recurrence. For distant metastases, the presence of positive margins, the nodal involvement, the size of the tumor, the undifferentiated histological grade were factors statistically significant.

Metastatic breast cancer

436 POSTER

Renal safety of intravenous ibandronate with short infusion times

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Background: Reducing treatment toxicity is an important consideration in MBD management, not least because of the unpleasant adverse effects associated with primary cancer therapy. Existing intravenous (i.v.) bisphosphonates for metastatic bone disease (MBD) are associated with renal toxicity, such that continual monitoring of creatinine clearance levels, hydration of the patient and lengthy infusion times (up to 2 hours) may be required. There is a clinical need for an i.v. bisphosphonate that can be infused over relatively short time periods without renal adverse effects. The pharmacokinetic and renal safety profile of i.v. ibandronate, a third-generation bisphosphonate, has been investigated over infusion periods of 1560 minutes.

Patients and methods: The pharmacokinetic and renal safety parameters of i.v. ibandronate were assessed in a parallel-group study of healthy male (n=27) and female (n=30) volunteers. Subjects received a single infusion of i.v. ibandronate 6mg administered over 60 (n=19), 30 (n=20) or 15 (n=18) minutes. Pharmacokinetic parameters included maximum plasma concentrations (C max), volume of distribution(Vz), half life (t1/2), renal clearance (CLr) and fraction of dose excreted (f e). Renal function was assessed by measures of urinary creatinine clearance, serum creatinine levels, and urinary excretion of microalbumin, a1 -microglobulin or N-acetyl-b-D-glucosaminidase (b-NAG) prior to, and up to 72 hours following, infusion. In a sub-analysis of a placebo-controlled, double blind, phase III clinical trial, patients with MBD from breast cancer were randomized to receive i.v. ibandronate 6mg (n=28) or placebo (n=23) infused over a 1hour period every 34 weeks, for a 3-month period. Proteinuria, albuminuria, a1 -microglobulin or b-NAG were assessed prior to drug infusion and 1, 2, 5, 10 and 28 days following each administration, as markers of renal function.

Results: In healthy volunteers, reducing the infusion time of a single dose of i.v. ibandronate 6mg from 60 to 15 minutes was associated with an increase in C max(mean ± SD: 308 ± 44.8 ng/mL vs 397 ± 94.5 ng/mL), but had little impact on Vz (118 ± 17.7L vs 141 ± 32.1L), t (10.6 ± 1.1 hours vs 10.3 ± 2 hours), CLr (70.6 ± 14.4 mL/min vs 88.2 ±24.0 mL/min) or f (percentage dose excreted: 51.6 ± 7.30% vs 52.3 ± 10.3%). S hortening the infusion time of i.v. ibandronate 6mg from 60 to 15 minutes had no adverse effects on any of the renal function parameters assessed (creatinine clearance, serum creatinine levels, urinary microalbumin, a1 -microglobulin or b-NAG).

In patients with MBD from breast cancer, infusion of ibandronate 6mg i.v. over a 1-hour period produced no significant changes in proteinuria, albumin, a1 -microglobulin or b1-NAG levels. Transient rises in proteinuria in both the ibandronate and placebo groups were considered to be related to previously existing renal dysfunction and individual biological variability.

Conclusions: In healthy volunteers, the pharmacokinetics of i.v. ibandronate 6mg are comparable when infused over 60 or 15 minutes. Shortening the infusion time to 15 minutes had no effect on renal function parameters. In patients with MBD, 1-hour infusion of i.v. ibandronate every 3-4 weeks was well-tolerated, with no significant renal toxicity. This contrasts with renal adverse event profile of other i.v. bisphosphonates (zoledronate and pamidronate). As the pharmacokinetics of ibandronate are clinically equivalent between healthy volunteers and MBD patients, i.v. ibandronate 6mg infused over 15 minutes may also have a favourable renal safety profile in this indication. Further investigation of renal functioning following 15-minute infusion of i.v. ibandronate 6mg in patients with MBD is warranted in future clinical trials.

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A multicenter Phase II trial to evaluate gefitinib ('Iressa', ZD1839) (500 mg/day) in patients with metastatic breast cancer after previous chemotherapy treatment

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Background Epidermal growth factor receptor (EGFR) is a key modulator of tumor cell function and is considered to be a viable drug target in a variety of solid tumors. The clinical benefit and safety of gefitinib ('Iressa', ZD1839), an orally active EGFR tyrosine kinase inhibitor (EGFR-TKI), was evaluated in this non-randomized, open-label, Phase II, multicenter study of patients (pts) with heavily pre-treated, metastatic breast cancer.

Methods Eligible pts had received anthracyclines and taxanes and 1 or more chemotherapy regimen for advanced breast cancer. Pts took gefitinib (500 mg/day), the majority as 3rd- or 4th-line treatment, until disease progression. A dose delay of up to 14 days or a dose reduction to 250 mg was permitted if toxicity was observed. The primary endpoint was the clinical benefit rate (CR + PR [RECIST criteria] + SD) at 6 months.

Results Data for 46 pts, median age 54 years (range 31-70), are available as the basis for this abstract. The metastatic sites of disease were liver (51 lesions), lymph nodes (24), lung (19), skin/soft tissue (11), bone (19), and others (19). After 12 weeks, 1 pt (2.2%) had a PR, 3 pts (6.5%) had SD (2 patients >3 months) and 42 pts (91.3%) had PD. The PR was seen in a pt with 4 liver lesions at study start. After 3 months, 1 of the 4 lesions was no longer detected and pleural metastases had diminished significantly. Currently, at 168 days of therapy the pt is still receiving gefitinib. Two pts reported a significant improvement in pain at metastatic sites (1 liver, 1 bone). Adverse events (AEs) were: facial rash, 7 pts (15%); nausea, vomiting, and bowel disturbance, 26 pts (57%). CTC grade 3 AEs considered gefitinib-related were seen in 3 pts (exanthema, diarrhea, and non-infectious wound). No grade 4 drug-related AEs were reported. One pt (2.2%) withdrew due to gefitinib-related AEs (grade 2 pruritus, peripheral edema and weakness). Dose interruptions occurred in 16 pts (35%) and 6 pts (13%) had a dose reduction due to persistent grade 1/2 skin or gastrointestinal AEs. Further details of efficacy, safety, and quality of life analyses will be presented. In addition, tumor samples are being collected and will be analyzed to try to identify which patients benefit from this innovative treatment.

Conclusion These preliminary data provide evidence that gefitinib may be effective as monotherapy in recurrent breast cancer. 'Iressa' is a trademark of the AstraZeneca group of companies

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Increased pretreatment serum lactate dehydrogenase (LDH) is the most important determinant of central nervous system (CNS) metastases in patients with metastatic breast cancer.

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Purpose: To identify predictive factors and estimate the risk of development of CNS metastases in patients with metastatic breast cancer.

Patients and methods: Data from 579 stage III-IV breast cancer pts treated between Nov. 1983- May 1995 with an epirubicin based chemotherapy were retrieved. Statistical analysis included Kaplan-Meyers survival plots, Cox proportional hazard analysis and competing risk analysis using the cumulative incidence (CI). The endpoints of interest: occurrence of CNS metastases. Meanwhile, two other event could preclude (were competitive)

to the occurrence of CNS metastases: either dead of breast cancer without proven CNS metastases or dead of other causes.

Results: A total of 124 pts (21%) developed CNS metastases, 411 pts (71%) died of breast cancer, 16 pts (3%) of other causes (cardiac toxicity (12 pts) other toxicity (4 pts), 28 pts (5%) are still alive. Median follow-up was 135 mts (range 0-183+mts). Median time to CNS involvement after start of chemotherapy: 12 mts (range 0-55mts). Following factors predicted CNS metastases: elevated pre-treatment LDH (1-2x upper normal limit (UNL) and >2 x UNL) liver, lung and lymph node metastases and estrogen receptor negative/unknown tumor (ERneg/unknown). Elevated LDH was a predictive factor for all three event, while lung and liver metastases and ERneg/unknown tumor were predictive factor dead of breast cancer too. Increased LDH was the most influential factor identified. CI in pts without any CNS risk factors was 9%. With 'LDH elevated 1-2xUNL' as only risk factor the CI rosed to 20% and up to 55% when 'LDH elevated>2xUNL'. For pts with lung metastases as only risk factor the CI was 18%, and reached 36%in combination with 'LDH elevated 1-2xUNL.

Conclusion: Elevated pre-treatment LDH was the strongest predictive factor for occurrence of CNS metastases in pts treated for metastastic breast cancer. Liver, lung and lymph node metastases were predictive factors too. The risk differed considerably between risk groups, and for some the risk of development of CNS metastases was greather than the risk for dying of breast cancer outside the CNS.

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Correlation between efficacy of single-agent Trastuzumab (T) and molecular markers in HER-2 positive advanced breast cancer patients.

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Background: HER-2 overexpression is the only known marker predictive of response to T. Nevertheless, 60% of patients with HER-2 amplified breast cancer will not benefit from T. The activation status of either the horizontal network (ErbB family receptors: EGFR, HER-2, HER-3, HER-4), or of the vertical signalling pathway (Akt, MAP kinases), might play a relevant role in this context.

Material and methods: Medical files from 247 patients registered in two national compassionate use programs have been reviewed. The targeted population of our study is represented by 89 patients for whom an assessment of the response to single-agent T was adequately documented. The following biological markers have been evaluated by immunohistochemestry on archival tumor samples from the same patients: EGFR, pEGFR, HER-2, pHER-2, HER-3, HER-4, pAkt, and pMAPK.

Results: Median age of the study population was 55.5 years (range 26-82 years). Median number of metatastic sites was 2 (range 1-4). Sixty-four of 89 patients (71.9%) had visceral disease (liver and/or lung). Fifty-one patients (57.3%) received previous hormonotherapy for metastatic disease (range 1-5 lines, median 2), and 84 of 89 patients (94.3%) were pretreated with chemotherapy (range 1-5 lines, median 2). A median of 16 T weekly cycles have been administrated to 89 patients, with a range of 6-87 cycles. After an independent response review, two complete and nine partial responses have been confirmed (overall response rate12.4%). Twenty-nine patients (32.6%) had stable disease as best response (*6 mos in 14 patients). Thirty-seven patients (41.5%) had progressive disease. In 12 patients (13.5%) clinical response and/or biological markers were not evaluable. Median time to progression for the 77 evaluable patients was 3 mos (range 1-34 mos), and median overall survival was 18 mos (range 2-38 mos). Analysis of biological markers on archival samples is currently ongoing.

Conclusions: The study hypothesis is that the activity of T is increased in the subgroup of tumors carrying HER-2 pathway activation, i.e.: HER-2 +, pHER-2 +, pMAPK, and/or pAkt +. Full results will be available for the meeting.

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Superiority of Tandem High-Dose (HDC) Over conventionally-dosed Chemotherapy(CDC) in Patients (Pts) with Metastatic Breast Cancer (MBC): Updated Results of the International Randomised Breast Cancer Dose-Intensity Study (IBDIS)

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In non-RCT, late-intensification HDC (usually single-cycle), produced promising outcomes in pts who had responded to CDC. This was not confirmed in PRCTs. We hypothesised that multi-cycle HDC with minimal CDC might be more logical, and we compared this approach to CDC in our PRCT.

Methods: Pts without prior CDC for MBC were randomised to CDC: Doxorubicin/Docetaxel (AT) x 4 (50/75-all doses in mg/m^2), followed by all i.v. CMF x 4 (600/40/600 days 1&8), or HDC: AT X 3, then ifosphamide/carboplatin/etoposide (12,000/AUC 18/1200), and 28 days later Thiotepa/Cyclophosphamide (800/6,000). Lenograstim was administered after all AT and HDC cycles, haematopoietic progenitors were leukapheresed after AT #2 and infused after both HDC cycles.

Results: Following ASCO 1999, and the Bezwoda incident, accrual failed, with 110 of a planned 264 enrolled. There were 6 deaths on treatment (4 HDC). The median follow-up is now 45 (range 68-21) months. The study is positive for its primary endpoint which is three-year event (relapse, or treatment-related death)-free survival (27% HDC, 20% CDC p=0.02, median EFS HDC-437 v 290 days respectively, p=0.014, RR 0.59), and for progression-free survival (468 v 300 days respectively p=.009). Med overall survivals were 961 and 812 days respectively (p=0.18). A 100% blinded audit is underway.

Conclusion: Despite the premature termination of accrual, HDC was superior to CDC in MBC. HDC remains a valid investigational strategy.

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A phase I study of oral vinorelbine and paclitaxel in metastatic breast cancer (MBC)

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Background: The combination of intravenous (IV) vinorelbine (VRL) generally given on days 1 and 8 of an every three-cycle and paclitaxel (PTX) is an effective option for the treatment of MBC. In an effort to improve patient convenience, IV VRL was replaced by its oral form used at equivalent doses.

Material and methods: We sought to determine the maximal tolerated dose (MTD) evaluated during the first cycle of oral VRL given on days 1 and 8 and PTX infused over 3 hours on day 1 every 3 weeks, maximum of 6 cycles. The dose of oral VRL was escalated from 60 to 80 mg/m2 in 10 mg/m2 increments. PTX was administered at 110 and then 135 mg/m2. Eligibility criteria included first-line chemotherapy of MBC. Three to 6 patients per cohort were treated.

Results: Twenty two patients were treated in the first 4 cohorts (oral VRL / PTX): 60/110, 70/110, 80/110, 80/135. In cohort 4, seven patients were treated, one patient being non evaluable for MTD; and 3 of them presented a dose-limiting toxicity (DLT) consisting of febrile neutropenia and neutropenic infection. Therefore 80/135 was the MTD. Because 36% of oral VRL administrations on day 8 were delayed to day 15 at 80/110, two additional cohorts were tested: in cohort 5, oral VRL 60 mg/m2 on days 1 and 15 and PTX 135 mg/m2 on day 1 and in cohort 6, oral VRL 80 mg/m2 on days 1 and 15 and PTX 110 mg/m2 on day 1, every 3 weeks. In cohort 5, six out of 8 patients had DLTs: omission of oral VRL on day 15 for 5 patients, grade 4 neutropenia > 7 days for another one. Therefore the recommended dose (RD) for further clinical testing was oral VRL 80 mg/m2 on days 1 and 15 and PTX 110 mg/m2 on day 1 of an every 3 week cycle. Three of the 8 evaluable patients treated at the RD had a partial response.