proportions of patients with disease progression in bone, 3/12 (25%) vs. 7/9 (78%) were statistically significant (p = 0.03, Fisher's exact test).

Conclusion: Measurement of NTX can be used to monitor the results of bisphosphonate therapy of bone metastases. The goal of treatment should be to normalize excretion of NTX.

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High-dose therapy with peripheral blood progenitor cell support (PBPC) for the treatment of advanced breast cancer

N. Fersis[1], R. Haas[2], D. Wallwiener[1], S. Hohaus[2], J. Huober[1], G. Bastert[1]. [1]*Frauenklinik;* [2]*Medizinische Poliklinik der Universität Heidelberg Voßstr.9 69115 Heidelberg, Germany*

Purpose: High-dose chemotherapy (HD-CT) and PBPC has been used with increasing frequency in the adjuvant setting for high risk patients with breast cancer (stage II and III). In a phase I and II trial we have studied a HD-CT regimen for the treatment of breast cancer in an attempt to improve antitumor activity.

Material and Methods: Since September 1992 60 patients with advanced breast cancer were treated with a tandem HD-CT and PBPC on these clinical trial. Two cycles of cytotoxic chemotherapy with ifosfamide (7500 mg/m^2) and epirubicine (120 mg/m^2) were administered. These drugs were given in equally divided doses over 3 days. PBPC were harvested during G-CSF-supported marrow recovery. We started leukaphereses as soon as distinct population of CD 34+ cells was detectable. Following tandem HD-CT consisted of 2 cycles with ifosfamide (12000 mg/m^2), carboplatin (900 mg/m^2) and epirubicine (180 mg/m^2) given equally over 5 days.

Results: The probability of disease free survival after 3 years was 79%. 8 patients have a relapse in the first year (median 8 months) after therapy. 4 of this patients have a locoregional relapse, 1 patient has bone and 3 visceral metastasis.

The OAS of the enrolled patients in this study is 85% (95% confidence interval between 41 and 100). Severe non hematological toxicities were not observed.

Conclusion: HD-CT for the treatment of advanced breast cancer is associated with prolonged event-free survival and it is well tolerated with low side effects and no mortality.

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Dose-intensified versus standard chemotherapy in high-risk breast cancer patients: Preliminary data of a randomized trial

C. Thomssen[1], M. Untch[2], E. Schill[3], D. Sattler[3], G. Konecny[2], P. Bauernfeind[2], F. Jänicke[1], H. Graeff[3] [1]*Frauenklink der Universität Hamburg-Eppendorf;* [2]*Frauenklinik der LMU München-Großhadern;* [3]*Frauenklinik der TU München, Germany*

Purpose: Breast cancer patients with ≥10 tumor infiltrated axillary lymph nodes have high risk of early relapse and death. Because conventional adjuvant chemotherapy is not effective in this subgroup, several high dose regimens were proposed.

Methods: We treated breast cancer patients with ≥10 tumor infiltrated axillary lymph nodes or extracapsular nodal disease within a randomized adjuvant protocol:

Arm A (HDI-EC): epirubicin 190 mg/m^2 and cyclophosphamide 600 mg/m^2 IV, q2 wks. G-CSF 5 μg/kg SC daily (day 2–12). Total 4 courses.

Arm B (EC/CMF): epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 IV; 4 courses, q3 wks followed by 3 courses of CME 500/40/600 IV day 1 + 8, q4 wks.

Results: To date, 163 patients were randomized, 115 courses in 32 patients of HDI-EC were evaluated for toxicity. Median dose-intensity was 55 mg/m^2/week (planned 60). We observed leucopenia <10^9/L in 12% of the courses and one case of acute cardiac toxicity. In 63 patient diary cards 6 episodes of severe nausea and vomiting were reported, 25 courses were followed by mild nausea. No significant deterioration of quality of life during therapy (LQE, LASA) was reported. The median total time of treatment (including radiation therapy) were 14 weeks in HDI-EC resp. 26 weeks in EC/CMF. At a median follow-up of 29 months (10–43 months) we had 6 recurrences in 41 evaluated patients treated by HDI-EC.

Conclusion: We conclude that the described dose-intense regimen is a well-tolerated therapy for breast cancer patients with high risk of relapse. Prelimenary results suggest at least equal efficacy as compared to a standard regimen, but a substantial shorter time of treatment.

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Activity of gemcitabine in metastatic breast cancer (MBC) patients previously treated with anthracycline-containing regimens

M. Spielmann[1], S. Kalla[2], A. Llombart-Cussac[1], M. Espié[3], M. Namer[4], J.M. Ferrero[4], C. Cuvier[3], P. Fumoleau[5], A. Ponzio[1], L. Kayltalire[6], P. Pouillart[2] [1]*Inst. Gustave Roussy;* [2]*Inst Curie,* [3]*H. St-Louis;* [4]*Ctr Lacassagne;* [5]*Ctr. René Gauducheau;* [6]*Lily, France*

Purpose: GEMZAR® (Gemcitabine, GEM) produced an overall response rate of 25% in MBC (Carmichael, JCO 1995, 13, 2731–6). We initiated a phase II trial of gemcitabine, as 2nd line chemotherapy for MBC, at 5 French centres in July 1994.

Methods: Major inclusion criteria were: ≥6 months of response to 1 prior anthracycline-based regimen for MBC, measurable lesions, adequate renal, hepatic and bone marrow function. GEM 1200 mg/m^2 (30 min infusion) was administered on days 1, 8, 15 of a 28 day cycle.

Results: 47 patients (pts) were recruited and all were evaluable for toxicity. 43 pts were evaluable for response: 4 pts were ineligible (1 pt had not progressed after 1st line anthracycline; 3 pts had received only 1 or 2 doses of GEM). Patient characteristics: median age 56 years (33–75), median KPS 100 (70–100), prior adjuvant chemotherapy in 14 pts, and hormonal therapy in 42 pts. Metastatic sites were mainly liver 60% and soft tissues 51% (lung 34%, bone 28%, pelvis and peritoneum 4%). 4 CRs (5 soft tissues, 3 lung, 1 liver) and 8 PRs (2 lung, 4 liver, 4 soft tissues) were confirmed for an overall response rate of 28%. The main and limiting toxicity was asthenia with 4 pts withdrawn for grade 3/4. 2 pts presented with severe cutaneous allergy requiring treatment (1 pt discontinued). Ankle oedema was occasionally noted, but 3 pts presented with mild to severe cutaneous reaction associated with oedema and pain in previously irradiated fields (1 pt withdrawn). Haematological toxicity was mild with grade 4 neutropenia in only 2 pts and 1 grade 3 thrombocytopenia with subcutaneous haemorrhage. No patient had infection related to treatment. No patients were hospitalized due to adverse events.

Conclusion: Our study confirms the activity and low haematologic toxicity of GEM as a single agent in pretreated MBC and warrants future combination trials with other cytotoxic drugs.

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Phase II study of gemcitabine in patients with metastatic breast cancer

M. Blackstein[1], C.L. Vogel[2], R. Ambinder[3], J Cowan[1], P. Pearce[2], J. Iglesias[4]. [1]*Mt. Sinai Hospital, Toronto,* [4]*Eli Lilly, Toronto, Canada;* [2]*Miami General Hospital, Miami;* [3]*The Walt Disney Memorial Cancer Institute at Florida Hospital, Orlando, USA*

Purpose: Gemcitabine (GEMZAR®) has single-agent activity in metastatic breast cancer. In a European study, gemcitabine 800 mg/m^2 weekly × 3 every 4 weeks produced a response rate of 25% in 40 evaluable patients (pts) with metastatic or locally advanced breast cancer.

Methods: The present study included stage IV breast cancer pts with histologically confirmed disseminated breast cancer who had not received chemotherapy for metastatic disease. Pts received gemcitabine 1200 mg/m^2 on days 1, 8 and 15 of a 28 day cycle. Inclusion criteria: bidimensionally measurable disease, Karnofsky PS ≥ 60, adequate bone marrow reserve.

Results: 39 pts were enrolled: 33 post-menopausal, 2 peri-menopausal and 4 pre-menopausal pts, aged 34–84 years (median age 58 years). 21 of the 39 pts had received prior chemotherapy in an adjuvant setting. 35 of 39 patients were evaluable for response (received ≥2 cycles of therapy). There were 4 complete responses and 9 partial responses for an overall response rate of 37.1% (95% CI – 23–57). 13 pts had stable disease and 9 pts had progressive disease. Currently the time to event data (calculated from first dose) are: median survival 17.8 months, median response duration >12.7 months, median time to progressive disease >7.4 months. Gemcitabine was well tolerated, the maximum WHO toxicity grades (G) and numbers of pts were neutropenia: G3–9 pts, thrombocytopenia: G3–2 pts, nausea/vomiting: G3–4 pts, dyspnoea: G4–1 pt. Other toxicities were hyperbilirubinaemia (1 pt), elevated liver enzymes (2 pts), cough and pleural effusion 2 pts. One case of grade 4 infection was reported No pts were hospitalized due to drug-related adverse events, and only 1 pt was discontinued due to a drug-related toxicity (neutropenia).

Conclusion: The encouraging activity and modest toxicity of gemcitabine in this group of patients deserve further exploration in combination chemotherapy regimens and as monotherapy in pts not able to tolerate more aggressive therapy.