Breast Cancer

81 P

EPIRUBICIN (EPI) + NAVELBINE (NVB) AS FIRST LINE CHEMOTHERAPY IN ADVANCED BREAST CANCER (ABC) PATIENTS (PTS): A MULTICENTRIC PHASE II STUDY.

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We are performing a multicentric phase II study to evaluate the activity and the toxicity of the combination regimen EPI + NVB as first line chemotherapy in ABC patients . Treatment: EPI 90 mg/sqm i.v. bolus day 1, NVB 25 mg/sqm i.v. day 1 and 8: the courses are repeated every 21 days. The treatment is administered on day 1 if WBC $\geq$ 3,500 u/L and/or ANC $\geq$ 1,500 u/L and PLT $\geq$ 100,000 u/L. The dose of NVB on day 8 is modified as follows: G 2 neutropenia: 25% dose reduction, G 3 neutropenia: 50% dose reduction, G 4 neutropenia: NVB omitted. In case of G 4 neutropenia lasting more than 72 hours or febrile neutropenia, G-CSF (300 ug/die subcutaneously) is administered until recovery and a 25% dose reduction is applied in the subsequent courses. Patient characteristics: so far 30 pts have been enrolled and 63% of the pts had visceral metastases: median age 64 years (range 39-72), PS 0= 15, PS 1= 6, PS 2= 9. A total of 121 courses have been administered, with a median of 5 courses (range 1-7) for each patient. The worst toxicities (WHO grade) observed at nadir are :

	G3(%)	G4(%)
Neutropenia	21.1	70.4
Thrombocytopenia	1.6	/
Anemia	/	0.8
Emesis	2.4	/
Mucositis	4.9	/
Diarrhoea	1.6	/

The median duration of G 4 neutropenia is 5 days (range 2-7). The doses on day 1 were reduced at 75% in 30.5% of the courses while the treatment was delayed in 14.8% of the courses. On day 8 NVB was omitted in 14.8% of the courses and reduced at 75% or 50% in 23.1% and 8% of the courses respectively. G-CSF was administered in 15.7% of the courses. Seven episodes of febrile neutropenia not requiring hospitalization have been reported.
Results : 25 pts are evaluable for response: the overall response rate is 68% (95% C.I. 46.5%-85%) with 3 CR, 14 PR, 6 SD and 2 PD. Five pts are not evaluable: 4 pts too early, 1 pt worsening PS. Conclusions: EPI + VNR is a very active combination regimen in ABC: however, considering the high percentage of neutropenia on day 8 requiring NVB dose reduction, we have modified the original schedule and NVB is now administered on day 1 and 5. The study is ongoing.

82 P

CA15.3: A BREAST CANCER MARKER PREDICTING LOCATION OF METASTASES EVEN BEFORE TREATMENT

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The aim of this study was to asses the ability of the antigenic tumor marker CA15.3 to identify, predict and exclude metastases in bone/viscera both in pretreatment determinations and during follow-up of breast cancer patients. Serum values of CA15.3 were measured in a prospective series of 164 patients prior to therapy and every 3 months during a minimum of 2 years-follow-up.
In our series, 8 out of 14 (57.2%) and 51 out of 150 (34.0%) of patients with normal and elevated **pretreatment** values of CA15.3 progressed ($p=0.085$). Whereas 21 out of 51 patients (41.2%) who showed progression of the disease with pretreatment CA15.3 normal values developed bone metastases, 8 out of 8 (100%) patients with previous CA15.3 determinations superior to 40 U/ml and progression had bone metastases (**$p=0.0180$**) showing a predilection for this site of relapse in this group of patients.
Considering the "**follow-up determinations**", 27 patients out of 51 (52.9%) with CA15.3 pretreatment values inferior to 40 U/ml and progression showed CA15.3 elevations during follow-up. CA15.3 correctly classified 64.4% of patients with progression (70.3% if only bone/viscera metastases are included) (sensitivity) and 94.3% without (specifity).
Our results seem to indicate that patients with **pretreatment** CA15.3 high values are prone to develop bone metastases more frequently than other any other type of progression. There is the possibility that tumor heterogenety plays a role in this question. Cells expressing CA15.3 would possibly have more "bone-affinity".

83 P

OCULAR TOXICITY OF TAMOXIFEN

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Tamoxifen is a nonsteroidal antiestrogen widely used in the treatment of breast cancer. Clinical reports have documented retinal toxicity caused by tamoxifen such as, more recently, in vitro studies have demostrated the occurrence of lens damage due to this compound. The aim of this study has been to verify ocular toxicity on a healthy women population. 750 women have been enrolled in a chemopreventive breast cancer study using tamoxifen v.s. placebo to decrease the incidence of breast cancer. A subset of population has been stratified to evaluate the ocular toxicity. Our results demostrate that at the used concentration of tamoxifen no ocular changes attributable to the drug occurred. Long-term follow-up are needed to verify the real involvement of tamoxifen to induce ocular toxicity.

84 P

Tissue expression and serum levels of HER-2/*neu* in patients with breast cancer

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The extracellular domain of the HER-2/*neu* (c-erbB-2) oncogene protein can be found in soluble form in the sera of patients with breast cancer.
We have analyzed serum levels of soluble HER-2/*neu* in 42 patients prior to any therapy and put it into relation to the overexpression and amplification of HER-2/neu in the primary tumor after surgical excision and to data obtained by patho histological staging. In addition, we have investigated the sera of 62 patients with stage IV breast cancer. We have further compared the possible prognostic value of serum HER-2/*neu* to two other known serological tumor markers CEA and CA15-3 in both patient groups.
We have observed an elevated serum HER-2/*neu* level (>20U/l) in 6/42 (14.2%) preoperative patients, out of whom those with HER2/*neu* tissue expression/amplification showed elevated serum levels in 42.8%. In contrast, 8.5% of patients without HER-2/neu expression /amplification in the primary tumor presented with elevated serum levels. There was a significant difference in soluble HER-2/*neu* serum concentrations between patients with tumors of different size ($p<0.0001$) and various degrees of axillary lymph node involvement ($p<0.0001$), thus reflecting a close correlation of tumor load with serum concentrations of soluble HER-2/*neu*. In patients with stage IV disease, 27 out of 62 (43.5%) had elevated soluble HER-2/*neu* serum levels. A highly significant correlation of serum concentrations of HER-2/*neu* with CA15-3 ($p<0.002$) was observed.
We conclude that the measurement of serum HER-2/*neu* levels at diagnosis defines a small subgroup of breast cancer patients with a relatively advanced stage of disease. Its strong correlation with tumor load in patients with stage II disease and the high prevalence in patients with stage IV disease make it a promising tool for the assessment of disease activity and biologic behaviour in breast-cancer.