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Sequential FEC-Taxol chemotherapy (CT) for advanced breast cancer (aBC) patients (pts). A 'Breast Cancer Cooperative Group' BC 97/01 Phase II study including QoL analysis

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Purpose: To test the hypothesis that the sequential use of non cross-resistant CT regimens could improve disease-free survival and overall survival in aBC pts., within a phase-II multicenter study.

Methods: From January '98 to date, 51 aBC pts. received an induction phase of 4 cycles of FEC (5-FU 600 mg/m^2, Epi 90 mg/m^2 and CTX 600 mg/m^2 every 21st day). Pts. experiencing at least a disease stabilization, received also 4 cycles of Taxol (175 mg/m^2 over a 3 hours-infusion period every 21st day), preceded by adequate premedication. *EORTC QLQ C-30* specific questionnaire was administered to all pts. before study entry, after the 4 FEC cycles, after the 4 Taxol cycles and then every three months.

Results: Of the enrolled 51 pts., 46 were evaluable for response after FEC CT; three pts. went off the study due to early death, refusal to continue CT or cardiac toxicity (1 pt. each). Four pts. progressed after FEC and were excluded from subsequent analysis. Of the 42 pts. who went on to receive Taxol, 35 pts. are at present evaluable. Overall results follow.

Response	4 FEC (46 pts.)	4 FEC + 4 Taxol (35 pts.)
CR (%)	5 (11)	7 (20)
PR (%)	24 (53)	24 (68)
SD (%)	13 (28)	0
P (%)	4 (8)	4 (11)

Conclusions: Despite the fact that this protocol is still ongoing, the sequential use of FEC and Taxol seems to be an active strategy to treat aBC pts.

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HMG-CoA inhibitor-lovastatin sensitizes highly aggressive breast carcinoma to PCD induced by vinorelbine, upregulating BAX, p53 and downregulating RhoA-GTPase, bcl-2

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Purpose: Breast cancer is one of the leading causes of cancer death among women. Various anticancer drugs, such as the microtubule inhibitor-vinorelbine, cause cell death through apoptosis. In this tudy, we investigate the combination of vinorelbine, and actin depolymerizer-lovastatin against advanced breast carcinoma.

Methods: Infiltrating ductal carcinoma cells of ipsilateral axillary nodes were isolated after surgical excision. Tumour cells were pretreated with lovastatin, and they were subsequently incubated with vinorelbine-tartrate. Morphological apoptotic signs were examined by transmission electron microscopy. Expression of cytoskeleton mediator protein RhoA, anti-apoptotic protein bcl-2, tumour suppressor gene p53 & proapoptotic protein bax was measured by IHC using paraffin-embedded, formalin fixed sections, while mRNA was measured by Northern blot. Assay measures were performed before and after treatment with lovastatin and vinorelbine. Control samples consisted of tumour cells treated only with vinorelbine Cell cycle was monitored by flow cytometry.

Results: Electron microscopy exhibits rounding up of tumour cells after lovastatin treatment. IHC analysis exhibited downregulation of poly-isoprenylated RhoA protein. Lovastatin disrupts the F-actin cytoskeleton through inactivation of RhoA proteins by preventing isoprenyla-tion. urthermore, HMG-CoA reductase inhibitor arrested tumour cells in G1, and it was accompanied by p53 over-expression. Subsequently, TEM has exhibited apoptotic signs of stage D1. After treatment with vinorelbine, there was de-polymerization of microtubules blocking cells in metaphase. Also, there were increases of transcribed bax nRNA intracellular levels, which translated into large amounts of bax protein. In contrast, bcl-2 was downregulated after phosphorylation by vinorelbine, following disruption of microtubule-architecture inducing irreversible stage F of apoptosis. After 72 hours, we observed D2 stage of apoptosis which leads to the formation of apoptotic bodies which are phagocytosed by adjacent tumour cell, eradicating them. This indicated a by-stander effect. Finally, pretreatment with lovastatin, enhanced induction of apoptosis by vinorelbine approaching 100%, compared to controls.

Conclusion: Lovastatin sensitizes human advanced breast carcinoma to apoptosis induced by vinorelbine, and this effect is accompanied by alteration of expressions in p53, bcl-2, bax and RhoA. Thus, lovastatin combined with vinorelbine might find potentially useful clinical applications in advanced breast cancer.

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Herceptin (R) plus cisplatin is active in patients with metastatic breast cancer

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Purpose: To assess the efficacy of Herceptin (trastuzumab) in combination with cisplatin in metastatic breast cancer.

Methods: Women with extensively pretreated metastatic breast cancer overexpressing HER2 received iv Herceptin as a loading dose of 250 mg on day 0 then weekly doses of 100 mg for 9 weeks. They also received iv cisplatin 75 mg/m^2 on days 1, 29 and 57.

Results: 37 patients were evaluated by a Response Evaluation Committee. There were 9 PRs (24.3%). A further 9 patients had a minor response or stable disease (24.3%). Median duration of response was 5.3 months (range 1.6–18 months). Median survival was 11 months. Grade 3/4 toxicity occurred in 56% of patients and was consistent with the toxicity expected from cisplatin alone. During the main study, the most common toxicities were myelosuppression (n = 10), nausea/vomiting (n = 9) and asthenia (n = 5). During the maintenance phase, grade 3/4 toxicity possibly related to Herceptin was infrequent (15%) (cytopenia, nausea, anorexia, asthenia and hyperbilirubinaemia).

Conclusions: Use of Herceptin and cisplatin in combination increased the response rate compared with either agent used alone.

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New approach to tumor marking. Clip implantation prior to primary chemotherapy on patients with mammary carcinoma

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Purpose: In a multicentric Phase II study, using Doxorubicin/Taxol, complete clinico-radiological remission in response to primary chemotherapy was recorded from three in twelve patients who had received treatment for T2 mammary carcinoma in our unit of gynecological oncology. Reliable preoperative marking of the original tumor bed for necessary surgical exstirpation is problematic in such cases. We have conducted our study with the view to developing a safe, easily applicable, patient-friendly method for accurate tumor marking.

Material and Methods: The lesion is sonographically localized with the patient in supine position. A 16-gage coaxial needle then is placed in the focus with the patient in local anesthesia. The mandrin is pulled, and an Ethicon* U-bent vascular titanium clip is inserted into the channel and by forward-movement of the mandrin is implanted in the tumor under sonographic control. Standard punch biopsy, subsequently, can be undertaken above the channel and bypassing the clip for necessary histopathological verification.

Results: Five patients so far have been marked by titanium clips with sonographically controlled mammary punch biopsy in the same session. The vascular clip continued to be visible for radiological differentiation in all sonographic follow-up checks on patients who had received primary chemotherapy. Also possible was safe preoperative mammographic wire marking in the area adjacent to the clip. An extinction phenomenon, only few millimetres in extension, depending on the mode of evaluation, was the only trace left for identification by magnetic resonance tomography.

Conclusion: The new method differs from previous procedures, in that it enables safe and easily applicable marking of a tumor region or tumor proper if the latter can no longer be clearly differentiated by imaging techniques, for example, following primary chemotherapy. Clip marking may as well prove helpful with regard to future therapeutic strategies, for example, in irradiation planning or follow-up control by imaging techniques in the context of recurrence diagnostics. The method might be useful also for treatment and follow-up of tumors of different genesis.