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A randomised phase II trial of pre-operative navelbine/epirubicin (NE) versus navelbine/mitozantrone (NM) versus adriamycin/cyclophosphamide (AC) for early breast cancer

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Purpose: Pre-operative chemotherapy in early breast cancer enables novel chemotherapy regimes to be tested using clinical response as a surrogate marker for longer-term activity. Navelbine is active and well tolerated in advanced breast cancer but has not been formally tested in early disease. We therefore performed a randomised trial comparing navelbine in combination with epirubicin or mitozantrone with standard AC chemotherapy.

Methods: 147 patients (117 accessible for response) with operable breast cancers ~3cms were randomised on a 2:2:1 (NE:NM:AC) basis. This randomisation was chosen to maximise the experience with the navelbine containing combinations. Chemotherapy regimens were as follows: AC - adriamycin 60mg/m2, cyclophosphamide 600mg/m2, q21; NE - navelbine 25mg/m2/d1+8, epirubicin 60mg/m2, q21; NM - navelbine 25mg/m2/d1+8, mitozantrone 12mg/m2, q21. Response was assessed clinically prior to each of the six cycles of treatment.

Results: Response rates were as follows: NE 86%, NM 73% and AC 65% (NS). The NM arm resulted in more grade 3/4 neutropenia: 57% vs. 35% (NE) vs. 32% (AC), neutropenic sepsis: 21% (NM) v. 12% (NE) v. 9% (AC). In addition treatment modifications were more common with NM, 70% v. 53% (AC) v. 50% (NE), as was the need for GCSF support, 42% (NM) v. 13% (NE) v. 9% (AC). The incidence of grade 3/4 alopecia however was lower with the NM arm, 19% v. 75% (AC) v. 51% (NE).

Conclusion: The navelbine combinations demonstrate good pre-operative clinical activity. The NM arm has been dropped because of increased haematological toxicities. This trial has now been expanded into a phase III comparing NE with AC.

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Exemestane combined with epirubicine, q1w x (8-12), as pre-operative chemo-endocrine treatment for patients with primary breast cancer: a phase I study

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Introduction: Recent preclinical studies on rats with DMBA induced mammary tumors provided first evidence that the aromatase inactivator EXE infers high cyto-toxic potential to subtoxic doses of EPI when given concomitantly, suggesting that chemo-endocrine treatment with EXE and EPI might be a treatment form for breast cancer both highly active and well tolerated. The phase I study summarized here has been designed to test this hypothesis by evaluating the dose-limiting toxicity of preoperative EPI, q1w x (8-12) given at 3 different dose levels (DL) (DL1= 25mg/m2, DL2= 30mg/m2, DL3= 35mg/m2) together with continuous EXE 25 mg/d. A standard two step model for dose escalation was applied with 4- 6 patients at each dose level. Endpoints: PE was the frequency of 3° and 4° hematological and non-hematological toxicities (NCI-CTC). SP were extent and rate of cCR + cPR. Patients: N=14, amenable to statistical analysis; Median age: 64,5y(54-79); TNM: T2, N=12/14; T3, N=1/14; T4b, N=1/14; N0, N= 8/14; N1, N= 6/14; M0, N= 14/14; ER pos, N=5/14; ER neg, N=8/14; ER n.d., N= 1/14; HER2 neg. or 1+: N=14/14. Hematologic toxicity: N=2/14 (DL1,DL2) (Neutropenia NCI-CTC 2°). Most frequent non-hematologic toxicities (NCI-CTC- 1° and 2°): Alopecia (N=10/14), Mucositis (N=7/14), Nausea and Fatigue (N=4/14). Yet no dose-limiting toxicity (incl. pathologic LVEF decrease) has been observed. Withdrawals: N=5; 1 x Neutropenia 2° (DL1); 1x DVT and pulmonal embolism (DL1); 1 x PD (DL2); 1 x "consent withdrawal"(DL3); 1 x traumatic fracture (DL3). Clinical best response: cCR, N=2/14; cPR, N=8/14; cSD, N=3/14; cPD, N=1/14. 14/14 patients obtained surgery, 10/14 had breast conserving surgery. Pathological response: Regression grade (Sinn): 0°, N=3/14; 1°, N=10/14; 40, N=1/14. Post-treatment pathological tumor-size: ypT0 (pCR), N=1/14; ypT1c, N=4/14; ypT2, N=6/14; ypT3, N=3/14.

Conclusion: These phase I data support and extend the idea that the combination of EXE and EPI given weekly up to doses of 35 mg/m2 (DL3) is a well tolerated preoperative treatment for PBC. In the current randomised multicenter Phase II trial patients will receive EXE in combination with either weekly EPI 30 mg/m2 or weekly EPI 20 mg/m2 to support the initial concept of the study (reduction of chemotherapy and therefore toxicity possible because of synergistic action of combination therapy with EPI and EXE).

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Clinical management with dose-escalated and tailored fec; a feasible therapy with G-CSF-support for fewer days

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Background: Dose-escalated and tailored fluorouracil, epirubicin and cyclophosphamide therapy given for 9 courses with G-CSF support is a highly active therapy for patients with high-risk early breast cancer. However, the major drawback of this regime was the risk of therapy-related myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Aim: The aim of the present study was to evaluate if 6 courses of tailored and dose-escalated FEC (dFEC) is a feasible therapy when G-CSF is used from day 5-12, these modifications are aiming at reducing the risk of MDS/AML.

Patients and therapy: From 1998 to 2000, sixty consecutive patients with high-risk early stage breast cancer (n=17) or locally advanced breast cancer (LABC) (n=43) were treated with dFEC. Adjuvant therapy was given for 6 cycles, patients with LABC received 4 preoperative cycles of dFEC, and responders (CR, PR) were treated with additional 2 courses. Patients with SD received taxanes postoperatively. G-CSF was given from day 2 to 12 or from day 5 to 15 in 1998, and was further reduced and given from day 5 to 12 in 1999-2000. All patients started on step +1 (5-FU (F) 600 mg/m2, epirubicin (E) 75 mg/m2, cyclophosphamide (C) 900 mg/m2, and dose modifications were made based on leukocyt and/or platelet toxicity. The patients were divided according to the G-CSF delivery; group 1 day 5-12, group 2 day 2-11/12, group 3 day 5-15, and comparisons between leukocyte/platelet counts at days 8, 11 or 12, and 15 were made.

Results: A total of 238 courses of dFEC was delivered; 80 at step one, 110 at step two, 94 at step three, 34 at step 4, and 12 at step -1 (standard FEC). The median leukocyte count after the sixth course at day 15 were 5.7 (group 1), 13.8 (group 2), and 33.7 (group 3). These data was also compared to those from the dose-escalated arm within the randomised Scandinavian trial. No differences were seen in number of infections, febrile neutropenia, transfusions or hospitalization. So far no clinical cardiac toxicity, secondary malignancies have been recorded.

Conclusions: Dose-escalated and tailored FEC is a feasible therapy with use of G-CSF at day 5-12. Prolonged G-CSF use resulted in higher leukocyte-values, but did not allow higher chemotherapy-doses or reduced side effects.

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Does immediate post mastectomy reconstruction delay adjuvant therapy?

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Introduction: Adjuvant chemotherapy, radiotherapy (RT) or both often follow mastectomy for breast cancer. The use of immediate post mastectomy reconstruction (IPMR) is increasing resulting in improved cosmesis, body image and quality of life. There is concern that delay in commencing adjuvant therapy may compromise efficacy.

Methods: We retrospectively reviewed the case notes of women who underwent mastectomy in our unit from May 1996 to May 2000, to assess for any delay in commencing first adjuvant therapy.

Results: 379 women underwent mastectomy. 88 received chemotherapy and 54 received RT as first adjuvant therapy. In the chemotherapy group 59 women had IPMR and 29 had no reconstructive surgery. Their mean delays to chemotherapy of 32.9 days (95% CI 23.9 - 41.9) and 29.4 days (95% CI 19.2 - 39.7) respectively were not significantly different. Also no difference was found comparing type of reconstruction, history of prior RT, patient age and unilateral vs bilateral mastectomy. In the RT group 19 women had IPMR and 35 had no reconstructive surgery. Their mean delays to RT of 52.9 days (95% CI 44.1-63.5) and 37.8 days (95%CI 33.7-42.3) respectively was significantly longer with IPMR than without ($p<0.0013$). No difference was found comparing type of reconstruction, patient age and unilateral vs bilateral mastectomy.

Our data showed that the time to RT post reconstruction was prolonged across the whole group and not just due to a few patients with a particularly long delay. In the women who had IPMR 31% waited 31-45days, 37% waited 46-59 days and 32% waited over 60 days for their RT.

This implies that the cause for the delay is likely to be in the referral system rather than due to any reconstruction-related complications.

Conclusion: Immediate reconstruction in our experience has resulted in a delay to first adjuvant RT but not chemotherapy. It is unclear whether such a delay is sufficient to reduce the efficacy of RT. However, delays in starting RT that can be anticipated should be avoided. Breast units should ensure that all patients are referred for post-mastectomy RT as early as possible following surgery.

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Late skin reactions after different chemotherapy schemes in irradiated breast cancer patients

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Purpose: Assessment of late changes of irradiated skin after CMF and EC-chemotherapy compared to patients with hormone therapy or no additional therapy.

Patients and methods: In 63 patients, irradiated at University of Ulm for breast cancer, thickness and structure of irradiated and non- irradiated skin was measured by 20 MHZ-ultrasound.

Results: 18/63 patients received either 6xCMF (3 cycles before and 3 cycles after radiotherapy) or 4xEC (before radiotherapy) in addition to breast irradiation. None of these patients received hormone therapy. 29/63 Patients were on tamoxifen during and after radiotherapy. Ultrastructural changes of corium thickness and structure were measured quantitatively by high-frequency 20 MHz-ultrasound. Corium thickness of non-irradiated skin (contralateral breast) showed significant difference in patients treated with chemo- and hormone therapy comparing with those treated without chemotherapy (p=0.03) or hormone therapy (p=0.019). EC showed significant more increase in corium thickness compared to CMF (p=0.0008). No changes in echogenity were observed.

In irradiated skin, reactions (according to corium thickness and echogenity of lower corium) were significant increased in the chemotherapy (p=0.001) and hormone therapy (p=0.003) group. EC showed significant more skin changes compared to CMF (0.0008) and to the hormone therapy group.

Conclusion: Chemotherapy and tamoxifen induce changes of normal (non-irradiated) skin, which increase significant after radiotherapy. Corium thickness and skin structure are more altered by EC-chemotherapy compared to CMF or tamoxifen.

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A pilot study with navelbine (NVB) + fractionated doxorubicin (DX) as neo-adjuvant chemotherapy for locally advanced breast cancer

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A phase II study of i.v. fractioned VNB and DX combination in previously untreated advanced breast carcinoma observed promising results with NVB 25mg/m2 on days 1 and 8, and DX 50 mg/m2 on day 1 (q 21 days); with 74% OR and 21% CR, mainly in visceral sites (JCO, 1994).

Our group observed the same responses with fractionated doses of DX (A. Anelli; et al) for advanced disease. In order to observe potential value of this association for neo-adjuvant chemotherapy (NA chemo) set, a pilot study was done in 25 patients, receiving 4 cycles of NA chemo (NVB 25mg/m2 i.v. + DX 25mg/m2 i.v. -D1 + D8 each drug; in cycles of 21 days), 24 patients were available for response and 25 for toxicity.

Stages IIA=2(8%), IIB=6(25%); IIIA=16(67%); <50 years old=13; >50 years old =12; hystology - ductal infiltrative =17; others not medullary =7.

Clinical responses: CR (1/24-4%); PR (23/24-96%); SD/PD (0/24); OR 100%. Two cycles were the minimal number to observe objective clinical response in 19 patients. Surgery was performed in 23 patients after 4 cycles of NA chemo. Conservative breast surgery was performed in 7/23-30,5%. A pathologic complete response (pCR) was observed in 5/23-22% for primary tumor, with 18/23-78% of pathological partial response (pPR). For nodes pN0, 9/23-39% and pN+, 14/23-61%. At this moment 18 patients went to complimentary radiotherapy, with 01 patient with recurrent disease on radiotherapy.

Grade 3 toxicity was observed in 20 patients with alopecia, 13 patients with neutropenia, 3 patients with nausea and vomiting, 2 patients with phlebitis, 2 patients with mucositis, 1 patient with cutaneous, 1 patient with diarrhoea, no patients with neurotoxicity and no grade 4 toxicity was observed.

Conclusion: neo-adjuvant fractionated is an important neo-adjuvant scheme for breast cancer with low toxicity profile and similar results than schedules with taxanes and/or anthracyclines.

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Significant higher health-related quality of life (HR-QOL) level in women treated with adjuvant hormonal therapy versus chemotherapy: prospective measurement during/after postoperative radiotherapy for breast cancer

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Purpose: To report the results of a prospective HR-QoL asseassment in women with brest cancer during/after postoperative radiotherapy.

Materials and Methods: Hundred-nine consecutivelly treated patients were analysed. For quality of life measurement the EORTC modules QLQ-C30 and BR23 were used. The HR-QoL was asseassed at beginn (T1), at end (T2) and 6 weeks after radiotherapy (T3). We segregated the patients in three prognostic groups: group I, n = 41 (radiotherapy and adjuvant chemotherapy), group II, n = 45 (radiotherapy and adjuvant hormonal therapy) and group III, n = 23 (radiotherapy alone). The reliability was tested. ANOVA analyses were performed.

Ergebnisse: The reliability testing revealed good median Cronbachs Alpha values of 0.77, 0.83, and 0.83 for the measurement points T1, T2 and T3, respectivelly. Twenty-one quality of life dimensions from global health status to arm symptoms were asseassed. The ANOVA statistics revealed significant better HR-QoL for patients in prognostic group II versus I. Patients treated with radiotherapy alone (group III) showed the best results in the quality of life analyses compared with groups I and II.

Conclusions: Measurement of HR-QoL using the EORTC core protocol QLQ-C30 and the breast module BR23 during/after radiotherapy is reliable (median Cronbachs Alpha values >0.7). Adjuvant chemotherapy lowered statistically significant the HR-QoL compared with adjuvant hormonal therapy or radiotherapy alone. The results suggest that the use of adjuvant hormonal therapy is more favorable in terms of quality of life versus chemotherapy.

Breast cancer genetics and biology

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High frequency of mitochondrial DNA mutations in breast cancer: potential application for cancer detection

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The human mitochondrial DNA (mtDNA) has a mutation rate at least 10 times higher than the nuclear DNA. Somatic mutations in the mtDNA have been recently observed in several tumor types and have been used to detect cancer cells in bodily fluids.To determine the frequency and distribution of mitochondrial DNA mutations in breast cancer, 18 primary breast tumors were analyzed by direct sequencing. Twelve somatic mutations were detected in 11 of the tumors screened (61%). Of these mutations, 5 (42%) were deletions or insertions in a homopolymeric C-stretch between nucleotide 303-315 (D310) within the D-loop. The remaining 7 mutations (58%) were single base substitutions in the coding (ND1, ND4, ND5, and Cyt b genes) or non coding regions (D-loop) of the mitochondrial genome. In three cases (25%), the mutations detected in coding regions led to amino acid substitutions in the protein sequence. We then screened an additional 46 primary breast tumors with a rapid PCR-based assay to identify poly C alterations in D310 and found 7 more cancers with alterations. Using D310 mutations as clonal marker, we detected identical changes in 5 of 5 matched fine needle aspirates and in 4 of 4 metastases positive lymph nodes. The high frequency of D310 alterations in primary breast cancer combined with the high sensitivity of the PCR-based assays provide a new powerful molecular tool for cancer detection.