PP-7-10 A Phase II Trial on High Dose (240 MG) Toremifene in the Treatment of Advanced Breast Cancer

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Toremifene (TOR) is a new triphenylethylene derivate that like other non-steroidal antiestrogen exhibits tumoristatic action, but at higher concentrations *in vitro* possesses also cytocidal ability. The aim of this open phase II multicentric study was to evaluate the efficacy, safety and tolerability of 240 mg TOR as a first line treatment for advanced breast cancer. From Oct 1986 to Jan 1991 altogether 73 menopausal pts were enrolled in this trial. 69 pts were evaluable for tolerability and 56 met the criteria for response evaluation. Complete response (CR) was evaluated in 12/56 pts (21.4%); partial response (PR) – 21/56 (37.5%); disease stabilisation (ST) – 16/56 (28.6%) and disease progression (PD) – 7/56 (12.5%). Objective response (CR + PR) was 58.9% with the median duration of response 653 days (range 28–2586). Median overall survival was 69 mo (23–92) for CRs: 37 mo (5–94) for PRs; 16 mo (2–73) for STs and 14 mo for PDs. Altogether 33/69 pts (47.8%) reported on transient mild to moderate drug related side effects. Majority of all the registered adverse reactions could have been attributed to antiestrogenic property of the drug (19/33). Less often were the gastrointestinal (10/33), CNS (4/33) and allergic (4/33) reactions. *Conclusions:* 240 mg TOR as a well tolerated medication could be safely used as a first-line treatment for metastatic breast cancer and could be recommended as an induction treatment also for menopausal pts with primary inoperable breast cancer.

PP-7-11 Phase I Study of Combination Docetaxel with Cyclophosphamide in the Treatment of Metastatic Breast Cancer

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Purpose: To determine the dose limiting toxicity and maximum tolerated dose of Docetaxel (D) plus Cyclophosphamide (C) combination in Metastatic Breast Cancer (MBC) patients and examine pharmacokinetics.

Background: D is a highly active drug in MBC. In Japanese late phase II study, 67 of 133 pts (50.4%) had responses (8 CR, 59 PR) at dose of 60 mg/m^2. *In vitro* and *in vivo* study, D plus C showed synergistic action. Based on these results we planed combination study of D with C.

Method: D was administered 1–2 hour infusion followed by C was given by IV bolus. DLT was defined 1) Grade 4 leukopenia or neutropenia for longer than 3 days, 2) Fever with Grade 4 leukopenia or neutropenia caused infection, 3) Other grade 3 or worse toxicity except alopecia, nausea/vomiting or anorexia. At least 3 pts were entered in each level.

Results: Dose levels-Level 1 D 40 mg/m^2, C 200 mg/m^2(3 pts); Level 2 D 40 mg/m^2, C 400 mg/m^2(3 pts); Level 3 D 50 mg/m^2, C 400 mg/m^2(6 pts); Level 4 D 60 mg/m^2, C 400 mg/m^2(3 pts). Fifteen pts with MBC were entered onto the study. DLT of Grade 4 neutropenia for longer than 3 days and grade 4 thrombocytopenia occurred in 3 of 3 pts treated with D 60 mg/m^2 and C 400 mg^2(Level 4).

PP-7-12 Dose-Finding Study of Weekly Oral Vinorelbine (VRL) in Patients (PTS) with Advanced Breast Cancer (ABC): Preliminary Results

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The aims of this Phase I study were to determine the maximum tolerated dose (MTD) of oral VRL administered weekly (= more than 50% incidence of grade 4 hematological or grade 3/4 non hematological toxicity), to define a recommended dose (RD) for further trials and to evaluate pharmacokinetic and activity profiles. The initial dose level was 60 mg/m^2/week and the dose was increased by a 20 mg/m^2 stepwise increment in subsequent cohorts of 6 patients each. The study was performed in PTS with ABC. Interim results are available on 24 PTS (mean age: 58.6 yo; range: 37–78): 7 at 60 mg/m^2, 11 at 80 mg/m^2 and 6 at 100 mg/m^2. PTS were pretreated by previous adjuvant chemotherapy for 5 of them and for advanced/metastatic disease for 15 of them. 50% of PTS had predominantly visceral disease (7 liver, 7 lung). 6 PTS had bone metastasis and 13 locally advanced/metastatic disease. 100 mg/m^2/week was shown to be the MTD (3 grade 4 neutropenia, 2 grade 3/4 constipation and 2 grade 3 vomiting). 80 mg/m^2/week was defined as the RD: Grade 3/4 neutropenia over 24% of cycles; no grade 3/4 nausea or grade 4 vomiting (grade 3: 1% of cycles; no grade 3 constipation, grade 4 over 1% of cycles. Alopecia never exceeded grade 2. Over 13 evaluable PTS treated at 80 and 100 mg/m^2/week, 6 partial responses were observed, 3 of them on visceral disease (2 lung, 1 liver).

It is concluded that oral VRL administered at the weekly dose of 80 mg/m^2 is well tolerated and has interesting activity in ABC.

PP-7-13 Phase I–II Trial of Mitoxantrone (M) and Taxol (T) in Advanced Breast Cancer (ABC)

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We reported an ongoing phase I–II study of T and escalating dose of M in patients with ABC. T was administered at 175 mg/m2 iv over 3 hrs, d-1 and M was escalated by 2 mg increments, starting from 10 mg/m2 (level I) to 12–14 mg/m2 (level II–III) iv d-1; cycles were repeated every 3 wks. From 11/94, 39 females were treated with TM. Pt characteristics: median age of 58 yrs (range: 34–70), KPS was 100–80% in 35 (90%) and < 80 in 4 (10%); primary tumors were ER+ in 12 and PgR+ in 6 pts; prior adjuvant CT was administered in 24 pts, CT for ABC in 17 pts and hormonal in 16 pts. Twelve pts received 3 or more chemotherapy treatments before TM. Disease sites included: lung 10 pts, bone 25 pts, lymph-nodes and skin 16 pts, liver 9 pts and others 16 pts (23 pts have 2 or more sites of disease). Ten pts received M at dose of level I, 14 pts at level II and 15 pts at level III. Of 31 evaluable pts, 4 (13%) obtained *CR* and 17 *(55%) PR (OR: 21/31 68%),* 8 had NC disease, 2 P disease. Nine pts were too-early. Myelosuppression was the most frequent toxicity: 2 pts (6%) experiencing leukopenia Gr. 1, 19 pts (61%) Gr. 2–3, 2 pts (6%) thrombocytopenia Gr. 2 and 6 pts (19%) anemia Gr. 2–3. Non-hematological toxicities superior to Gr. 2 included: Vomiting (22%), alopecia (80%), neurotoxicity (42%) and cardiotoxicity (6%). No dose limiting toxicities occurred at level III.

PP-7-14 Third-Line Chemotherapy with Bendamustin for Metastatic Breast Cancer — A Prospective Pilot Study

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From 9/1994–2/1996 18 patients with metastatic breast cancer were treated with Bendamustin monochemotherapy. 15 pts. were evaluable.

The median age was 53.4 years. All pts had been pretreated with chemotherapy, 13 pts with hormontherapy. 4 pts were pre- and 11 pts postmenopausal.

The following regimen was used: Bendamustin at 150 mg/m2 D1–2 every 3 weeks. A total of 38 courses had been given (2.5/patient – ranging from 1 to 6).

Tumour response (according to WHO criteria): PR 3/15 (20%) pts., NC 9/15 (60%) pts., PD 3/15 (20%) pts. Progression-free survival (Kaplan-Meier) was 5.87 months (PR 7.13; NC 4.68 months). Survival after therapy (K-M) was 7.87 months (PR 10.16; NC 9.37; PD 7.38 months).

Side effects of this treatment modality were moderate (WHO criteria): Only 2 pts showed anemia grade III–IV, grade III–IV leucopenia occured in 4 patients, grade III thrombopenia in 6 pts. No pts with grade III–IV vomiting/nausea or alopecia grade II–IV were observed.

PP-7-15 Org-OD14 Significantly Inhibits DMBA Induced Mammary Tumor Growth in Rats: Effects of Combination Therapy with Tamoxifen or the Antiprogestin Org-31710

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The steroid Org-OD14: (7α, 17α)-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one which has weak estrogenic, progestational and androgenic

activities, has been used for the treatment of postmenopausal symptoms. In this paper we report the antitumor effects of OD14 treatment in rats bearing DMBA induced mammary tumors. In the 1st experiment, treatment was started when the average tumor burden was about 290 mm^2. Treatment with 1 mg/kg/2xd/po OD14 for 3 weeks resulted in 491 ± 163 mm^2 vs 1743 ± 354 mm^2 tumor burden of control rats ($p < 0.005$, $n = 8$). The effectivity of OD14 is confirmed by significantly less tumor weight: 6.1 ± 2.1 g vs 23.3 ± 7.3 g of control rats. Cumulative results of 4 experiments showed that OD14 treatment resulted in 182 ± 25% increase vs 463 ± 57% of tumors grown in control rats ($n = 32$, $p < 0.03$). In another experiment the antitumor effect of OD14 was compared with those of tamoxifen. 2 mg/kg/2xd/po, the antiprogestin Org31710 1 mg/kg/2xd/po, and in combination. After 3 weeks, tumor burden of control group was 1070 ± 290 mm^2, OD14 group was 358 ± 117 mm^2, tamoxifen group was 463 ± 283 mm^2, Org31710 group was 409 ± 145 mm^2, combined OD14 & tamoxifen group was 266 ± 139 mm^2 and of OD14 & Org31710 group was 208 ± 132 mm^2. Treatment with OD14 was shown to be as effective as treatment with either tamoxifen or Org31710; combination therapies were clearly better then treatment with single agent; they even resulted in reduction of tumor burdens. These results indicate that OD14 has no stimulatory but an inhibitory effect on DMBA induced mammary tumors.

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PP-7-16 Cardioxane Still Induces Effective Cardioprotection in Anthracycline Pretreated Breast Cancer Patients

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Cardioxane (dexrazoxane) is a cardioprotective agent which demonstrated cardioprotection in patients treated prospectively by anthracyclines (Speyer et al., *J Clin Onc* 1992, Vol 10: 117–127). Cardiotoxicity may be the limiting factor for the treatment of patients where reintroduction of anthracyclines is considered.

A retrospective analysis of all the available data (62 pts) from clinical studies with Cardioxane in breast cancer patients pretreated with anthracyclines was performed. All patients had received ≥ 100 mg/m^2 of doxorubicin or equivalent doxorubicin.

30 pts had been treated previously for metastatic disease: mean age 48 (32–64). Among them, 14 (47%) had received a cumulative dose of ≥ 300 mg/m^2 of doxorubicin. They received second line treatment with anthracyclines + Cardioxane up to 400 mg/m^2 (5 pts), 400–600 mg/m^2 (15 pts), 600–800 mg/m^2 (4 pts) > 800 mg/m^2 (6 pts).

32 patients had received previous adjuvant anthracycline treatment: mean age 54 (32–64). Among them, 65% had received ≥ 200 mg/m^2 anthracyclines. They received second line treatment with anthracyclines + Cardioxane up to 400 mg/m^2 (5 pts), 400–600 (14 pts), 600–800 (9 pts), > 800 mg/m^2 (4 pts).

Only 4 pts presented cardiac events and none presented clinical signs of heart failure, which is far less than expected in patient with high cumulative dose without cardioprotection. Other toxicities were similar to those observed in the usual anthracyclines treatment: grade 3 + 4 toxicities were: Nausea-vomiting (23%), mucositis (4%), alopecia (74%), anemia (13%), leucopenia (64%), thrombopenia (26%).

12 patients were not evaluable for response. Response rate in evaluable patients was 4% CR, 14% PR in second line treated metastatic patients; 4% CR, 50% PR in adjuvant pretreated patients. These response rates are similar to those reported in identical patients groups.

In conclusion, Cardioxane is an effective cardioprotective agent in anthracycline pretreated breast cancer patients allowing anthracycline reintroduction without compromising anticancer treatment efficacy.

PP-7-17 Paclitaxel and Carboplatin with G-CSF Support in Advanced Breast Cancer Resistant to Anthracyclines

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Paclitaxel at the dose of 200 mg/m^2 as 3-hour infusion and Carboplatin at 7 AUC with G-CSF support was given to patients (pts) with advanced breast cancer resistant to anthracycline or mitoxantrone containing chemotherapy. Treatment was to be repeated every 28 days and G-CSF was administered from day 3 to 13. Pts had to have measurable or evaluable disease and only one previous treatment for metastatic disease. As of January 1996, 32 pts with a median age of 55 (range 36–69) and a performance status of 1 (range 0–2) entered the study. 17 pts had previous hormonal treatment, 21 presented with 2 or more metastatic lesions and 21 with visceral disease. A total of 121 courses has been delivered. Eighty-five percent of cycles was given at full dose and 98% of them on schedule. Grade 3–4 toxicities included leucopenia-neutropenia (19%), thrombocytopenia (15%), infection (9%) and neuropathy (3%). So far, 2 (6%) pts demonstrated a complete and 6 (18%) a partial response. There was one toxic death due to infection. In conclusion, this combination can be given on an outpatient basis and is well tolerated and effective for pts with advanced breast cancer previously treated with anthracyclines. The study is still open.

PP-7-18 Paclitaxel Combinations with Weekly High Dose 5-FU/Folinic Acid and Cisplatin in the Treatment of Metastatic Breast Cancer — There is a Possible Role of Combining Paclitaxel with Anthracycline Non Cross Resistant Chemotherapeutic Agents in the First and Second Line Treatment I

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Introduction: Based on the results of a phase II study with a weekly (x6) schedule of a 24 h infusion of high dose 5-FU/Folinic acid (HDFU/FA) demonstrating high efficacy (RR 41%, 13/32 pts) and low toxicity in intensively pretreated metastatic breast cancer patients (pts), we added Paclitaxel (P) to HDFU/FA in a phase I/II trial. P was chosen because of its activity in pretreated metastatic breast cancer pts, different mode of action than HDFU/FA and the lack of overlapping hematologic toxicities between the combination partners.

Treatment: Pts were treated with HDS-FU (24 h infusion)/FA (2 h infusion prior to FU) weekly for six weeks (d1, 8, 15, 22, 29, 36) and P (3 h infusion) was administered additionally on day 1 and day 22. Each cycle comprised of six weeks followed by two weeks rest. All pts were treated as outpatients using i.v. port systems and portable pumps. During Phase I we chose the following dose levels (dl): Fixed doses of FA dl 1–4 500 mg/m^2 followed by HDFU 24 h infusion dl1: 1.5, dl2: 1.8, dl3 and dl4: 2.0 g/m^2. 3 h inusion of P, given prior to HD5-FU/FA, on d.1 and d.22 dl1–dl3: 135, dl4: 175 mg/m^2. Dl4 was chosen to be further evaluated during phase II.

Patient Characteristics: 51 pts entered this ongoing trial during phase II. Up to now 48 pts were evaluable for response and toxicity. Age 47 yrs (26–63), WHO PS 1 (0–2), metastatic disease sites 2 (1–4). All pts had bidimensionally measurable disease.

Pretreatment: Pts had adjuvant chemotherapy 17/51, prior chemotherapy for metastatic disease 12/51, chemotherapy both adjuvant and for metastatic disease 22/51; prior treatment with anthracyclines 34/51, resistance to anthracyclines with disease progression while treatment prior to study entry 29/51.

Toxicity: (n = 51). 153 treatment cycles at dl4 had the following toxicities (WHO grade) in (n) cycles: leucopenia 3°/4° (28); mucositis 2° (49); diarrhea 2° (35), 3° (15); hand-foot syndrome 1° (85); PNP 1° (41); nausea/vomiting 2° (37); myalgia 1° (66).

Results: (n = 48). CR 4% (2/48), PR 58% (28/48), SD 34% (16/48), PD 4% (2/48). RR (Response rate) 62%, 95% confidence interval 48–76%. Response concerning 29 patients with anthracycline refractory disease (26 pts were evaluable for response so far): RR 58% (15/26), 95% confidence interval 38–78%. Time to maximum response 2 months (1–5), remission duration 8+ months (2–11).

Conclusions: The combination of P with weekly HDFU/FA is well tolerated and indicates high efficacy also in anthracycline refractory metastatic breast cancer. In an ongoing phase II study we estimate the value of the addition of cisplatin to the regimen in the first line treatment of metastatic breast cancer.