1291 PUBLICATION

Phase II study results on safety and efficacy of CAELYX® (DOXIL®) in combination with paclitaxel in the treatment of metastatic breast cancer

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The combination of doxorubicin and paclitaxel has produced encouraging response rates in the treatment of metastatic breast cancer. However, this regimen has considerable toxicities, in particular cardiac toxicity with high cumulative doses. CAELYX® is a doxorubicin formulation in which the drug is encapsulated within pegylated (STEALTH®) liposomes. The altered characteristics imparted by the encapsulation may reduce the risks of myelosuppression and cardiotoxicity in combination with paclitaxel. Forty three patients with confirmed metastatic cancer have been treated with paclitaxel and Caelyx to investigate the efficacy and toxicities of this combination. Patients were permitted up to 2 prior chemotherapy regimens which could have included prior anthracyline (16 pts) and/or taxane (3 pts). Median age 54.5 (range 73–31). The starting dose of CAELYX was 50 mg/m^2 every 6 weeks (n = 6), but was changed to 30 mg/m^2 every 3 weeks mg/m^2 (n = 37). Twenty five patients are currently evaluable for efficacy: 1 complete response, 14 partial responses, 3 stable disease, 7 progressive disease. (Five patients are not assessable for efficacy and 13 are too early for assessment) Twenty four patients have completed treatment with a median of 5 doses (range 1–10) of paclitaxel and 4 doses (range 1–8) of CAELYX was administered The most commonly observed toxicities were mucositis when Caelyx was given every 6 week, palmar-plantar erythrodysaesthesia (PPE) when Caelyx was given every 3 weeks and neutropenia. Accordingly dose reductions and delays were scheduled for >grade 2 PPE, myelosuppression or mucositis.. CAELYX doses were reduced in 13 patients and paclitaxel doses in 2 patients. Dose delays were required in 18 patients. Eighteen patients are still being treated of whom 11 have had dose delays and 2 reductions in the dose of Caelyx.

1292 PUBLICATION

A Phase II study of IncelTM (biricodar, VX-710) in combination with paclitaxel in women with advanced breast cancer refractory to paclitaxel

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IncelTM/VX-710 is a potent inhibitor of MDR mediated by P-glycoprotein and MRP expression. We conducted a Phase II study evaluating safety, tolerability and efficacy of Incel/paclitaxel (P) in breast cancer patients (pts) refractory to prior P therapy. Inclusion criteria: * 2 prior chemotherapy regimens for advanced disease, progressive disease on P, or relapse within 3 months of prior P therapy, ECOG performance status * 2; normal bilirubin, AST and ALT * 1.5 × ULN; baseline ANC and platelets * 1500 and 100,000, respectively. Pts received Incel (120 mg/m^2/hr) as a 24-hr infusion with 3-hr P at 80 mg/m^2 (P AUC and time > 0.05 mM comparable to 175 mg/m^2 P). The study enrolled 38 pts. Demographics, treatment, and safety data are available from 30 pts who received 76 treatment cycles. Demographics: median age 49 yr. (range 29 to 65 yr), 27/30 with ECOG performance status 0 or 1, prior treatment included adjuvant chemotherapy (18 pts), 2 prior regimens for advanced disease (17 pts), and P as initial therapy for advanced disease (13 pts). The majority of pts were resistant to initial P therapy. Incel/P has been well tolerated with myelosuppression as the principal treatment toxicity. Hematology data available for 34 cycles shows that median WBC and ANC nadirs for the first 2 cycles ranged from 2.1 to 2.6 × 103/mm3 and 0.5 to 0.70 × 103/mm3, respectively. Gr 3 or Gr 4 neutropenia was observed in 32% and 53% of cycles, respectively. Incel/P had no effect on platelet counts. Myelosuppression observed with Incel/P is similar to 24-hr P infusion. Non-hematological toxicities included: mild to moderate asthenia, fever, anemia, paresthesia, headache, nausea and myalgia. Analysis of P pharmacokinetics for 19 pts indicates a mean weight normalized CLs of 0.120 L/hr/kg and Vss of 1.65 L/hr/kg indicating P exposure is comparable to a 3-hr 175 mg/m^2 infusion. Thirty five pts are evaluable for response: 3 pts achieved PRs, 2 pts had minor responses (~30% shrinkage) and 5 pts are continuing therapy. These results suggest that Incel/P therapy can benefit some breast cancer pts with strictly defined P refractory disease, and provides a rationale for studies in pts with less advanced disease.

1293 PUBLICATION

Phase II trial of docetaxel and Herceptin (R) as first- or second-line chemotherapy for women with metastatic breast cancer whose tumours overexpress HER2

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Purpose: Women with metastatic breast cancer whose tumours overexpress HER2 have more aggressive disease and shortened survival. Herceptin (trastuzumab) as a single agent has shown activity in such patients and the addition of Herceptin to chemotherapy has improved the response rate and time to disease progression. Docetaxel is an active agent in the treatment of metastatic breast cancer and has shown response rates superior to that of doxorubicin.

Methods: This trial was the first to assess the safety and efficacy of combining Herceptin and docetaxel. The treatment regimen was docetaxel 75 mg/m^2 every 3 weeks for 6 cycles, with Herceptin initiated on day 1 as a 4 mg/kg loading dose followed by 2 mg/kg weekly until disease progression. Patients were premedicated with a standard 3-day dexamethasone regimen of 8 mg po bid. Herceptin was administered first, followed by a 1-hour docetaxel infusion. Eligibility criteria included: measurable metastatic breast cancer; 2+ or 3+ HER2 overexpression (DAKO kit); no prior taxoid therapy; less than or equal to one prior regimen for metastatic breast cancer; cumulative doxorubicin dose < 250 mg/m^2; and normal LVEF. Primary endpoints included: response rate; response duration; time to treatment failure; and safety/tolerability.

Results: To date, a total of 14 patients have received more than 50 cycles (range 1+ to 7+) of therapy. There have been 2 confirmed PRs, 3 minor responses and no reports of serious toxicities. One patient who was ineligible secondary to laboratory parameters was inadvertently enrolled and experienced an early death attributable to progressive disease.

Conclusions: These preliminary data indicate that the combination of docetaxel and Herceptin is well tolerated and accrual continues to a total of 30 patients. Further response data will be presented at the meeting.

1294 PUBLICATION

Phase I/II trial of oral UFT/Leucovorin (LV) and paclitaxel (P) in the second line treatment of patients (PTS) with metastatic breast cancer (MBC)

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Introduction: Phase II studies demonstrate efficacy and low toxicity for the continuous infusion of low dose 5-FU (Ann. Oncol. 7: 807–13, 1996) in pretreated pts with MBC. In our hands P in combination with weekly 5-FU/LV constitutes an active salvage regimen for pts with MBC (Ann. Onc. 9: 45–50, 1998). UFT/LV allows delivery of prolonged exposure to 5-FU without the need for central venous catheters or infusion pumps.

Patients and Methods: UFT, which is composed of 1-(2-tetrahydro-furyl)-5-FU (ftorafur) and uracil in a molar ratio of 1:4, was administered orally plus LV and in combination with P. Pts were treated as a part of an ongoing phase I/II protocol in order to determine the safety, activity and pharmacokinetics of this combination. After premedication, pts received a fixed dose of P 175 mg/m^2 3 h i.v. on day (d) 1 at all dose levels (dl). UFT was administered in combination with 90 mg/d of LV in three divided doses for 14 d's. The UFT dl's were dl1 300, dl2 400, dl3 500, dl4 600 and dl5 700 mg/d. The cycles were repeated every 21 d's. So far 26 pts entered the trial: 6 pts dl1, 5 pts dl2, 3 pts dl3, 6 pts dl4 and 6 pts dl5. All pts have had prior CTX either as an adjuvant, for MBC or in both settings.

Toxicity and Results: The main hematological toxicity (CTC grade III/IV) was neutropenia in 32%. CTC grade I/II toxicity including PNP, arthralgia and myalgia were common but not dose limiting Dose limiting toxicities (DLT) were: dl1–3: 14 pts (74 cycles) no DLT's; dl4: 6 pts (28 cycles) febrile neutropenia; dl5: 6 pts (20 cycles) diarrhea, nausea/vomiting, thrombopenia > 35 d. MTD was reached with dl5 and dl4 is used within the ongoing phase

II trial. We observed objective responses at all dl's (n = 26): CR2, PR6, (RR 31%, 95% CI 14–52%), SD 15, PD 3.

Conclusions: The combination of P and oral UFT/LV seems to be a convenient and effective regimen for the second line treatment of MBC.

1295 PUBLICATION

Metastases within the breast from extramammary primary solid tumors: A retrospective analysis

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Purpose: Only few cases of breast metastases (BM) from solid tumors are reported in literature. In our study we evaluated the characteristics and clinical bahavior of 48 cases of BM identified at Institut Gustave Roussy (IGR).

Methods: From 1950 to 1998, seventy-seven cases of BM from solid tumors were identified at IGR. We included in our analysis only patients (pts) with intraparenchymal breast lesions and all cutaneous, subcutaneous or axillary lesions were excluded, as were pts with metastasis from contralateral breast cancer and from non-solid tumors. A total of 48 cases of intraparenchymal BM were analysed. In all cases diagnosis was histologically confirmed.

Results: Forty-one female pts (85%, 27 premenopausal, 14 postmenopausal) and 7 male pts were identify. BM appeared in pts with a known metastatic malignancy in 35 cases (72%), in 9 (19%) BM allowed the diagnosis of an extramammary tumor, in 4 (9%) the breast lesion was diagnosticated during staging of the primary tumor. The median time from diagnosis of primary cancer to detection of BM was 18.5 months (range 0–296), with differences between the histologic types. BM were secondary to carcinomas (54%), malignant melanoma (27%), sarcomas (17%) and neuroblastoma (2%).

Conclusions: BM may occur during the course of the natural history of various malignancies. In the absence of a control cohort it is not possible to draw definitive conclusions about why a higher incidence of BM is observed in the premenopausal population.

1296 PUBLICATION

Standard radiotherapy potentiation with intra-tumoral fluorouracil injectable gel (5-FU gel) in patients with locally advanced or locally recurrent breast cancer

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Purpose: Use of 5-FU as a radiopotentiator has involved the side-effects and inconveniences of continuous intravenous administration. A new site-specific intratumoral delivery system has been designed to provide high drug concentrations for extended periods. 5-FU is formulated in a viscous aqueous gel using purified bovine collagen as a biodegradable carrier matrix. We are examining the effect of dose and schedule of 5-FU gel on safety in patients receiving standard radiation therapy for locally advanced or locally recurrent breast cancer.

Methods: The ongoing Phase I/II study includes patients with breast or chest wall involvement who are receiving radiation therapy to a previously unirradiated field. The open-label, dose-escalation safety study uses 0.2 mL of 5-FU gel/cm^3 of tumor (5-FU dose range, 5 to 40 mg/mL). 5-FU gel is injected once or thrice weekly during a standard course of radiation but not during the radiation boost phase. Treatment-related side-effects will determine maximum tolerated dose.

Results: No dose-limiting, treatment-related side-effects, soft tissue necrosis, or systemic toxicity have been observed to date in patients in the first four treatment groups. All patients have completed treatment except one in whom radiation was discontinued when she developed widespread distant metastases. No drug-related systemic toxicity or soft tissue necrosis has been noted. Skin reactions, including dry and moist desquamation, occurred as expected at these radiation dose levels.

Conclusions: Combined 5-FU gel plus radiation was feasible and well tolerated in the lower levels of a dose-escalation scheme in treating patients with locally advanced or locally recurrent breast cancer. Intratumoral administration of 5-FU gel may prove a practical and effective potentiator of radiation therapy.

1297 PUBLICATION

Thermoradiotherapy (TRT) for locally recurrent breast cancer (LRBC)

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Purpose: The efficacy and side effects of TRT for microscopic residual disease or unresectable/R2-resected LRBC with skin involvement was investigated in extensively pre-treated pat.: 62% radiation therapy (RT) with median 50 Gy (range 40–115 Gy), 64% chemotherapy, 36% hormonal therapy, and 13% miltefosin.

Methods: Between 5/1995 and 8/1998, 65 fields in 39 pat. with LRBC were treated with twice weekly local hyperthermia (HT: BSD2000-system, MA150-/MA120-/SA115-applicator) and RT. Twelve fields were treated for microscopic residual disease after local excision, 17 fields after resection with flap-reconstruction of LRBC, and 36 fields for macroscopic nodular skin involvement. Mechanically mapped temperatures (T) were monitored throughout all epicutaneous fields.

Results: All fields received median 7 local HT (range 2–12) and RT with median dose of 60 Gy (range 30–68). Averages maximum and average epicutaneous T were 42.1°C, and 41.0°C, respectively. Average intratumoural T of 41.1°C and max. T of 43.0°C were measured in 9 pat. Median follow up was 23 months (range 4–44), median time to LF 18 months. Actuarial 1 and 2 year local tumour control was 85% and 67% for microscopic disease, and 71% and 0% for macroscopic tumours, $p < 0.02$. Actuarial 1 year local tumour control after <60 Gy vs. ≥60 Gy, and CR vs. PR after TRT was 50% vs. 86% ($p < 0.05$), and 91% vs. 56% ($p = 0.002$), respectively. Necrosis occurred in 3 fields after delayed wound healing or above a silicon implant. Moist desquamation appeared m 15 fields. Median survival after TRT was 24 months, 3/39 pat. died of cancer en cuirass and 13/39 pat. of distant metastases.

Conclusion: Significant predictors of local turnout control in extensively pre-treated pat. with LRBC are resectability, irradiation dose, and response to TRT.

1298 PUBLICATION

Docetaxel (TXT) monotherapy & lenograstim (G-CSF) for advanced breast cancer in the elderly

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With the purpose of evaluate the therapeutic data on elderly advanced breast cancer patients, we report a separate analysis of the p. treated with Docetaxel monotherapy in a phase II trial previously reported.

Methods: Between 6.96 to 12.98 we study 15 p aged >65 (65–81.7 p > 70 y). TXT 75 mg/m^2 for frail 6 p. and 100 mg/m^2 for 9 p every 3 weeks with G-CSF (Lenograstim) since day +2 for 5–7 days. Treatment was given until PD and for at least 3 courses with stable disease. Premedication were anti 5HT3 & Dexametasone 40 mg only before the chemotherapy. P. Characteristics: 8 p were anthracycline resistant (2 p refractory). Prior treatment for advanced disease with 2 or more regimens in 5, one in 6 p and 4 p not pretreated. Radiation completed at least >4 weeks before entry and not given to a site used to assess response in 7 p. Sites of disease: liver 4 p, lung 2 p, bone 6 p, nodes 2 p, thoracic wall 2 p, contralateral breast 1 p. PS (ECOG) 0–1: 9 p, 2: 6 p.

Results: A mean of 6.7 courses (2–13) for a total 101 cycles. Toxicities (n = 15): Anemia G3: 1 p, Neutropenia G3: 1 p (toxic death due to sepsis) G4: 5 p, Diarrhea G2: 2 p, Mucositis G2: 2 p, Alopecia all. Other toxicities: mild fluid retention in 2 p. Responses (n = 14): OR 10/14 (71% CI 95%: 50–92); CR 4/14 (28%): 3 hepatic (14 m, 6 m, 4 m) & supraclavicular (6 + m), 3 were anthracycline resistant; PR 6/14 (43%). With a median follow-up of 11 m 12/15 (80%) are alive; median survival not reached.

Conclusion: Docetaxel & G-CSF offers a very high objective response rate (71% CI 95%: 50–92) in pretreated elderly women with advanced breast cancer, with acceptable hematologic toxicity. Although premedication with dexametasone was limited to 40 mg once, after a mean of 6.7 courses significant fluid retention was not found. Elderly women benefit from active treatment with Docetaxel.