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PUBLICATION

Phase II-trial of vinorelbine in 120-hours continuous infusion in metastatic breast cancer refractory to anthracyclines

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Purpose: To evaluate the efficacy and toxicity of vinorelbine in continuous infusion of 96 hours (CI-96) in heavily pretreated patients with metastatic breast cancer refractory to anthracyclines.

Patients and Methods: Between 07-95 and 10-96, 19 patients with metastatic breast cancer (CNS metastasis excluded) refractory to anthracyclines and paclitaxel (progressive disease on treatment or duration of response less than 2 months) received vinorelbine 8 mg/m² bolus day 1 and 7 mg/m² days 1 to 5. Courses every 21 days for a maximum of 6 cycles in non-progressing patients. 2 patients were found non-eligible. Median age 53 years. Dominant sites of disease were bone (8), visceral (7) and soft tissue (4). 14 patients had received 2 or more previous palliative treatment regimens. Performance status (ECOG) distribution showed PS 0-1-2-3 in 2-7-6 and 3 patients, respectively.

Results: 57 cycles were administered. Objective responses were recorded in 14/17 patients. No CR observed. PR were recorded in 4 patients and No Change in 10 patients. Median TTF was 4.4 months. Toxicity (grade 3-4) was moderate, with myelosuppression as limiting toxicity, mainly leukopenia in 66% of patients. Anemia and thrombocytopenia were mild. Other significant toxicities included mucositis (27%), peripheral neuropathy (10%), asthenia (17%) and drug related fever (17%).

Conclusion: Vinorelbine (CI-96) is an active regimen in heavily pretreated breast cancer patients. Further trials should explore a 4-days regimen restricted to patients with ECOG performance status 0-2 only.

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PUBLICATION

^{99m}Tc-Tetrofosmin in breast cancer

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Purpose: Tetrofosmin is currently under investigation for its tumor seeking properties. We now evaluated tetrofosmin in 10 patients with breast cancer for sensitivity and specificity in detecting metastatic lesions.

Methods: Ten patients (median age 57 years) were evaluated by tetrofosmin scintigraphy, computed tomography (CT) or magnetic resonance imaging (MRI) for staging of disease. Histology, CT-scans or MRI were used to confirm positive correlation with tetrofosmin scintigraphy.

Results: Tetrofosmin scintigraphy correctly diagnosed breast cancer and metastatic lesions in 89% of patients. There was only one false positive finding. In the patient in whom the primary site of cancer was unknown tetrofosmin scintigraphy showed three consecutive nodules within the left mammary gland in a coronary fashion. Magnetic resonance imaging then confirmed two single nodules of 0.8 cm.

Conclusion: From our results it is evident that tetrofosmin scintigraphy can effectively help detect metastatic disease in soft tissue. The low costs of tetrofosmin scintigraphy and its high correlation with CT scan suggest its use as a screening test for metastatic disease in the restaging process of cancer patients.

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PUBLICATION

Contralateral breast cancer and distant metastases

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Purpose: To find whether there is correlation of contralateral breast cancer (CBC) with distant metastases.

Methods: In nonrandomised retrospective study we analysed 304 women with breast cancer (January 1985-January 1990). Median age was 53 (28-80). We studied significant differences between group of women with no contralateral breast cancer (NCBC) and women with CBC, according to age, HP type, tumour size, type of breast surgery, Nodal status, Menostatus, Adjuvant therapy, type of radiotherapy and according to particular distant metastases.

Results: Incidence of CBC was 9% (26 pts.). Median time from Breast Surgery to CBC occurrence was 60 months (24-144). Among women with CBC, 54% (14 pts.) and among women with NCBC, 40% (112 pts.) had distant metastases. We found correlation between CBC and distant metastases in group of pts. between 46-55 years of age, and in group of pts with postoperative radiotherapy. Pulmonary metastases were found to be more frequent among women with CBC.

Conclusion: There is no statistically significant difference between this two groups of women (CBC and NCBC) (chi square = 1.55144; p > 0.05).

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PUBLICATION

Correlation between the urinary DPD-crosslinks excretion and the course of bone metastases in breast cancer

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Purpose: Urine/serum sample pairs were collected from 12 patients (pts) with bone metastases from breast cancer in order to correlate the deoxypyridinoline (DPD)-secretion to the clinical and radiological course of the bone metastases under hormonal or cytotoxic and biphosphonate therapy

Methods: DPD-crosslinks were measured by a new chemiluminescent immunoassay with a very good correlation ($r > 0.9$) to the standard high performance liquid chromatography (HPLC). A median of 5 measurements were done at a 3 week interval during a median follow-up of 8 months.

Results: 7 pts were under hormonal, 4 pts under cytotoxic treatment. All pts received pamidronate 90 mg iv q3w. The pts were classified as having progressive (6 pts), stable (5 pts) or regressive (1 pt) bone metastases according to their symptoms and x-rays. 5/6 pts with progressive bone metastases started with DPD-levels below 10 nmol/mmol creatinin and increased to 11-15 nmol/mmol creatinin during progression. All pts with stable disease showed levels between 3-9 nmol/mmol creatinin. Having shown a level of 14 nmol/mmol creatinin before treatment, 1 patient presented complete osteoplastic stabilisation of her lytic processes. She displayed DPD-levels between 6-12 nmol/mmol creatinin during regression.

Conclusions: Using the limit of 10 nmol/mmol creatinin, a clear biochemical evaluation of bone metastases seems to be possible.

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PUBLICATION

Docetaxel (D) in combination with amifostine (A) in metastatic breast cancer (MBC): A feasibility and pharmacokinetic study of the EORTC-investigational drug branch for breast cancer (IDBBC)

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Amifostine is an organic thiophosphate developed as a radio- and chemoprotective agent. A has displayed chemoprotective activity in preclinical studies of paclitaxel (P) + D, and in an early clinical study of P (Schuchter, ASCO 1996). In this ongoing study, the impact of A on the toxicity and pharmacokinetics of D is to be assessed in patients with MBC.

D (100 mg/m² q 21 d) is administered as 1st or 2nd line therapy for MBC and combined with A (910 mg/m²) from the second cycle. Premedication consists of dexamethasone, ondansetron and lorazepam. Toxicity is the primary endpoint. Pharmacokinetics of D are to be performed with and without A (first two cycles). Five patients, of a planned twelve, have been treated to date (total 15 cycles): the regimen is thus far well tolerated with no toxicity related to A. Accrual will be completed in March, at which time efficacy evaluation of A and pharmacokinetic analysis of D will be performed.

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PUBLICATION

Breast conserving surgery and PDR-Brachytherapy for recurrent breast cancer after primary breast conserving treatment including EBT and HDR-Brachytherapy - Preliminary results

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Purpose: Until now radical mastectomy is commonly performed in case of

local failure after breast conserving primary treatment. The purpose of this work is to report about the treatment results of 13 patients treated with local excision of the tumor recurrence followed by PDR-Brachytherapy.

Methods: From 1994 to 1996 thirteen patients with recurrent breast carcinoma after initial breast conserving therapy were treated with local tumor excision in association with postoperative PDR-Brachytherapy. Primary treatment consisted of lumpectomy or quadrantectomy followed by 50 Gy adjuvant external beam irradiation on the whole breast in eleven cases. A boost of 10 Gy was additionally given in seven of these patients. Another two received an HDR-Brachytherapy boost of 7 Gy and 8 Gy respectively. One female received 60 Gy on the whole breast and one was treated with 42 Gy orthovoltage therapy. Recurrences occurred mean 59 months (from 11–208 months) after primary treatment. In all cases PDR-Brachytherapy was given in a curative intention after a second try of breast conserving surgery. Treatment was performed under general anaesthesia using the classical plastic tube technique. For treatment planning orthogonal images in two planes were used. Dose calculation and prescription was performed according to the recommendations of the Paris system. Clinical target volume (CTV) was defined as the former tumor bed with a 2 cm safety margin. The peripheral dose entirely encompassed the CTV. Prescribed dose was 0.8 Gy per puls, total dose ranged from 16 to 50 Gy. In eight cases radiotherapy was performed by PDR-Brachytherapy alone. Five patients with got an additional EBT from 12 to 30 Gy.

Results: Eleven out of thirteen patients are locally free of disease with a median follow up of 19 month (range 5–38 month). In two cases another local recurrence after treatment occurred 4 and 8 month later and consequently those women were salvaged with mastectomy. Another two patients without evidence of local relapse failed distantly with bone metastases. Despite of the previously performed radiotherapy no severe side-effects are observed at present. Side effects are a moderate fibrosis grade 1–2.

Conclusion: Local tumor excision combined with PDR-Brachytherapy in case of small local failure after primary breast conserving therapy is a feasible and well tolerated method, which can prevent breast cancer patients from mastectomy. Although follow up time is short preliminary experience is encouraging.

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PUBLICATION

A new active combination of tamoxifen (T)-vinorelbine (V)-anthraciclines in metastatic breast cancer (MBC)

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Purpose: Experimental data show that T acts through several cellular pathways which are not always Estrogen Receptor-dependent (Gelmann EP, 1996). Chadja (ASCO, 1993) and Spielmann (JCO, 1994) obtained significant results with a combination of anthraciclines (Adriamycin A – Epirubicin E) and Vinorelbine (V). We started the present study to assess the clinical benefit of the new following schedules: TAV: T 60 mg/die, d 1-2-3; A 25 mg/m² d 2; V 25 mg/m², d 2 every 2 weeks or TEV: the same doses of T and V plus E 50 mg/m², d 2, every 3 weeks.

Methods: From 2/93 to 10/96, 35 patients (21 TAV and 14 TEV), average age 58.8 (38–79), 10 pt over 65 years old, PS 0–2, are evaluable for response and toxicity assessment. Previous treatments included chemotherapy (65.7%), 13 pt as 2nd line, 6 pt as 3rd line and 4 pt as 4th line, hormones (28.5%) and radiotherapy (45.7%). Sites of metastatic disease were bone (63%), lung (46%), liver (40%), lymph nodes (28.5%), skin (20%), retina (5.7%). A total of 203 cycles was administered, average 5.8 cycles/pt, range 2–17. The patients were treated since achievement of CR, or since progression disease or since unacceptable toxicity.

Results: Because we included in this study also patients heavily pre-treated, we considered in our results the overall objective tumor response inclusive of stable disease (total tumor growth control). Response rate was 85.7% (CR 8.5%, PR 45.7%, SD 31.4%). The median duration of CR was 12 months, of PR and SD was at least 3 months. 5 pts (14.3%) showed progressive disease during chemotherapy. WHO grade II and III leukopenia occurred in 10 pts (28.5%) and it was observed in 5 pts after 2nd cycle and in 5 pts after 4th cycle; in 5 pts G-CSF was given. Cardiac impairment grade 2 was observed in 2 pts.

Conclusions: these results confirm the high activity of TAV-TEV combinations, the excellent tolerance profile, low morbidity. This interaction between T and V+anthraciclines should be particularly studied for first-line treatment in metastatic breast cancer to provide more impressive results.

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PUBLICATION

Induction preoperative chemotherapy with high-dose epirubicin in locally advanced breast cancer (LABC)

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From January 1994 to June 1996, 47 patients (pts.) with LABC were treated with Epirubicin 150 mg/m² i.v. every 15 days for 3 courses + G-CSF. Characteristics of the pts.: median age 47 years, performance status (ECOG) 0–1, T > 3 (median tumor size 7 cm), N1, M0.

Results in 47 evaluable pts.: 2 (4.2%) complete pathologic responses, 21 (44.7%) partial responses >50%, 4 (8.5%) partial responses <50%, 20 (42.6%) stable diseases; 6 (12.7%) pts. showed pathologic negative axillary nodes. After median follow-up of 10 months (range 6–30), 3 pts. had disease relapse and 6 pts. died.

A longer follow-up to define the disease free survival and overall survival is needed.

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PUBLICATION

Phase II trial of paclitaxel (P) and cisplatin (CDDP) in patients with advanced breast cancer refractory to anthracycline (A) therapy

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Introduction: The observation of clinical response induced by P among pts with A-resistant breast cancer were of particular interest after the demonstration of in vitro cross-resistance between P and other agents to which resistance is due to P-glycoprotein-mediated pleiotropic drug resistance.

Methods: From March until December 1996, 22 consecutive pts entered this phase II trial; all pts had received previous chemotherapy containing doxorubicin or Epirubicin, and all pts showed disease progression while receiving the A-containing regimen or after a response lasting less than six months. 12/22 pts had received two or more chemotherapeutic regimens for advanced disease. Metastatic sites included liver (10), lung (9), bone (13), lymph nodes and skin (4). Liver was predominant site in 8/22 pts; multiple metastatic sites in 18/22 pts. P 135 mg/sqm was administered IV by a 3-hour infusion, followed by intravenous CDDP 75 mg/sqm, on day 1, every 3 weeks.

Results: At the present analysis 112 cycles of treatment have been given (range: 2–8; median: 5), and two pts are not yet evaluable for response. Among 20 pts evaluable (4 of whom are still receiving therapy), 7 (35%) have had a partial response, 11 (55%) achieved a stabilisation of metastases, and 2 progressive disease. Neuropathy and arthralgia/myalgia syndrome were the most frequently occurring toxicities. Treatment was delayed because of slow haematological recovery in 13/112 courses. Nausea-vomiting G2-G3 WHO in 25/112 courses, mucositis G3 in 11/112.

Conclusion: P-CDDP is a safe regimen in the treatment of pts with advanced breast cancer refractory to A therapy. In a patient population with a very poor prognosis it has showed moderate clinical activity and the rule of higher dosages of P should be investigated.

Colorectal cancer I

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ORAL

Are disseminated tumor cells detected by RT-PCR in patients with colorectal cancer of prognostic value?

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Purpose: In a prospective study we evaluated the consequences of the detection of disseminated tumor cells on survival in patients with colorectal cancer.

Methods: We developed a cytokeratin 20 specific nested RT-PCR for the detection of disseminated tumor cells in bone marrow and venous blood. Samples of both compartments were aspirated prior to operation.

Results: Bone marrow from 79 patients and blood specimens from 53 patients were analysed. For the statistical analysis only patients with R0