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Dose-finding study of docetaxel plus 5-fluorouracil (5-FU) in patients with metastatic breast cancer

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Purpose: To determine the dose-limiting toxicity (DLT), maximum tolerated dose (MTD) and recommended dose of docetaxel plus continuous infusion 5-FU in patients with metastatic breast cancer previously treated with an anthracycline-containing regimen. The maximum tolerated dose was defined as three or more DLT events in six patients. Additional objectives were to evaluate response rate and the duration of response. This was a multicentre, open-label, non-randomised study. The recommended doses in this combination regimen are to be used for further phase II/III evaluation.

Methods: 28 Patients were enrolled over the course of the study. Patients received docetaxel (60 mg/m2, 1-hour infusion q3 weeks on day 1), folinic acid (500 mg/m2, 2-hour infusion on Days 1 and 15) and 5-FU (1.8 g/m2, 24-hour infusion on Days 1 and 15). Patients then received either of the following doses of docetaxel (Day 1) and 5-FU (Days 1 and 15) during subsequent cycles: at dose level 1 (60 mg/m2, 1.8 g/m2); at level 2 (75 mg/m2, 1.8 g/m2); at level 3 (85 mg/m2, 1.8 g/m2); at level 4 (100 mg/m2, 1.8 g/m2); at level 5 (100 mg/m2, 2.1 g/m2). Anthracycline pre-treatment was given for adjuvant purposes (7/28 patients) or for palliative purposes (21/28 patients). Of the 28 patients enrolled, 17 received six or more treatment cycles. Treatment was stopped in the case of progressive disease (PD; 4/28 patients), stable disease (SD; 11/28 patients), partial response (PR; 9/28 patients) or DLT (4/28 patients).

Results: With respect to DLT: none was observed at level 1 (n=3); one serious infection related to a portacath and one diarrhoea NCI-CTC grade IV occurred at level 2 (n=6); one serious infection due to staphylococcal pneumonia at level 3 (n=7); one febrile neutropenia grade IV and one staphylococcal sepsis at level 4 (n=6); one serious infection related to a portacath and one erythema grade III/IV at level 5 (n=6). Four patients were not evaluable for tumour response because they only received two treatment cycles. Of the remaining 24 patients, there were 4 PD, 11 SD and 9 PR. The response duration for the patients with PR was 195 days.

Conclusion: Although the MTD was not reached, the recommended dose is docetaxel 100 mg/m2 and 5-FU 2.1 g/m2. This regimen displays promising antitumour efficacy and is suitable for further phase II/III evaluation in patients with metastatic breast cancer.

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Effect of cardiac dysfunction on treatment outcome in the herceptin pivotal trial

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Background: H, a humanized monoclonal antibody directed against HER2, increases time to progression, response rate, and survival in combination with first-line chemotherapy and induces durable responses as a single agent in women with HER2-positive metastatic breast cancer. In the pivotal trials of H, treatment was associated with cardiac dysfunction (CD) similar to the cardiomyopathy associated with anthracycline (A) administration. CD occurred at greatest frequency (28%) in patients simultaneously receiving A compared to 7% in patients receiving A alone. CD was less common and less severe in patients treated with paclitaxel (T) plus H: 11% of patients receiving T plus H and 1% of patients receiving T alone. The majority of patients (75%) improved with treatment for congestive heart failure, and 77% continued to receive T for a median of 25 weeks.

Methods: The effect of CD on treatment outcomes was evaluated in the 469 patients in the pivotal H combination chemotherapy trial (H0648g). For the purposes of this analysis, time to treatment failure (TTF) was defined as the time to disease progression or CD and CD-free as the time to symptomatic CHF (NYHA grade III or IV) or death.

Results: As shown below, H produced improvements in TTF and CD-free survival.

TTF (months) (95% CI):
H + C 6.5 (5.8,7.0); C 4.6 (4.4,5.3);
H + AC 6.6 (5.5,7.3); AC 6.0 (4.8,6.9);
H + T 6.6 (5.3,7.1); T 2.8 (2.0,4.3)

CD-free survival (months) (95% CI):
H + C 22.2 (17.7,25.4); C 20.0 (16.5,24.0);
H + AC 22.3 (16.6,25.7); AC 20.9 (16.8,28.6);
H + T 22.1(17.1,26.3); T18.4 (12.7,24.4)

Conclusions: Improvements in treatment outcomes when H was added to chemotherapy were observed despite the development of CD. These results suggest that risk/benefit considerations in the metastatic disease setting favor the use of H plus T.

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Phase II study of weekly docetaxel (Taxotere; txt) and trastuzumab (Herceptin; H) for patients with HER-2 overexpressing (HER2+) metastatic breast cancer (MBC)

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Combination of H with chemotherapy improves response rates, time to progression (TTP) and survival in patients (pts) with HER2+ MBC. Txt is one of the most effective treatments for MBC. Txt and H are synergistic in vitro. A phase II trial was designed to evaluate the efficacy and safety of weekly Txt + H in patients with HER2+ MBC. H was given on day 1 as a 4 mg/kg loading dose (cycle 1 only), followed by 2 mg/kg per week (wk). Txt was administered at 35 mg/m2/wk. One cycle is defined as 3 weekly administrations of Txt + H followed by 1 week of rest. HER-2 status was defined by immunohistochemistry (IHC, score 3+) or by flourescence in situ hybridization. Results are reported for all 30 patients enrolled in this study. Median age 45 (33-78) years. Twenty-six pts (87%) had received prior chemotherapy, either adjuvant or for MBC. A median of 6 (2-16) cycles was given per pt. Number of weekly doses delivered: 589. The median time on study was 24 (8-64) weeks. Hematological toxicity: grade 3/4 neutropenia (8 pts); 1 patient developed neutropenic fever; no grade 3/4 anemia or thrombocytopenia. Non-hematological toxicity (grade 3/4): catheter-related bacteremia (1 pt), diarrhea (1 pt), neuropathy (1 pt), fatigue (6 pts), pleural effusion (1 pt), asymptomatic transient LVEF decline below 50% (3 pts), pulmonary edema (1 pt). All 30 pts are evaluable for response to therapy. Eighteen pts (60%) had a partial response; 4 pts (13%) had a minor response; 4 pts (13%) had stable disease; and 4 pts (13%) had progressive disease (PD) as best response. FISH data are available for 23 pts (20+, 3-). The response rate in pts whose tumors were FISH+ was 65%. Three patients had brain metastases at the time of recurrence. In two of them the brain was the only site of disease. These patients were treated with whole brain irradiation and H was continued until PD. Twelve patients continue on study. The estimated median time to progression is 6 months. In summary, weekly Txt + H is a safe and effective regimen for pts with HER2+ MBC. Support: Genentech, Aventis

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Markers of bone turnover in metastatic breast cancer (MBC) patients having progressed on tamoxifen: Short term effect of further treatment with either exemestane (EXE) or megestrol acetate (MA)

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Bone turnover markers and their correlation with tumor response in pts on hormonal treatment for MBC has seldom been explored. We performed a prospective study on bone turnover markers on 53 pts enrolled in a large randomized study of (24 pts) EXE 25 mg/day vs (29 pts) MA 160 mg/day in MBC pts having progressed on tamoxifen (Kauffman M. et al., JCO 2000). The two groups were well-balanced and 40 pts had MBO spread to bone. The bone serum markers analyzed were bone alkaline phosphatase (BAP), and type-I collagen telopeptide (ICTP). Tumor response and clinical benefit (CR + PR + SD $\geq$ 24 wks) were 12.5% and 54.2% on EXE and 10.3% and 34.5% on MA. Pts were sampled at baseline, 8 wks, 24 wks and every 12 wks thereafter until PD. Only the 8-wks data (51 pts) are reported due to pts drop-out for PD as geometric mean.

No correlation was found with tumor response for BAP or ICTP. There was a significant correlation between the ICTP increase and E_1S suppression ($p < 0.01$ for EXE and $p < 0.05$ for MA), but not with BAP. In conclusion, bone turnover markers ate affected by estrogen suppression in MBC. The increase in ICTP, but not of BAP, on MA might suggest a modest catabolic