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CGS 16949A versus TAMOXIFEN in the treatment of advanced breast cancer - an ongoing phase III study

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For the Swiss Group for Clinical and Epidemiological Cancer Research SAKK.

Tamoxifen (TAM) is a common primary treatment of hormone-dependent metastatic breast cancer in postmenopausal patients (pts). Aminoglutethimide (AG), an aromatase inhibitor, shows a similar efficacy, but is more toxic. A new non-steroidal aromatase inhibitor, CGS 16949 A, that is 400 - 1000 x more potent than AG, was developed as a result of efforts to develop a less toxic compound. A randomised phase III study comparing CGS 16949A p.o. 1 mg bid and TAM p.o. 20 mg daily as first line treatment and with subsequent crossover has been started. Emphasis has been given to aspects of toxicity and quality-of-life. From Oct. 1988 to Jan. 1990 51 non-pretreated postmenopausal advanced breast cancer pts who were amenable to hormonal treatment were accrued. Only 4 pts had previous adjuvant hormonal treatment completed > 12 months before study entry. 35 patients are assessable for the first interim analysis of response and toxicity to first assigned treatment:

	TAMOXIFEN	CGS 16949A
No pt.	16	19
PR	5	4
median TTF	9 mos	9,5 mos
(range)	(4+ - 11+)	(4+ - 17+)
NC	8	11
median TTF	6 mos	4,5 mos
(range)	(4+ - 11)	(3 - 13+)
PD	3	4

Interestingly, responses to second treatment were observed also in patients who did not respond to the first treatment. In both regimens adverse side effects were rarely observed and mild.

We conclude that both CGS 16949A and Tamoxifen are similarly tolerable and effective as first line treatment in advanced breast cancer. More pts are needed for assessing the frequency of response to second treatment especially in case of primary failure.

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ESTROGENIC - RECRUITMENT-THERAPY A PILOT STUDY IN DISSEMINATED BREAST CANCER.

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The present study includes 24 patients who have metastasizing breast cancer. The treatment-modalities contain a sequential combination of hormonal and cytotoxic drugs according to the method published by the EORTC-study group. The treatment starts with the daily oral administration of the aromatase-inhibitor Aminogluthetimide and the substitution with Hydro-cortisone. The daily dosis are 1000 mg Aminogluthetimide and 40 mg Hydrocortisone. After 3-weeks-interval the patients receive additionally a single oral dose of 20 mg Ethinylestradiol. 24 h later the cytotoxic drugs consisting of Cyclophospamide, 600mg/m² body surface (bs) Mitoxantrone 12 mg/m² bs, 5-FU 600 mg/m² bs, are administered intravenously.
The grade and duration of remission are mesured according to the UICC-criterias.
Up to now 9% CR, 69% PR and 22% progressive disease were observed.
A tendency become obvious that receptor positive tumors react better to this type of treatment.
Responding patients have a better overall-survival.

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LOCALLY ADVANCED/INFLAMMATORY BREAST CANCER (LAIBC) TREATED WITH PREOPERATIVE CHEMOTHERAPY AND HORMONAL CELL SYNCHRONIZATION (HCS)

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A total of 15 patients with LAIBC of the stages IIIb(n=7) and IV(n=8) was treated pre- and postoperatively as published recently by Lippman (J Clin Oncol 84) and Swain (Cancer Res 87): d1 cyclophosphamide 500 mg/m² i.v. and doxorubicin 30 mg/m² i.v.; d2 until d6 tamoxifen 40 mg p.o.;d7 and d8 conjugated estrogens 0.625 mg p.o. q 12 hours (3 times);d8 alternating each second cycle methotrexate 300 mg/m² or 375 mg/m² i.v. and 5-fluorouracil 500 mg/m² or 625 mg/m² i.v.;d9 calciumfolinate 15 mg p.o. q 6 hours (6 times). An objective response rate of 80% was achieved (CR n=1, PR n=11);NC n=2 ,PD n=1.The progressive-free interval was median 8 months, the median survival was 24 months.Maximal WHO grades of toxicity were: alopecia 3(n=6), gastrointestinal 4(n=1),diarrhoea 3(n=1),fever 2 (n=2), stomatitis 2(n=2).In conclusion,this therapeutic concept proves feasibility and high efficacy.

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ENHANCEMENT OF CYTOTOXIC DRUG ACTION ON GROWTH OF HUMAN BREAST CANCER CELLS BY MEDROXYPROGESTERONE ACETATE.

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The static response rate to chemotherapy or endocrine therapy led us to develop a combined cyclical-sequential hormo-chemotherapy regimen for treatment of patients with advanced breast cancer. Results from a preliminary study were very encouraging (Ghilchik et al., Brit. Med. J., 295, 1171, 1987). In order to investigate the mechanism by which pre-treatment with medroxyprogesterone acetate (MPA) might enhance the efficacy of cytotoxic drug action we have developed an in vitro model using human MCF-7 breast cancer cells. For this cells are exposed to MPA for 48hrs followed by exposure to methotrexate (MTX), Vincristine (VCR) or Adriamycin (ADR) for 24hrs. Results from these studies have shown that pre-treatment of MCF-7 cells with MPA (10-100nM) significantly enhanced the effects of MTX, VCR and ADR on cell growth. It is concluded that pre-treatment of MCF-7 breast cancer cells can enhance the effects of cytotoxic drugs tested.