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.

265 POSTER

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

267 POSTER

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.

Table 1

Study	Pts (n)	Median follow-up (mo)	Median survival (mo)	Median TTP (mo)	CB (%)
Buzdar et al. 1998:					
Anastrozole	263	31.2	26.7	4.8	42.2
Dombernowsky et al. 1998:					
Letrozole	174	5.5[a]/18–20[b]	25.3	5.6	34.5
Buzdar et al. 2001:					
Letrozole	199	18.0 (max)	29.0	3.2	29.6
Kaufmann et al. 2000:					
Exemestane	366	13.6	NR	4.7	37.4
Rose et al. 2002:					
Anastrozole	357	30.0 (max)	20.3	5.7	23.0
Letrozole	356	30.0 (max)	22.0	5.7	27.0
Robertson et al. 2003:					
Fulvestrant	428	15.1[c]/27.0[d]	27.4[e]	5.5	43.5
Anastrozole	423	15.1[c]/27.0[d]	27.7[e]	4.1	40.9

TTP, time to progression; CB, clinical benefit (complete response + partial response + stable disease ⩾24 weeks); NR, not reached; [a]Follow-up for TTP and CB; [b]Follow-up for TTD; [c]Follow-up for TTP and CB; [d]Follow-up for TTD; [e]Pippen et al. 2003.

Conclusions: Fulvestrant is at least as effective as anastrozole in terms of clinical efficacy and survival with indirect comparisons suggesting that fulvestrant also offers comparable efficacy to other second-line treatments for postmenopausal women with advanced breast cancer.

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Does systemic chemotherapy improve outcome in breast cancer patients with carcinomatous meningitis?

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Introduction: Carcinomatous meningitis is not common, but serious complication of advanced breast cancer, the incidence of which has recently been increasing. The established methods of treatment ie. intrathecal methotrexate and whole brain irradiation (WBI) are not sufficient in term of prolonging survival in these patients (pts).

Purpose: The aim of the study was to assess the role of systemic chemotherapy undertaken after the diagnosis of carcinomatous meningitis in prolonging the survival.

Material and Method: The study is based on the observation of 37 breast cancer pts with carcinomatous meningitis treated in Cancer Center, Warsaw, Poland, between January 2000 and October 2002. The mean age was 51 years (29–78). In 8 (22%) pts leptomeninges were the only site of metastases. The most common clinical signs and symptoms were: headache (73%), confusion (43%), vomiting/nausea (38%), cerebellar syndrome (38%), pain in thoraco-lumbal region (32%) and paresis/plegia (27%). Cancer cells in cerebrospinal fluid were detected in 100% of cases. Two out of 37 pts were not treated because of poor clinical status. Intrathecal methotrexate treatment, 10 mg per dose, was performed in 35 pts. The number of cycles was 1–15, the mean total dose was 70 mg. In 16 (43%) pts the whole brain irradiation was performed. Twenty-one (57%) women apart from intrathecal methotrexate treatment received systemic chemotherapy. Individual schedules of systemic treatment were used, but the most common were vinorelbine with fluorouracil (9 pts), antracyclines (7 pts), cisplatin (5 pts) and taxanes (4 pts).

Results: Clinical and laboratory response was achieved in 28 pts (76%). The mean survival since diagnosis of carcinomatous meningitis was 16 weeks (1–80 weeks), 25 weeks (8–80) for pts treated with systemic chemotherapy and 10 weeks (1–25) for pts without systemic chemotherapy. The comparison of survival depending on systemic chemotherapy was undertaken. Test log rank stratified for Karnofsky status was highly statistically significant (p=0.0003).

Conclusions: Our observations suggest, that systemic chemotherapy added to intrathecal treatment is the important factor prolonging the survival of breast cancer patients with carcinomatous meningitis.

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Oral Vinorelbine in combination with capecitabine: phase I study in patients with metastatic breast cancer

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Intravenous vinorelbine (VRL) associated with capecitabine (CAPE) has shown promising activity in patiënts with metastatic breast cancer (MBC). The present study investigated the combination of oral VRL and CAPE which offers the convenience of an all-oral combination regimen in patients who had received a maximum of one prior line of chemotherapy (CT) for MBC disease. The study was designed to determine the maximal tolerated dose (MTD) and the recommended dose (RD) of oral VRL at 60 or 80 mg/m^2 on days (d) 1 and 8 and CAPE at doses ranging from 1650 to 2500 mg/m^2/d from d1 to d14 every 3 weeks. At the RD, a weekly administration of oral VRL was tested. The protocol was subsequently amended to test an every 4 week-schedule. A total of 35 patients were included in 7 dose levels. Age ranged from 31 to 69 years; 71% had received prior adjuvant CT and 26% were given prior CT for MBC. When using the every 3 week-schedule, MTD was reached at DL3 (VRL 60 on d1, 8 and CAPE 2500) and DL4 (VRL 80 on d1, 8 and CAPE 1650). Dose-limiting toxicities (DLTs) consisted in persisting neutropenia which resulted in delay in starting cycle 2 for 5 patients and febrile neutropenia in 1 patient. The weekly administration of oral VRL was tested at DL2 (VRL 60 and CAPE 2250) but met the criteria of MTD: 2 out of 6 patients experienced DLTs (one persisting neutropenia and one grade 3 thrombocytopenia). The dose level below (VRL 60 and CAPE 2000) was well tolerated and was therefore the recommended dose when using a weekly administration of oral VRL. Five objective responses among 16 evaluable patients were seen. The 4-week schedule is still being investigated: VRL 80 mg/m^2 on d1, 8 and CAPE 1650 mg/m^2/d from d1 to d14 every 4 weeks was well-tolerated. Higher doses of CAPE (1850 and then 2000) are going to be explored.

In conclusion, the combination of oral VRL and CAPE can be safely administered in MBC patients. The currently recommended regimen is oral VRL 60 mg/m^2/week and CAPE 2000 mg/m^2/day from d1 to d14 every 3 weeks.

270 POSTER

Gemcitabine and vinorelbine as first line therapy in elderly advanced breast cancer (ABC)

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Introduction: Based on a previous studies demonstrating the safety and activity of Vinorelbine (V) and Gemcitabine (G) in a first or second-line treatment for ABC, we decided to test the same regimen in elderly patients (>65a).

Materials and methods: From March 2001 to March 2003, we treated 26 consecutive patients (pts) affected by ABC, with the combination of V and G. The dose were for V 25 mg/m^2 intravenous (bolus) and for G 1000 mg/m^2 intravenous (30′ infusion), on day 1 and 8 every 3 weeks. The therapy was continued until progression or for a maximum of 8 cycles. Median age was 74 (range 65–84), PS was 1 in 16 and 2 in 10 cases. 13 patients received prior antracyclin based adjuvant chemotherapy, 8 CMF adjuvant chemotherapy, 5 any therapy. 12 patients had visceral and bone disease, 5 only liver disease, 4 cutaneous disease, 5 bone only.

Results: A median of 4 cycles were performed in all pts (range 3–8). The delivered dose intensity was 89%. The median follow up was 14 months. Objective response (OR) was reached in 14 patients (53.8%). CR was reached by 4 pts (15.3%) (3 skin and 1 liver) and PR by 10 pts (38.5%). Moreover 7 pts (26.9%) had a stable disease (SD) with a mean duration of 6 months (range 3–9). 5 pts out of 26 (19.2%) progressed during therapy. The mean duration of CR and PR were respectively of 10 (range 7–19) and 7 (range 4–14) months. Haematological toxicity was commonly observed, but WHO grade 3–4 neutropenia occurred only in 5 (19.2%) cases without febrile neutropenia and was rapidly resolved by use G-CSF. Grade 3 anemia was noted only in 2 (7.7%) pts after a mean of 5 courses of therapy. Non-haematological toxicity was rare and consisted mainly in grade 2–3 nausea/vomiting (6 pts, 23%) and constipation (3 pts, 11.5%).

Conclusions: These results confirm that the combination of V and G is an effective and well tolerated regimen for the treatment of ABC in elderly patients. The routinely use of haemopoietic growth factors could improve these results permitting to give a Dose Intensity higher than 89% of this study.