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 ≤ 480mg/m2) 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/m2, up to the maximum tolerated dose (MTD) of T35/A25/X2000 mg/m2 (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%), ≥ 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 ≥ 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 (Myocet™) 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 mg/m2/w for the first 3 adm and subsequently increased to 80 mg/m2/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 IIIb/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 IIIb/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/m2, 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/m2 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 mg/m2/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,

the 10-day schedule we evaluated appears useful in reducing the incidence of neutropenic episodes and treatment delays, allowing an adequate dose-intensity of the drug with moderate toxicity.

715 POSTER

The upregulation of cellular adhesion proteins following transfection of the keratin 18 gene into human breast cancer cells is accompanied by a dramatic decrease of invasion and metastasis in vitro and in vivo

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In vitro experiments as well as clinical studies revealed that the expression of keratin 18 (K18) in breast cancer tumors is associated with a favorable prognosis and a less aggressive phenotype of the carcinoma. To prove the principle we transfected the human K18 gene into the aggressive MDA-231 cell line and isolated a permanently overexpressing clone. These cells grow in dense monolayers with epithelial morphology whereas wild type and mock transfected control are of the dedifferentiated, malignant type with cells being spindle shaped, motile, and only loosely attached. The K18-transfected clone is characterized by a high expression of the adhesion proteins plakoglobin, desmoglein and E-cadherin in contrast to wild type and control which are virtually devoid. In addition, keratin 8 the indispensable dimerisation partner of K18 in keratin filament formation is upregulated too. Conversely the mesenchymal filament protein vimentin, forming the intermediate filaments of the cytoskeleton in MDA-231 wild type and control, is completely downregulated in the K18 clone. The high invasiveness of the wild type in the Boyden chamber is dramatically reduced for the K18-clone. In the nude mouse no metastasis could be observed for the K18-cells whereas wt and control metastasized into lung, liver, and bone marrow. In epithelial cells the intermediate filaments of the cytoskeleton are formed by keratins and K18 is a marker of well differentiated mammary lumenal cells. The loss of K18 and its replacement by vimentin is part of a general loss of differentiation along with the malignant transformation. An additional aspect of this process is the loss of adhesion proteins. This dedifferentiation seems to be reversible, at least in part, by the re-expression of K18. To reconfirm this hypothesis by approaching from "the opposite" we established an epithelial subclone of the MDA-231 cells without gene transfer by selecting adhesive cells in weekly trypsinations over a period of 9 month. This clone is not only characterized by the expression of plakoglobin, desmoglein, and E-cadherin but also by the expression of keratins 8 and 18! In addition the same impressive drop in invasiveness and metastasis as for the K18-transfected cells could be observed.

716 POSTER

Five-day Infusion Fluorouracil and Vinorelbine as chemotherapy for advanced breast cancer patients previously treated with anthracyclines

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Vinorelbine (VNR) has proven to be effective drug in metastatic pretreated breast cancer patients. Particularly, no cross resistance with anthracyclines has been demonstrated. The long term continuous 5-Fluorouracil (5-Fu) infusion presents better pharmacological profile than its bolus administration.

Purpose: We investigated the combination of this two antitumor drugs in patients (pts) with MBC who were previously treated with anthracycline-containing regimens.

Patients and Methods: From February 1998 to January 2000, sixty five pts were enrolled into the study. The pts mean age was 48 years (range 31-70). The most important inclusion criteria was as follows: Karnofsky 70-100, measurable or evaluable disease, normal renal, hepatic, bone marrow and cardiac function.

Fourteen of the sixty five women have already received more than one chemotherapy line. Twenty three pts were previously treated with taxanes.

Sites of metastatic lesions were as follows (% of pts): lungs 50%; liver 37%; soft tissue 72%; bone 58%; other sites 32%.

Treatment consisted of VNR 25 mg/m2 administered on day 1 and 6 every 21 days and 5-Fu 700 mg/m2/day for five consecutive days (1-5) every 21 days. The total number of cycles was 340, (mean: 5 cycles).

Results: The scheme was well tolerated. Febrile neutropenia was observed in 4,6% of pts. 14% of pts experienced grade 3 or 4 neutropenia, and 3% grade 3 thrombocytopenia. Grade 3 stomatitis was observed in 9,2% of pts, grade 3 neurologic toxicity was observed in 1,5% of pts, and grade 3 cardiotoxicity in 4,6% of pts. Grade 3 local reaction occurred in 3% of pts.

Sixty pts were evaluated for response. One (1,7%) patient attained a complete clinical response and twenty eighth (46,7%) achieved a partial response. In twenty two (36,6%) cases stable disease was documented, and nine (15%) pts progressed while on treatment. Median time to progression was 24 weeks, median duration of response: 35 weeks, and median overall survival was 41 weeks.

Conclusion: VNR with five-days infusion of 5-Fu is an active and manageable scheme in MBC patients previously treated with anthracyclines. Overall response was 48,4% and median overall survival was 41 weeks.

717 POSTER

Serum IL-6 (sIL-6) predicts overall survival in patients with metastatic breast cancer (MBC)

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Purpose: IL-6 is a pleiotropic cytokine that is implicated in a variety of cellular functions in immune, hematopoietic and hepatic systems. IL-6-type cytokines have diverse actions on breast cancer cell lines. The prognostic value of sIL-6 in patients with MBC remains unclear.

Patients and Methods: IL-6 was measured by an ELISA in serum of 96 consecutive patients with progressive MBC. SIL-6 levels were correlated with clinicopathological variables and survival. Survival was calculated in days from the sampling date until time of dead or until the end of the study. The survival fractions are calculated using the Kaplan-Meier method and compared with the Mantel-Haenszel test.

Results: The median value sIL-6 value was 6.6 pg/ml (95% c.i.: 8.6-17 pg/ml; range: < 0.7-162.3 pg/ml). Median sIL-6 differed significantly between pts with two or more metastatic sites (8.15 pg/ml) and only one metastatic site (3.06 pg/ml,) ($p < 0.001$), between pts with or without liver metastasis, 8.3 pg/ml and 4.5 pg/ml, ($p = 0.001$), between patients with and without pleural effusion, 10.65 pg/ml and 5.45 pg/ml, ($p= 0.007$), between patients with dominant visceral disease (8.15 pg/ml) and dominant bone disease (4.5 pg/ml) ($p=0.0077$). No correlation between sIL-6 and age, menopauzal status, tumour grade, histiotype, receptor status, initial tumour staging, prior adjuvant therapy and number of prior therapies for metastatic disease. Patients with a sIL-6 above the median had a significant shorter survival ($p<0.001$) of 277 days, whereas the median survival for the low sIL-6 group has not yet been reached.

Conclusion: In patients with MBC sIL-6 levels are positively correlated with survival. Higher sIl-6 levels are observed in pts with more metastatic sites, with liver metastasis, pleural effusion or lymfangitis carcinomatosis and with dominant visceral disease. This suggests that sIL-6 adequately characterizes poor prognosis in patients with progressive MBC.

718 POSTER

Elevation of the serum HER2/neu level is associated with shorter progression-free survival after chemotherapy in metastatic breast cancer

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Purpose: Circulating levels of the shed, extracellular domain of HER2/neu have been shown to be a predictive parameter for response to (high-dose) cytotoxic and anti-hormonal therapy in HER2/neu positive patients [Harris et al., JCO 2001; Lipton et al., Breast Cancer Res Treat 2000].

Methods: We measured the serum HER2/neu baseline (and longitudinal) levels in 95 patients with metastatic breast cancer enrolled to different chemotherapy trials (mostly anthracycline- and/or taxane-based), and correlated the results to treatment outcome.

Results: Using a cut-off of serum HER2/neu positivity of 15 ng/ml for the Oncogene Science® (Cambridge, MA, USA) kit, we found that 63% of patients had elevated levels of the extrecellular domaine of HER2/neu which is in line with serum HER2/neu results for stage IV disease found by other investigators [Andersen et al., Acta Oncol 1995]. The overall response rate to chemotherapy was 31%. There was no statistically significant difference of the response rate to chemotherapy between serum HER2/neu positive patients (29%) and serum HER2/neu negative patients (33%). However, the progression-free interval after initiation of chemotherapy was significantly longer for serum HER2/neu negative patients (mean: 48.2 weeks)