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ERLANGEN TUMOR MARKER STUDY ON BREAST CANCER

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In order to examine if a medical treatment of breast cancer at the time of increasing tumormarkers is of benefit for these patients we started a randomized study on lymph-node positive breast cancer patients in 1986, where all patients with hormone-receptor positive tumors were asked to send a blood sample to the laboratory in monthly intervals. If in these samples CEA and/or CA 15-3 serum levels exceeded the 97th percentile of healthy women, patients were screened for metastases (mets). If mets were found patients were treated according to the standards of the clinic. If, however, no mets could be detected at that time, patients were randomized either to untreated control or MPA (1,000 mg Farlutal/d) treatment. From the time of randomization on the whole screening program was repeated in each of the patients in 3-4 months intervals. In January 1993 an intermediate analysis of the study was performed. 46 patients were randomized (20=treated (TG), 26=untreated (CG)). According to KM estimations the median time interval between increase of markers and detection of mets was 4 months for CG and and >24 months for TG. The median survival time after randomization was 12 months for CG and >36 months for TG. To further evaluate the significance of this approach in a shorter period of time an international multicenter study should be established.

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PHASE I-II FEASIBILITY TRIAL OF THE ADDITION OF CISPLATINUM TO EPIRUBICIN-VINORELBINE COMBINATION (PEV) IN METASTATIC BREAST CANCER (MBC)

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The combination of an anthracycline - either Epirubicin or Adriamycin - and Vinorelbine has proved effective in MBC demonstrating very encouraging objective response (OR) rate. Cisplatinum which has shown a 47 % OR rate when administered as first line single agent chemotherapy for MBC (JCO, 1988 : pp 1811-1814) has demonstrated in vitro a synergistic antitumoral activity with Vinorelbine.
In order to evaluate the feasibility and efficacy of the combination, 14 consecutive women with untreated measurable MBC which had given informed consent were enrolled from 08/91 to 01/92. There were given every 4 weeks = Epirubicin 25 mg/sqm/d IV on day 1 and 8, Vinorelbine 25 mg/sqm/d IV on day 1 and 8, Cisplatin 90 mg/sqm on day 1. Median age was 52 y.o [37-62] . 7 patients (pts) were menopausal. Median performance status (WHO criteria) was 0 [range : 0-2]. Five pts (38.5 %) had received prior adjuvant chemotherapy, 4 of them with anthracyclin containing regimen ; 3 pts had received Tamoxifen and 8 (61.5 %) adjuvant loco-regional radiotherapy. Only 4 pts received PEV combination at time of diagnosis.
Two pts had 1 metastatic site (liver ; lung) ; 4 pts had 2 sites, 4 pts had 3 and 3 pts had 4 metastatic sites. Median number of cycles was 4 [2-6]. OR was observed in 8 pts (61.5 % ; IC 95 : 35-88 %) including 1 CR ; 4 pts had disease stabilisation. Median duration of OR was 13 months [3-17 + m.]. After 16 months of median follow-up, 10/13 pts were still alive.
Main toxicity was hematological, 12/13 pts experienced at least one cycle with neutropenia (nadir) grade 3 (n = 3) or grade 4 (n = 9). However 52/58 cycles were delivered without any septic complication. Only one life-threatening episod occurred in a pt who developped septicemia and reversible paralytic ileus. Nausea-vomiting and alopecia were observed in most of the pts. There were 7 grade 1 constipation, 7 grade 1 neuropathia and 5 grade 1 ototoxicities. No renal nor cardiac toxicities were noted.
In summary PEV proved efficient in MBC but the association of Cisplatinum seems to increase the toxicity without improving dramatically the results obtained with Epirubicin-Vinorelbine combination. However dose intensity analysis will be discussed and considering preliminary survival datas, PEV combination should require further studies using colony stimulating factors.

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CONCOMITANT RADIO-CHEMOTHERAPY FOR LIVER METASTASES IN BREAST CANCER PATIENTS

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Liver is the most frequent site for blood borne metastases and is involved in up one-third of metastasising cancer. Patients with breast hepatic metastases have a poor response either with systemic or local arterial chemotherapy. In order to evaluate tollerability and effectiveness of irradiation (RT) of the liver and syncronous chemotherapy, a phase I-II trial is ongoing in a group of pts affected by multiple liver metastases from breast carcinoma. Before and after therapy pts undergo US and CT scan and pathologic specimens of normal parenchyma and of neoplastic nodules are obtained. Treatment includes chemotherapy with 5-FU 1 g/m^2 continuous infusion d 1-4 and 15-19, Mitomycin 10 mg/m^2 d 1 and RT on the whole liver for a total dose of 24 Gy, 80 cGy bid 5d/w. From 01/92 9 pts entered the study, 6 are evaluable with a follow-up ranging from 4 to 12 months. At the end of the combined treatment we obtained a complete disappearance of the liver metastases in 4 pts and a partial reduction in 2. The only diagnostic procedure able to fully investigate the irradiated liver was the CT scan, while the US scan in these conditions demonstrated a low-grade specificity. This "short time consuming treatment" was well tolerated without significant modification of standard functional liver tests.

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MMM as second line treatment for advanced breast cancer. Evidence of cross-resistance with antracyclines.

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Fifty patients with advanced breast cancer and progressive disease after previous antracycline treatment were treated with the MMM regime i.e. mitoxantrone 8mg/m2 and methotrexate 30mg/m2 days 1 and 22, and mitomycin C 8mg/m2 day 1. Cycle length has been 42 days. Median age of the patients was 47 years. 143 cycles of MMM was administred with a median of two per patient.
Overall response rate was 14% with one complete and six partial remissions and a median response duration of eight months. Overall survival was five months and thirteen for responders. Treatment tocixity was generally mild but a marked haematological tocixity was recorded for patients receiving multiple courses of MMM (22% WHO grade IV for leukocytes). No tumour response was seen among patients with disease progression during antracycline treatment. However 29% (7/24) with a previous response benefited from MMM.
MMM is effective as second line treatment for breast cancer and is generally well tolerated with moderate side effects. Our study clearly shows that lack of response to antracyclines also implies resistance to mitoxantrone and MMM.

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VOROZOLE-RACEMATE (R 76713) : A SPECIFIC NON-STEROIDAL AROMATASE INHIBITOR. PILOT STUDY IN ADVANCED POSTMENOPAUSAL BREAST CANCER

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We report on the efficacy and pharmacodynamic results of a pilot trial with vorozole-racemate (R 76713), a novel non-steroidal aromatase inhibitor, in patients with advanced postmenopausal breast cancer. Between October 1989 and March 1991, 28 patients were entered. They were randomly assigned to one of two treatment arms : vorozole-racemate 2.5 mg OD (n=14) and 5 mg OD (n=14). The objectives were the determination of clinical and pharmacodynamic efficacy, safety and tolerability. All patients had been heavily pretreated. The median time from diagnosis to entry was 5.2 years (range 1.5-14.9 years). In 35% of the patients the oestrogen receptor (ER) status was positive whereas in 57% of them the ER status was unknown. Bone was the most frequent site of metastasis (n=24) of the patients, followed by liver (n=6), skin and subcutaneous tissues (n=6), lymph nodes (n=2) and lung (n=4).
The median treatment duration was 208 days (range 30-855 days). Objective responses were obtained in 2 pts : 1 CR (skin) and 1 PR (liver). There were 15 patients with NC and 9 with PD. One patient was withdrawn because of a protocol violation and another patient was lost to follow-up before the first response assessment. One patient with malignant hypercalcaemia was successfully treated with vorozole-racemate as monotherapy. The median time till progression was 203 days (range 28-753 d.). Improvement in performance status and bone pain due to metastatic disease was observed in a substantial number of patients. No difference was observed in oestradiol suppression between the two therapy regimens; all oestradiol trough levels were suppressed to at least the detection limit of the assay (i.e. 10 pmol/l). Eleven patients had elevated (i.e. > 10 ng/ml) CEA levels at baseline. In seven of them a more than 50% decrease was noted. This correlated with the clinical and subjective responses observed. An ACTH test performed at entry and after 1 month of treatment proved that vorozole-racemate did not alter adrenal glucocorticoid and mineralocorticoid steroid biosynthesis. There were no significant changes in either cortisol or aldosterone levels. There were no relevant changes in body weight or blood pressure either. Clinical tolerability was excellent.
It may be concluded that vorozole-racemate effectively reduces circulating oestradiol levels and induces objective and clinical responses in patients with advanced postmenopausal breast cancer.

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BROMOCRIPTIN (B) AND LANREOTIDE (L) IN ADVANCED BREAST CANCER : A PHASE II STUDY.

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Eighteen postmenopausal patients with advanced breast cancer previously treated with 1 or 2 hormone therapy lines received L - a somatostatin analogue - at a dose of 6mg/d as a protracted subcutaneous infusion together with B 7,5 mg/d orally. L dose was increased to 10,5 mg/d in case of progressive disease after 1 month or stabilization after 2 months of treatment. Two patients were found to be non eligible : one had received 3 previous hormone therapies and another one had a diagnosis of myelodysplasic syndrome at the time of initiation of treatment. 3 patients were not evaluable due to a treatment of less than 15 days. 13 patients were evaluable for efficiency at L dose of 6 mg. Median age was 68 years (48-78). Previous treatments were hormonotherapy (1 line: 9, 2 : 4), chemotherapy (1 line : 3, 2 : 6, 3 : 1). Tumor sites were breast (4), lymph node (4), skin (4), lung (5), bone (4), liver (1); 6 patients had one tumor site, 5 had 2 and 2 had 3. No response was found. 3 patients were stabilized. 11 patients received 10,5 mg L (two patients refused the increase of dose). One patient experienced a partial response of 7 month duration ; another one has been stabilized for 5 months. Responses were observed in lymph node and skin ; stabilization in breast, lymph node, skin and lung. Tolerance was good; grade II toxicities were: abdominal pain (1), diarrhea (1), nausea and vomiting (1), vertigo (1), constipation (1). Prolactin plasma level decreased in 11 cases out of 12. IGF1 concentration decreased in 7 patients out of 11 at the beginning of L treatment at the dose of 6 mg. No further decrease was observed when the patients were given 10,5 mg. Conclusion : tumor response may be observed in patients receiving B (7,5 mg) and L (10,5 mg); the role of B as well as the mechanism of action of this treatment are poorly defined.