

Patients and Methods: Pts with locally advanced (LA) or metastatic breast cancer (MBC) and ≤ 1 prior neo/adjuvant regimen discontinued ≤ 12 months before study entry were eligible. A maximum of 8 cy could be given (A total dose $\leq 480\text{mg/m}^2$) without routine G-CSF support.

Results: Sixty-six cy (median 4, range 1-6) have been given so far to 19 pts (11 with LA and 8 with MBC) with 8 pts still under treatment. Four dose levels have been tested from T30/A20/X1650 mg/m^2 , up to the maximum tolerated dose (MTD) of T35/A25/X2000 mg/m^2 (6 pts). DLTs after the 1st cy at MTD were FN (4 pts), G3 diarrhoea (1 pt) and delayed absolute neutrophil count (ANC) recovery (1 pt). Overall, G4 neutropenia occurred in 26% of cy with 6 episodes of FN (9%), \geq G2 diarrhoea and mucositis complicated 21% and 18% of cy, respectively. Eleven pts (58%) required either dose reductions (32%), treatment delays (16%) or both (10%), as a consequence of \geq G2 GI toxicity in 3 pts (28%), haematological toxicity or the combination of both in 4 pts each (36%). The preliminary ORR in 18 evaluable pts who received at least 2 cycles is 50% (45% in LA disease, 50% in MBC) with stable disease in 39% of pts.

Conclusions: The TAX regimen proved to be safe and active in ABC. The cumulative toxicity profile needs however to be better defined, mainly on its impact on quality of life and on feasibility to deliver adequate total doses of the combination. A direct comparison with TEF might be a reasonable project to select the most cost-effective regimen in the individual patient.

712

POSTER

Cardiac safety and efficacy of TLC D99 (D99) and trastuzumab in patients with advanced breast cancer

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Purpose: D99 (MyocetTM) is a liposomal doxorubicin (D) with significantly reduced cardiotoxicity compared to conventional D. Trastuzumab (T) is intrinsically cardiotoxic, but has additive or synergistic efficacy with D against breast cancer. To determine the safety of D99 + T, and to obtain preliminary efficacy data in advanced breast cancer (ABC), we performed this phase I/II study in patients (pts) with HER2+ tumors: 2-3+ by immunohistochemistry or gene amplification by fluorescence in-situ hybridization.

Methods: Left ventricular ejection fraction (LVEF) by multigated acquisition scan at baseline and after every even cycle; protocol-defined cardiotoxicity = LVEF reduction by 20 points or more to a value within the normal range; by 10 points or more to below the normal range; or congestive heart failure. Regimen: D99: 60 mg/m^2 intravenously (IV) every 3 weeks; T: 4 mg/kg IV week 1 followed by 2 mg/kg IV weekly. Eligibility: ABC; one or fewer prior T regimens; 2 or fewer cytotoxic regimens for ABC; prior adjuvant D permitted (up to 240 mg/m^2).

Results: n = 29; 136 cycles of therapy given. 13 pts had adjuvant D; 11 pts had prior chemotherapy for ABC; 4 had T. Median #cycles/pt: 6 (range 1-11). 23 pts had cumulative D + D99 dose of 360 mg/m^2 or greater (range 120-780 mg/m^2). No cardiotoxicity has been seen to date; 14% pts had grade 3 neutropenia (0 grade 4); other toxicities have been manageable. 20/29 pts evaluable for measurable response (secondary objective): 1 complete response, 11 partial responses, 60% overall response (95% confidence interval: 36-81%). 3 stable disease; 6 progressive disease (2 who had previously progressed on T); 2 pts with non-measurable disease normalized tumor markers; 6 pts are not yet evaluable for response.

Conclusions: D99 + T appears to be a well tolerated, active regimen in pts with HER2+ tumors. No cardiotoxicity has been observed to date among 29 pts treated with D99 + T, 45% of whom had prior D. A 60% overall major response rate was observed in these pts in a 1st-3rd-line setting. Accruals are continuing to a maximum of 40; additional trials are planned.

713

POSTER

Efficacy and safety of navelbine oral (NVBO) in first line metastatic breast cancer (MBC)

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Purpose: Navelbine intravenous (NVBi.v.) is highly active in MBC. Given the ease of administration (adm) and greater patient convenience of oral

chemotherapy, a capsule of Navelbine has been developed. Here are the preliminary results of an open-label, multicenter phase II study of NVBo in the first-line treatment of MBC.

Methods: NVBo was administered at a dose of 60 $\text{mg/m}^2/\text{w}$ for the first 3 adm and subsequently increased to 80 $\text{mg/m}^2/\text{w}$ if no severe neutropenia occurred. From 12/97 to 08/00, 72 patients (pts) were enrolled. Pts characteristics at entry were: median age 63.4 years, 23.6% stage IIb/IV at diagnosis, 47.2% visceral involvement and 56.9% with ≥ 2 organs involved.

Results: A median of 10 adm per pt of NVBo were given. Relative median dose intensity was 88.6%. All responses were reviewed by an independent panel: 2 CR and 15 PR were validated giving a RR of 23.6% [95% CI=14-33] in the intent-to-treat (ITT) population (n=72) and 27% [95% CI=16-38] in the evaluable population (n=63).

Pts were stratified at study entry by 3 strata (S): S1= prior adjuvant hormonotherapy, S2= prior adjuvant chemotherapy, S3= no prior adjuvant therapy.

For the S3 RR was only 14.3% and 15% in the ITT (n=21) and the evaluable (n=20) populations, respectively. Actually, this group consisted mainly of pts with very poor prognosis features: 52.4% with stage IIb/IV, 71.4% with DFI ≤ 2 years and 57.1% with ≥ 3 organs involved. This is in contrast with the 2 other strata in which a smaller proportion of pts presented such bad prognosis factors.

In S1 RR were 27.8% and 31.3%, in the ITT (n=18) and evaluable (n=16) populations, respectively. And in S2 RR were 27.3% and 33.3%, in the ITT (n=33) and evaluable (n=27) populations, respectively.

G4 neutropenia was reported in 28.6% of pts (3.3% of adm). One febrile neutropenia and 2 neutropenic infections were reported. G3-4 nausea, vomiting and diarrhoea were observed in 12.8%, 10% and 8.5% of pts, respectively. No primary prophylactic antiemetic was recommended. Neurotoxicity was minimal. No toxic death nor unexpected adverse event were reported. These results show the efficacy of NVBo is comparable to NVBi.v. and its safety profile is qualitatively similar.

Navelbine Oral represents a good alternative to NVBi.v. Accrual is ongoing. Updated results will be presented at the meeting.

714

POSTER

Activity and feasibility of a ten-day schedule of single agent vinorelbine (VNR) in advanced, pretreated breast cancer (BC): a phase II study

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Purpose: VNR has been shown to be active against advanced BC as both 1st-line and salvage treatment, with acceptable toxicity. Previous published studies reported the need of G-CSF support when intravenous (i.v.) VNR was given weekly at 25-30 mg/m^2 , with neutropenia being dose-limiting. Our prior single-centre experience also confirmed a high incidence of leukoneutropenia in 10 earlier treated patients (pts) given a weekly regimen; thus we designed a phase II study to test the activity and tolerability of a ten-day schedule of single agent VNR in the advanced setting.

Patients and Methods: Thirty consecutive pts aged 35-72 years (median 49) with histologically confirmed, evaluable advanced BC entered the trial. All pts had received prior anthracyclines for the metastatic disease, and 25 of them had also been treated with taxane (23 with paclitaxel and 2 with docetaxel). The number of prior chemotherapy regimens ranged from 1 to 4 (median 2, mean 3); 27 pts had previously received hormonal treatment. The most represented metastatic sites were visceral (liver 47%, lung 27%); 13 pts had bone lesions, alone or combined with loco-regional disease. VNR was given i.v. at a dose of 25 mg/m^2 over 10 minutes, every 10 days, on ambulatory basis. Treatment was continued either for 6 months, until disease progression or unacceptable toxicity.

Results: A total of 192 cycles were given (median 9, range 4-18 per patient); the median DI was 22.5 $\text{mg/m}^2/\text{wk}$. One complete (CR) and 10 partial responses (PR) were achieved, for an overall objective response (OR) rate of 37% (95% confidence interval, 20% to 55%). Five out of 24 pts (21%) whose disease progressed while receiving anthracycline (clear resistance) had a PR, and 24% taxane-pretreated pts had an OR, including the CR at the bone level. Additional 7 MRs and 6 SDs were found. Median TTP was 19 weeks (range, 12-36) and median survival time was 38 weeks. Treatment compliance was good, with mild non-haematological toxicity (WHO gr.1 peripheral neuropathy in 12 pts, gr.1 phlebitis in 9, grade 1-2 constipation in 13); gr.3 neutropenia, lasting 7-12 days, occurred in 4 pts (23% of cycles).

Conclusions: Our results confirm that VNR is able to produce major responses in advanced BC, also in heavily pretreated pts. Specifically,