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Liposomal daunorubicin in combination with paclitaxel in metastatic breast cancer: A dose finding study

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Anthracyclines and paclitaxel are effective drugs in the treatment of advanced breast cancer. A combination of doxorubicin with paclitaxel showed remarkable antitumor activity with 94% overall response rate (Gianni 1995), although the cardiac toxicity was unusually high. 18% of patients developed congestive heart failure after a median cumulative doxorubicin dose of 480 mg/m^2.

In order to reduce cardiac toxicity we initiated a phase I trial using a new anthracyclin formulation, liposomal encapsulated daunorubicin (DaunoXome®), which replaced doxorubicin in its combination with paclitaxel. The trial is open for women with metastatic breast cancer in need of first- or second-line palliative chemotherapie. The starting dose of DaunoXome® is 30 mg/m^2 and will be escalated in steps of 10 mg/m^2. DaunoXome® is administered by 1-hour infusion and paclitaxel by an 3-hour infusion at a fixed dose of 200 mg/m^2. The treatment is repeated every three weeks until best response, which will be followed by two additional cycles.

As to now, the cardiotoxicity of the regimen seems to be substantially lower when compared to Gianni's data. Furthermore the results indicate good efficacy too. Detailed results concerning toxicity will be presented.

702 PUBLICATION

4-hydroxyandrostenedione (4-OHA) as third-line endocrine therapy in postmenopausal patients with advanced breast cancer

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Purpose: Patients who relapse on antiestrogen treatment frequently continue to have ER positive tumors, though there is a 20% reduction in ER positive status. The role of 4-OHA as third-line endocrine therapy was evaluated in 75 patients.

Methods: To be eligible for inclusion in this study, women were required to have histologically documented carcinoma of the breast, measurable disease, an ECOG performance status ≤2 and a life expectancy of greater than 3 months. A regimen of 250 mg intramuscularly every two weeks was used. A total of 75 patients have been treated. Sixty-eight were naturally postmenopausal and 7 had undergone ovariectomy. All of them had previously responded to first-line tamoxifen therapy and 58 had also responded to second-line treatment with Megestrol acetate.

Results: Among the patients who received at least four injections, 18 (24%) had a partial response and 15 (20%) showed disease stabilization. Median survival was 580 days in responders and 260 days in non responders. Toxicity was minimal.

Conclusion: 4-OHA is an effective and well tolerated third-line treatment in postmenopausal patients with hormone-responsive breast cancer.

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Phase I study of weekly docetaxel (Taxotere®) in heavily pretreated breast cancer patients

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Docetaxel has proven to be an active agent in the treatment of breast cancer when administered with the recommended dose of 100 mg/m^2 every 3 weeks. Several dose dense application strategies (e.g. Epirubicin, 5-FU, Paclitaxel) resulting in an increased frequency of tumor targeting have shown high activity and remarkable low toxicity. For these reasons, we conducted a phase I study to define the maximum tolerated dose (MTD) of docetaxel administered weekly in pretreated breast cancer patients.

Patients and Methods: 16 patients with metastatic breast cancer refractory to anthracycline and/or paclitaxel containing regimens were entered in this trial so far. After premedication with 4 mg i.v. dexamethason 30 min. before docetaxel administration patients received a 1 h infusion of docetaxel, weekly until best response or on unacceptable toxicity using the following dose levels: level 1: 30 mg/m^2, level 2: 35 mg/m^2, level 3: 40 mg/m^2, level 4: 45 mg/m^2, level 5: 50 mg/m^2.

Results: No dose limiting toxicity occurred in dose level 1–4 and the MTD has not been reached. At all dose levels responses could be observed.

Conclusions: Weekly Docetaxel seems to be effective although the MTD has not been reached. No grade 3/4 hematologic and non hematologic toxicity occurred and further dose escalation is planned to evaluate the recommended dose for phase II trials.

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Phase II studies of two trial regimens of topotecan as second-line single agent therapy in advanced breast cancer

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Purpose: Topotecan (T), a semisynthetic analog of camptothecin, is a selective topoisomerase-1 inhibitor with demonstrated activity as second-line treatment in advanced ovarian and small cell lung cancers. T, 1.5 mg/m2/d for 5 d q 3 wk, has also shown activity against metastatic breast cancer (*Proc ASCO* 14: 105, 1995). The efficacy and safety of different regimens of T was to be examined in women with advanced breast carcinoma who had failed standard first-line chemotherapy, including cyclophosphamide, fluorouracil, epirubicin or doxorubicin.

Methods: Two open-label, non-comparative, multicentre Phase II studies were conducted. Study 1 comprised 18 patients (pts) who received T, 22.5 mg/m^2, 30-min infusion q 3 wk. Study 2 comprised 16 pts who received T, 1.5 mg/m2, 24-h infusion q 1 wk. Half of the pts had failed one or more regimens. All pts had metastatic disease, 32/34 had secondaries in the liver and 30/34 in the thorax. The majority of pts had also received prior radiotherapy, hormone therapy, and had undergone surgery for their breast cancer. Performance status was 0–2. Mean age was 53.4 y (range 32–74 y).

Results: One patient had a partial response (PR) and 3 had stable disease (SD). In study 2, 37 courses (136 infusions) were administered (median = 2.0/pt). No pts had either a complete or partial response. 2 pts had SD. Haematologic toxicity was predictable, transient, and reversible in both studies. Neutropenia was the principal toxicity. Non-haematologic toxicity was generally mild and tolerable with no marked clinical sequelae.

Conclusion: In these populations with poor prognositic features, these 2 regimens of T used do not demonstrate the efficacy previously shown with the 1.5 mg/m2/d × 5d regimen.

705 PUBLICATION

Phase II studies with GI147211 (GI) in breast (B), colorectal (C) and non small cell lung cancer (N)

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GI is a water soluble analog of camptothecin, showing antitumor activity in a broad range of tumor xenografts.

The ECSG performed Phase II studies in B (2nd line), C (1st line) and N (1st line) at the recommended Phase II dose of 1.2 mg/m^2/d × 5q3wks. A total of 66 eligible patients (pts) were entered (24B, 19C, 23N). At present, 18B, 19C and 23N pts are evaluable for response.

A total of 167 cycles (c) was administered (median 2, range 1–12) with dose reductions to 0.9 mg/m^2/d in 18 c, and escalations to 1.5 mg/m^2/d in 46 c. Main hematologic toxicities were neutropenia and thrombocytopenia although neutropenic fever/infections occurred rarely. Main non-hematologic toxicities were nausea, asthenia and alopecia, rarely > grade 2. One PR was observed in B and 2 in N. Stable disease was seen in 9B, 7C and 6N.

We conclude that GI in this dose and schedule is only marginally active in B (2nd line) and N (1st line) and inactive in C (1st line).