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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.

681 POSTER

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	

6 complete responses (16.6%) and 22 partial responses (61.1%) for an overall RR of 77.7%. Responses were observed at all dose-levels.

Conclusions: The alternating administration of D and M is feasible and safe. This schedule allowed a dose intensification of mitoxantrone up to 108% without reaching yet the MTD.

683 POSTER

Endocrine effects of toremifene (TOR) at the level of CNS in advanced breast cancer patients

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Purpose: To differentiate the antagonistic and agonistic effect of TOR (Fareston[R]) at the level of the hypothalamus-hypophysis (HT-HP) axis, LHRH test was performed during a phase II clinical trial.

Methods: In 15 postmenopausal patients with advanced breast cancer FSH, LH and PROL release – induced by LHRH agonist (Suprefact[R] 0.5 mg sc) – was monitored during a 16-week TOR treatment (60 mg/day po). The functional test was carried out prior TOR therapy and then 4, 8, 12, 16 weeks afterwards. Hormone levels were measured by RIA method.

Results: TOR sensitizes the HP to the action of gonadotrophins, the LHRH induced FSH and LH release has a considerable increasing tendency during the therapy. The fall of the base levels of FSH and LH in postmenopausal patients may be due to a partial agonostic activity on the HT or an antagonistic activity on the HP. An increased LH secretion was characteristic to the responders. Non-responders did not show a normal response to LHRH. It seems that a very sensitive HP function would predict the patients sensitivity to TOR treatment. The PROL release, induced by LHRH, was more pronounced in responders.

Conclusion: The antagonistic effect of TOR seems to be more dominant than the agonistic property. The LHRH test proved that TOR exerts its effect at the level of the HP. TOR did not affect adversely the normal endocrine regulation of breast cancer patients at the level of CNS.

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Navelbine (NVB) plus mitomycin (MMC) or mitoxantrone (MTZ) as salvage regimen in metastatic breast cancer (MBC): A randomized trial

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NVB is a new semisynthetic vinca alkaloid that shows a 24% response rate (RR) in previously treated MBC cancer. As anthracyclines are often used as initial treatment for advanced disease, new drugs and combinations are required for relapsed or refractory patients. Between 4/93 and 4/95, 86 patients were included in a randomized trial to receive NVB 25 mg/m^2 days 1 and 8 IV plus MMC 7 mg/m2 IV (A) or MTZ 8 mg/m^2 IV (B). The 3 drugs each 21 days. Characteristics of population: (A/B) evaluables: 40/40, mean age: 56.2/55, number of metastatic sites: 1 = 14/11, 2 = 19/24 3 = 10/8. Dominant metastatic pattern: nodes-bone-soft tissue: 27/27 visceral: 13/13. Previous hormono: 36/37. Previous chemo: advanced disease (40/40), adjuvant: (8/8) all anthracyclines. RR: A: 50% (20/40 PR) B:50% (2/40 CR 18/40 PR). Survival: (median): A:7 m B:7.2 m (p 0.667) Mean N° of cycles A:3 B:3 Toxicity G3–4 (by cycles) A/B:153/153 cycles Neutropenia A = 18 B = 14 (p0.65). Thrombocytopenia A:2 B:1 (p:0.72) Alopecia A:2 B:0 (p0.0045). There were no drug related deaths.

Conclusion: 1) A and B were similar in RR, survival and toxicity 2) Both schedules are easy to administer with low toxicity profile.

685 PUBLICATION

Preliminary results from an early phase II combination of gemcitabine and taxol in metastatic breast cancer

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Purpose: Gemcitabine, a nucleoside analog, has single agent activity in breast cancer with a 25% response rate in phase II trial. The different toxicity profiles and mechanisms of action of gemcitabine and paclitaxel suggested their use in combination, and 22 patients with pretreated metastatic breast cancer have received a biweekly gemcitabine-paclitaxel treatment.

Methods: Paclitaxel was given at a dose of 135 mg/m2 over 3 hours days 1 and 15, followed gemcitabine at a dose of 2500 mg/m2 over 30 min. dayus 1 and 15. To date 22 patients have been included evaluable for response. Median age is 51 (44–69), performance status (0–1) in 19 patients and 2 in 4 patients. Every women have been received previous salvage chemotherapy treatment; 20 patients have received antracycline based chemotherapy and 8 have received paclitaxel for metastatic disease. Metastases were localized in lung (9), liver (6), bone (6), pleura (3) and lymph nodes (4).

Results: Analysis of toxicity data (WHO grade) after 116 cycles is a follow: neutropenia grade 3 or 4 occurred in 28% of cycles –3% grade 4 with one neutropenic fever episode- and thrombocytopenia grade 3–4 in 5%. In general hematological toxicity was moderate. Non-hematological toxicity included mild nausea and peripheral neuropathy. One reversible episode of cardiac toxicity grade 3 has been observed. Of the 22 patients enrolled so far there are 2 CR, 7 PR, 6 SD and 7 PRO with an OR rate of 41%.

Conclusion: These results indicate that the association of gemcitabine-paclitaxel biweekly is well tolerated and highly effective in anthracyclin-resistant pretreated metastatic breast cancer. Patients accrual is still ongoing and definitive results will be presented.

686 PUBLICATION

Taxotere in the treatment of patients with advanced breast cancer

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Methods: Twenty eight pts with morphologically proven advanced breast cancer were treated with taxotere. Taxotere was administered in dose 100 mg/m^2 every 3 weeks. The prophylactic medication with methylprednisone 32 mg per os has to be given 13, 7 and 1 hour before the infusion and should be continued on the day of administration and for 96 hours after at the same dose twice daily (b.i.d.). The average age pts was 49.3 (32–67), WHO PS 0–2, 19 pts previously operated. 22 pts have received previously chemotherapy: neoadjuvant – 2, adjuvant – 13 (5 with anthracyclines, 9 – CMF), curative – 8 (7 with anthracyclines, 1 – CMF). Taxotere was used as the first line of treatment in 20 pts, as the second line in 8 pts.

Results: The results of treatment were the following: overall response was 15/28 (53.7%), CR – 3/28, PR – 12/28, SD – 3/28, PD – 10/28. The best results (OR – 11/20) were observed in pts who had only adjuvant chemotherapy, or previously untreated. 3 pts had the improvement of results after the study termination. The toxicity in 184 cycles were the following: anemia 22.8% (Gr II – 16.3%), neutropenia 57.6% (Gr III–IV – 37.5%), but only in 4 cases the dose was reduced, because of febrile neutropenia. All cases of neutropenia were reversible and had short duration (<7 d). There were no cases of trombocytopenia. We did not observed any nausea and vomiting. The incidence of mucositis was 66/184 (35.8%), Gr II 14/184 (7.6%), diarrhea – 37/184 (20.1%), Gr II – 7/184 (3.8%), fluid retention syndrome 38/184 (20.7%) Gr II 2/184 (1.0%), neurotoxicity 43/184 (23.3%) Gr II 15/184 (8.2%), myalgia, arthralgia 16/184 (8.7%). Skin toxicity Gr I 23/184 (12.5%).

Conclusion: Taxotere as a single agent is a high effective cytostatic agent against advanced breast cancer.

687 PUBLICATION

Experiences with thermoradiotherapy of locally recurrent breast cancer

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Background: In inoperable or R1/2 resected recurrent breast cancer thermoradiotherapy is established. We analysed acute side effects of thermoradiotherapy in locally recurrent breast cancer depending on duration, applicator arrangement, electric field parameters, bolus temperature, placement of temp. probes and applicators.

Material and Methods: Thermoradiotherapy was performed in 17 pat. with median dose of 58 Gy (30–60 Gy) combined with twice weekly hyperthermia applications (BSD 2000, MA150, MA120, SA115). In group 1 (6 pat.) skin cooling by bolus temp. of 15–20°C and intratumoral and epicutaneous temp. mapping was performed. Group 2 (11 pat., 2 × patchwork) with cutaneous lymphangiosis or infiltrated skin or R1-resection received bolus temp. of 40°C, monitored by epicutaneous temp. mapping.

Results: In group 1, median intratumoral temp. of 41.5°C (41.1–42.3°C) and max. temp. of 42.6–44.0°C were recorded in a median of 8 (2–12)