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.

278 POSTER

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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279 POSTER

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.

280 POSTER

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

the individual response of metastatic breast cancers to docetaxel and trastuzumab, however, the clinical responses were observed in all patients with Bcl-2-negative tumors.

Conclusion: weekly docetaxel and trastuzumab is safe and effective combination method for HER-2-overexpressing metastatic breast cancer.

281 POSTER

An exploratory analysis examining proportion of patients responding for 1 year or more in two phase III studies of fulvestrant versus anastrozole

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Background: Fulvestrant ('Faslodex') is an estrogen receptor (ER) antagonist that has no agonist effects. Two Phase III trials have shown fulvestrant to be at least as effective as anastrozole and associated with a longer median duration of response (DOR; 16.7 months vs 13.7 months, respectively) in patients with advanced breast cancer who had progressed on prior endocrine therapy. This abstract reports an exploratory combined analysis of DOR by categorical time period (⩾1 year), in the patients who experienced an objective response (OR; complete [CR] or partial response [PR]) or clinical benefit (CB; CR + PR + stable disease [SD] ⩾24 weeks) in these two trials.

Methods: Duration of OR and CB was calculated from the date of randomisation until disease progression and percentages were calculated using the total number of patients per treatment group as the denominator (fulvestrant n=428; anastrozole n=423).

Results: A total of 186 patients gained CB with fulvestrant treatment (CR: n=20; PR: n=62; SD ⩾24 weeks: n=104) compared with 173 patients receiving anastrozole (CR: n=11; PR: n=59; SD ⩾24 weeks: n=103). Table 1 shows the proportion of patients with OR or CB in these studies who maintained their response ⩾1 year.

	Fulvestrant 250mg [n=428] (%)	Anastrozole 1mg [n=423] (%)
Total number of patients with OR	82 (19.2)	70 (16.5)
Number of patients with OR ⩾1 yr	43 (10.0)	30 (7.1)
Total number of patients with CB	186 (43.5)	173 (40.9)
Number of patients with CB ⩾1 yr	82 (19.2)	59 (13.9)

OR, objective response; CB, clinical benefit.

A greater proportion of patients on fulvestrant achieved OR and CB for ⩾1 year, these data being supportive of previously reported increased median DOR observed with fulvestrant in these trials.

Conclusion: Fulvestrant is as effective as anastrozole in terms of all major efficacy endpoints evaluated and may have advantages with respect to proportion of patients with prolonged DOR.

282 POSTER

Breast cancer with synchronous metastases: trends in survival over a 14-year period

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Purpose: Although new drugs have been approved during the 1990s for the treatment of metastatic breast cancer, it is not clear whether or not their use has changed the outcome of patients in daily practice. This study sought to determine whether survival has improved over time for breast cancer patients who had metastases at diagnosis.

Methods: 724 patients have been treated in 3 French Cancer centers for an initially metastatic breast cancer between 1987 and 2000. 343 have been diagnosed between 1987 and 1993, and 381 have been diagnosed between 1994 and 2000. Tumor characteristics, treatments and outcome of these patients were compared by χ^2 test, log rank test and Cox regression analysis.

Results: Characteristics were not different between the patients diagnosed between 1987–93 and those diagnosed between 1994–2000. Ten percent of patients treated between 1987 and 1994, and 58% of patients treated between 1994 and 2000 have received either a taxane or a new aromatase inhibitor. The 3 year overall survival rates were 27% for patients treated between 1987–1993 and 44% for patients treated between 1994–2000 (p<0.001). The treatment period (1994–2000 versus 1987–1993) was a prognostic factor in multivariate analysis (relative risk: 0.6, p<0.001).

Conclusion: The survival of breast cancer patients presenting with metastases at diagnosis has improved over the time. This study highly suggests that this improvement is related to treatment.

283 POSTER

Intravenous and oral ibandronate reduce the risk of skeletal-related events (SREs) in patients with breast cancer and bone metastases

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Background: Ibandronate is a highly potent aminobisphosphonate that has recently been approved in Europe for the treatment of metastatic bone disease. Phase III clinical trials have investigated the impact of intravenous and oral ibandronate on the occurrence of SREs in women diagnosed with breast cancer and bone metastases.

Methods: Three multicenter, randomized, double-blind, placebo-controlled trials were conducted. In a trial of intravenous ibandronate, a 6 mg dose (n=154) was compared with placebo (n=158) infused over 1–2 hours every 3–4 weeks. In two trials of oral ibandronate, a 50 mg daily dose (n=287) was compared with placebo (n=277). Data from the oral trials were pooled for analysis, as pre-specified in the study protocols. The primary efficacy endpoint was the Skeletal Morbidity Period Rate (SMPR), defined as the number of 12-week periods with new bone complications. Secondary analysis of SREs was conducted using a multivariate Poisson regression model. A post-hoc analysis using the Andersen-Gill method (time to multiple SREs) was also performed, as used to assess SREs in a 2-year trial of zoledronic acid in patients with metastatic bone disease [1].

Results: Mean SMPR was significantly reduced with ibandronate (6 mg dose, 1.19 versus 1.45 with placebo, p=0.004; 50 mg dose, 0.95 versus 1.18 with placebo, p=0.004). The multivariate Poisson regression analysis demonstrated that intravenous ibandronate 6 mg led to a statistically significant 40% reduction in the risk of SREs compared with placebo (RR 0.60, 95% CI = 0.43, 0.85; p=0.0033). The effect of oral ibandronate 50 mg on the risk of SREs was similar (38% reduction versus placebo, RR 0.62, 95% CI =0.48, 0.79; p<0.0001). The Andersen-Gill analysis showed a 29% reduction in SREs for intravenous ibandronate (RR 0.71, p=0.018) and a 35–42% reduction for oral ibandronate (p<0.005) compared with placebo.

Conclusions: In patients with metastatic breast cancer, intravenous ibandronate 6 mg and oral ibandronate 50 mg similarly reduced the occurrence of SREs. The risk reductions reported with intravenous and oral ibandronate for the prevention of bone events appear to be comparable to zoledronic acid [1], warranting further investigation in comparative studies. As an effective alternative to intravenous bisphosphonates, oral ibandronate offers the choice of convenient at-home dosing to eliminate time-consuming hospital visits for bisphosphonate therapy.

References

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284 POSTER

Longitudinal changes in serum her-2/neu oncoprotein levels in trastuzumab-treated metastatic breast cancer patients

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Background. To evaluate longitudinal variations of serum HER-2/neu extracellular domain (sHER-2) in metastatic breast cancer patients receiving combined trastuzumab treatment.

Patients and methods. 33 patients were monitored by serial sHER-2 ELISA (Oncogene Science) before and during treatment. Results were compared to time to progression (TTP) and survival from treatment initiation. Non parametric statistical tests were used.

Results. Median sHER-2 before 1st injection was 41.37 ng/ml (range 7.54–1597.00 ng/ml, n=32). Mean sHER-2 levels differed significantly between responders (n=20) and non responders (n=13) (P<0.0001). Median TTP (266 days, range 35–1000 days) was unrelated to clinico-biological variables at diagnostic or number and site of metastases before trastuzumab-based treatment. Patients with sHER-2 levels ⩽30 ng/ml