regimens at recommended doses. We conducted a Phase I study to define the maximum tolerated dose (MTD) when epirubicin and docetaxel are combined and delivered as a weekly treatment in patients with advanced breast cancer. Treatment comprised epirubicin and docetaxel administered every seven days for 6 doses. Following a two week interval patients tolerating treatment were given a further twelve treatments at the next dose level. The MTD for docetaxel was determined before escalating the dose of epirubicin.

Eleven patients were entered with median age 55 years (range 35 to 67) and performance status 0 to 1. One patient (with extensive bone disease) was unable to tolerate dose level 1 due to repeated grade 3 neutropenia. Three patients completed 6 weeks at dose level 1 and 12 weeks at dose level 2. Of the three patients starting at dose level 3, two experienced dose limiting toxicity (DLT) with grade 3 neutropenia and one patient died from progressive disease after 3 doses, without treatment toxicity. Of the four patients commencing at dose level 2A, one patient completed 17 weeks of treatment and one underwent further escalation of docetaxel dose. Two patients at dose level 2A had DLT due to neutropenia. No grade 4 neutropenia and no febrile episodes occurred. 1 patient required admission for non-neutropenic, non-febrile infection. MTD was defined by dose limiting grade 3 neutropenia, at dose level 3 and 2A. Worst non-haematological toxicities were alopecia, mucositis, nausea, diarrhea, nail changes, asthenia and skin changes (all grade 2). Cardiac function was unaffected. Tumour reduction was seen in all but 2 patients. Formal response evaluation CR 1, PR 3, SD/Not assessable 7. This schedule confers the ability to deliver combination docetaxel and epirubicin at a dose density in excess of standard 3-weekly dosing schedule without significant myelosuppression and acceptable non-haematological toxicity. The schedule is active with responses seen at all dose levels. The recommended dose level for phase II study is epirubicin 30 mg/m^2 and docetaxel 30 mg/m^2 with dose descalation to 25 mg/m^2, 30 mg/m^2 in the event of grade 3 neutropenia.

Dose escalation schedule

Schedule			Number of patients	
Dose level	Epirubicin (mg/m^2)	Docetaxel (mg/m^2)	Entered	Escalated to
1	25	25	4	
2	25	30		3
3	25	35	3	
2A	30	30	4	
3B	30	35		1

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Fulvestrant: an effective second-line treatment for postmenopausal women with advanced breast cancer

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Background: Fulvestrant ('Faslodex') is an estrogen receptor (ER) antagonist that has no agonist effects. Two randomised, Phase III clinical trials including postmenopausal women with advanced breast cancer who have progressed following prior endocrine therapy have shown that fulvestrant is at least as effective as anastrozole in terms of time to progression (TTP), objective response (OR) and clinical benefit (CB) rates. More recently, survival data have also become available.

Methods: Literature review and indirect comparison of efficacy data from second-line trials including fulvestrant, anastrozole, letrozole, and exemestane.

Results: Fulvestrant is at least as effective as anastrozole in terms of survival and indirect comparisons with other second-line treatment trials show that fulvestrant is comparable in terms of efficacy (including survival) to letrozole and exemestane. Efficacy data across second-line treatment trials using these agents is summarised in Table 1.