

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 rose 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 metastatic 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 greater than the risk for dying of breast cancer outside the CNS.

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POSTER

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 immunohistochemistry 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 metastatic 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 hormone therapy 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 administered 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 rate 12.4%). 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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POSTER

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/m²), followed by all i.v. CMF x 4 (600/40/600 days 1&8), or HDC: AT X 3, then ifosfamide/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 leukaopheresed after AT #2 and infused after both HDC cycles.

Results: Following ASCO 1999, and the Bezvoda 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=0.009). 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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POSTER

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.