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Taxol™ (Paclitaxel), Epirubicin and Cyclophosphamide (TEC) in the treatment of metastatic breast cancer (MBC): Results of a phase I study

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This phase 1 study evaluated the feasibility and toxicity of chemotherapy combining Paclitaxel (T) (1-hr. infusion), Epirubicin (E) and Cyclophosphamide (C) in patients (pts) with MBC. Pts were treated in cohorts of 6 with dose escalation of T as follows: DL1: 135 mg/m^2; DL2: 175 mg/m^2; DL3: 200 mg/m^2, DL4. 225 mg^2 and DL5: 250 mg/m^2 with E 50 mg/m^2 and C 500 mg/m^2 q.3 weeks maximum 10 courses). Toxicity is graded according to WHO criteria. Thirty-three pts without previous anthracycline, median age 48 years (30–71) were enrolled (173 courses), 6 pts at DL1 and DL2 and 7 pts DL3, DL4 and DL5. Dose-limiting toxicity has been reached at DL5 (2 pts, grade 3 neuropathy). Median neutrophil nadir for DL1 through DL5 respectively was: 0.6, 0.55, 0.9, 0.8, and 0.22 $\times$ 10^9 with 2 cases of febrile neutropenia. Five pts experienced decrease of left ventricular ejection fraction (MUGA scan). One pt had grade 4 vomiting, and 9 pts other grade 3 toxicities. Responses (28 pts) were as follows. 1 CR (4%), 16 PR (57%), 8 SD (29%), and 3 PD (11%). The maximal tolerated dose of T d_2 (1-hr infusion) is 225 mg/m, when given with E 50 mg/m^2 and C 500 mg/m^2. This regimen has significant activity in pts with MBC.

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Phase I dose finding study of high dose vinorelbine (VNR), mitoxantrone (MTX) and cyclophosphamide (C) with bone marrow support in metastatic breast cancer (MBC)

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We studied the toxicity of high dose (HD) VNR (96-hour infusion), MTX and C after response to induction chemotherapy (ICT) as first line therapy of MBC. Thirty-one patients (Pts) were treated with one course of HD VNR and fixed doses of MTX (64 mg/m^2) and C (6 gm/m^2) followed by autologous peripheral stem cell transplantation (APSCT) and G-CSF. Dose levels (DL) of VNR were increased as shown: DL1: 45 mg/m^2 (3 Pts); DL2: 55 mg/m^2 (3 Pts); DL3. 65 mg/m^2 (3 Pts); DL4: 75 mg/m^2 (3 Pts); DL5: 85 mg/m (11 Pts) and DL6: 95 mg/m^2 (8 Pts). Toxicity was graded (GR) according to WHO criteria. Pt population was as follows: mean age: 44 years (30–64); previous CT: 16 Pts (52%), 6 Pts with adriamycin (A) (20%); ICT: taxane-based CT (18 Pts), either Taxolere-A-C (TAC: 11 Pts) or Taxol-epiA-C (TEC: 7 Pts), FAC or FEC (13 Pts). Haematologic toxicity post-HDCT consisted of GR 4 neutropenia and thrombocytopenia (median duration: 11.5 and 10 days). Infections were documented in 38% of cases. Dose limiting toxicity was reached at DL6 (95 mg/m^2) with 3 reversible acute psychotic episodes (GR4) while using narcotics because of increased mucositis (GR 4:3 cases). As well, 4 Pts had GR, 3–4 fatigue. No peripheral neuropathy was seen except 1 GR 3 at DL6 (3%). Reversible decrease of left ventricular ejection fraction (LVEF) (MUGA scan) was seen in 6 Pts (26%) from DL1 to 5 and in 7 of 6 Pts at DL6 (CHF: 1 pt, 3%). There was no toxic death. The maximal tolerated dose of VNR by 96-hour infusion is 85 mg/m^2, when given in combination with MTX 64 mg/m^2 and C 6 gm/m^2 with APBSCT in MBC.

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Phase II study of taxotere monotherapy in previously treated patients (pts) with advanced breast cancer (ABC)

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Aim: In this phase II study we assessed the activity of Taxotere (TxT) monotherapy in ABC pts previously exposed to chemotherapy (CT).

Patients-Methodology: TxT 100 mg/m2, IVI/1 hr, q.3 wk, with corticosteroids premedication, was administered to 49 pts, median age 60 and PS > 60. Six pts (12%) had received only adjuvant CT before TxT (1st line) while 43 (88%) had received therapeutic CT (2nd line), including an anthracycline in 41 pts (84%). 31 pts (63%) had skeletal metastases, 24 (49%) lung and/or pleural, 28 (57%) soft tissue, and 15 (31%) liver metastases. Unless an early progression was observed, response was evaluated after 3 and 6 courses. Pts still in PR after the 6th course, received 9 courses in total. All pts followed for at least 4 wks after the 1st course, are considered evaluable.

Results: 48 of 49 pts (98%) were evaluable. 38 (79%) completed 3, 31 (64%) 6 and 20 (42%) 9 courses. *2nd line TxT:* after 3 courses, 27 pts (64%) had a PR After 6 courses, 25 pts (52%) were in PR and 1 (2%) in CR. *1st line TxT:* 3 pts (50%) demonstrated a PR after 3 and 6 courses. Median response duration was >8 months and median survival >10 months. Toxicity was assessed in a total of 295 cycles and it was found manageable with only 1 toxic death.

Conclusion: TxT is a very active drug in previously treated ABC and surely deserves upfront movement as first line polychemotherapy.

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Conventional-dosage of Adriamycin and Paclitaxel vs. high-dose-chemotherapy with Cyclophosphamide, Mitoxantrone and VP-16 in the treatment of metastatic breast cancer – A randomized study

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In metastatic breast cancer there is controversy concerning the use of high-dose-chemotherapy (HD-CTX) vs. conventional chemotherapy. The data seems to favor HD-CTX with respect to remission rate, disease-free-interval and overall survival. Until very recently no randomized study was performed and Bezwoda et al. have been the very first to show in a randomized manner a clear benefit of their HD-CTX-arm when compared to conventional doses with Cyclophosphamide, Mitoxantrone and Vincristine. However this study has been criticized because of its low remission rate, short follow up-time as well as the mismatched use of tamoxifen. We, therefore, conducted a randomized study to analyze the benefits of the high-dose regimen as published by Bezwoda et al. vs. today's most effective polychemotherapy-regimen as published by Gianni et al., i.e., 200 mg/m^2 Paclitaxel and 60 mg/m^2 Adriamycin. Both regimen can be conducted in an out-patient-setting and PBSCT were mobilized by stimulation with G-CSF for 5 day. Remission rates as well as both cardiac and pulmonary toxicities and quality of life aspects will be discussed. Furthermore pharmacokinetic data of Mitoxantrone and Cyclophosphamide as evaluated in the HD-CTX-arm, will be presented.

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Phase I/II study of alternating docetaxel and mitoxantrone with G-CSF support in advanced breast cancer (ABC)

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Purpose: To investigate the alternative administration of Docetaxel (D) and Mitoxantrone (M) in the treatment of ABC.

Methods: Forty chemotherapy-naive patients with histologically confirmed (ABC) were enrolled in the study. The median age was 60 years, the median PS (WHO) was 0 and all patients had measurable disease. Intrapatient dose-escalation was permitted. The dose escalation levels and grade 4 toxicity are presented in the Table.

Results: A total of 137 cycles were administered. The main toxicity was myelosuppression. Granulocytopenia grade 3 and 4 occurred in 15 (11%) and 33 (24%) cycles, respectively; 4 out of 18 (22%) patients with grade 4 neutropenia developed neutropenic fever. There was no treatment-related death. The MTD has not yet been reached. There were

D mg/m^2 (d1)	M (mg/m^2) (d8)	rhG-CSF (5 μg/Kg)	No. of patients	No. of patients with hematologic toxicity	No. of patients with non-hematologic toxicity
75	8	–	6	4	1
75	8	+	7	2	–
75	10	+	11	2	–
100	10	+	13	2	–
100	12	+	14	–	–
100	14	+	11	1	1
100	16	+	11	1	–
100	18	+	7	–	–
100	20	+	7	1	–
100	25	+	7	ongoing	