SURVIVAL ANALYSIS OF A RANDOMIZED TRIAL

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From 1975 to 1980, 466 patients with advanced breast cancer were entered a trial designed to compare concurrent versus sequential hormono- and chemotherapy. After randomization, patients received hormonal treatment (oophorectomy for premenopausal and Tamoxifen for postmenopausal women) and a chemotherapy either at the same time (arm A: concurrent) or at the moment of hormonal treatment failure (arm B: sequential). At randomization patients were also assigned to one of three different chemotherapy regimens representing minimal (only oral), conventional or intensive (including Anthracyclines) cytotoxic treatment. A first analysis reported a tendency of doing better for premenopausal women treated concurrently and postmenopausal patients treated sequentially (BMJ 286: 5-8, 1983).
The final analysis, at more than 12 years median follow-up, demonstrates no difference in survival between patients in arm A and B (13.6 % at 5 years, median 23 months). For each treatment arm no significant survival difference is seen between the three chemotherapy schedules. Major predictors of survival in the multivariate regression analysis are performance status, the presence of metastasis in the liver and the risk category (high vs. low, determined prospectively according to extension of tumor and free interval since mastectomy). Menopausal status does not influence survival.
We conclude that the timing of chemotherapy (immediately or at the moment of hormonal treatment failure) does not influence the survival of women with untreated advanced breast cancer. Reasons for the different outcome of the preliminary results as compared with the final analysis will be discussed.

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An open between patient phase 1 study of CGS 20267 a non-steroidal aromatase inhibitor comparing 0.1, 0.5 & 2.5 mg po od has been performed in 3 successive groups of 7 postmenopausal patients with metastatic breast cancer (total = 21). No toxicity was seen at any of the three doses. Endocrine data are available on all 21 patients. There was a statistically significant suppression of oestrone (E1) and oestradiol (E2) levels in all patients ($p<0.0001$). E2 and E1 fell from mean pre-treatment levels of 22pM and 69pM to below the detection limits of the assays (3pM and 10pM) in 8 and 16 patients respectively. There was a trend towards more efficient E1 suppression with the higher doses. CGS 20267 had no significant effect on follicle stimulating hormone, luteinising hormone, thyroid stimulating hormone, cortisol, aldosterone, 17-hydroxyprogesterone, or androstenedione. So far of 21 assessable patients 6 have responded to treatment (1 CR and 5 PR according to UICC criteria) giving an overall response rate of 28.6% (95% CI 11.3-52.2%) in addition a further 6 have had stable disease for greater than 3 months. These results suggest that CGS 20267 is a very potent and specific oral aromatase inhibitor and phase II studies are now required to determine its clinical efficacy.

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SEQUENTIAL ESTROGEN RECEPTOR DETERMINATIONS FROM PRIMARY BREAST CANCER AND AT RELAPSE: PROGNOSTIC AND THERAPEUTIC RELEVANCE

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We retrospectively evaluated 401 patients who had estrogen receptor (ER) assays both at primary surgery and at relapse. The median time between ER assessments was 27 months (range: 2-122 months). The median follow-up time from diagnosis was 6 years (range: 2-12 years). For patients with ER+ tumors at primary diagnosis, 29% (76/261) had ER- tumors at relapse, while for ER- primaries, the conversion rate was 33% (46/140). Conversions from ER+ to ER- occurred more often when the time interval between assays was less than one year ($p = 0.004$), while conversions from ER- to ER+ tended to occur late (beyond 3 years; $p = 0.0003$). Treatments received between assays (usually adjuvant therapy) had only a slight influence on ER status conversion. Post-relapse survival was poor for patients who had the biopsy accessible recurrence within one year. Among patients whose accessible relapse was beyond one year, those with ER- primaries who converted to ER+ had a longer survival than those whose recurrence was classified again as ER- ($p = 0.006$). This group of patients with ER- primaries who recurred beyond one year with and ER+ tumor in an accessible site represented 29% (40/140) of all patients with ER- primaries, and had an estimated overall survival rate of more than 60% at 6 years from the accessible relapse.
We conclude that reassessment of ER status upon relapse is of little clinical value for patients who recur within one year, but is important for patients who recur later especially for those with ER- primaries.

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SECOND LINE ENDOCRINE TREATMENT OF ADVANCED BREAST CANCER - A RANDOMISED CROSS-OVER STUDY OF MEDROXYPROGESTERONE ACETATE AND AMINOGLUTETHIMIDE

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Females with advanced breast cancer, progressing after an initial response to tamoxifen frequently respond upon further endocrine treatment. Presently progestins and aromatase inhibitors are used for such therapy. Which is most effective and least toxic has been investigated by randomising 200 patients in a prospective study where half were first given medroxyprogesterone acetate (Farlutal®), the other half aminoglutethimide (Orimetene®). Upon progression patients crossed over to the other drug. The main issue was which sequence resulted in the longest total period of time with tumor control and best quality of life.
Method: Patients progressing on tamoxifen were randomised to (MPA) T. Farlutal 500 mg b.i.d. and upon failure to (AG+C) T. Orimetene 250 mg b.i.d. and cortisone acetate 37.5 mg daily or the reversed sequence. Accrual of patients were made at 13 hospitals in Sweden May 1986 through January 1989. Follow-up with objective response classification according to UICC and quality of life estimate according to Nottingham Health Profile (NHP) were made every three months for up to 18 months.
Results: Median duration in the sequence AG+C→ MPA was 11.7 months, while time in the sequence MPA → AG+C was 9.8 months, not significantly different. No difference in median survival (21 months) were seen. NHP estimate disclosed a wellbeing at least as good for AG+C as for MPA reflecting pain relief, physical mobility and capability of household work. Side effects were unexpectedly small for AG+C.
Conclusion: Significant differences concerning efficacy and quality of life was not found. Toxicity profiles were different but acceptable for both regimens.

292 LOW DOSE AMINOGLUTETHIMIDE WITHOUT HYDROCORTISONE AS SECOND-LINE TREATMENT IN ADVANCED BREAST CANCER.

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53 postmenopausal pts (in age > 70 years) with metastatic breast cancer were submited to second-line treatment with aminoglutethimide at dose of 250 mgs/day without hydrocortisone. All patients were previously treated with tamoxifene.
Prior treatment with tamoxifene showed objective responses in 63% of patients.
16/53 patients (30.2%) had objective remission by aminoglutethimide treatment (2 complete and 14 partial), 14/53 (26.4%) a stable disease and 23/53 (43.4%) a progression.
Of 16 responder patients 14 (87.5%) had osseous or soft tissue metastases and 12 (75.0%) positive hormonal receptors in the primary breast tumor.
Time to progression was 187 +/- 58 days in the group of patients with remission and 135 +/- 44 days in that with stable disease. All patients responders to aminoglutethimide responded to first line therapy with tamoxifene.
No significant side-effects were observed and, in particular, plasma cortisol levels were unchanged during the treatment. In conclusion, low doses aminoglutethimide without hydrocortisone replacement is effective, without toxicity, as second line in advanced breast cancer.

293 SOMATULINE PLUS TAMOXIFEN IN POST MENOPAUSAL BREAST CANCER PATIENTS.

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Thirty previously untreated post menopausal breast cancer patients (pts) were given Tamoxifen (10 mg t.i.d.) and a long acting Somatostatine analogue (Somatuline, Ipsen) 20 mg s.c. weekly for almost six months or until disease progression. Main pts characteristics were: median age 77.5 yrs, range: (68-83), median initial WHO PS 0(0-1) and median DFI 13 yrs (0-15). Disease sites were skin: 9 pts, nodes: 3 pts, bone: 7 pts, breast: 13 pt, pleura: 1 pt, lung 3 pts. All pts were evaluable for toxicity and for response (UICC criteria). Median duration of treatment was 6.5 months (2-32). Objective response rate was 36% (3 RC and 9 RP); median response duration was 13 months (9-32). Treatment was well tolerated; without inducing major effects. The behaviour of serum GH and IGF-1 levels during treatment is shown below.

SERUM GH AND IGF-1 LEVELS (N=7 PTS)

	Time 0	14 days	1 month	3 months	6 months
IGF-1	70(51.8-113.4)	49(45.2-58.2)	39.2(37.8-72.8)	45.5(42-119)	43.4(43.4)*
GH	0.61(0.1-5.83)	0.2(0.2-3.7)	0.6(0.2-6.8)	1.2(0.1-9.1)	4.4(0.1-16)

Median value in mg/ml; *p<0.05 (Mann-Whitney U Test)

Overall a significant decrease in IGF-1 levels was produced by combined treatment, while an opposite trend was observed with respect to GH levels. In addition GH behaviour was extremely variable among pts and in the same pts following each Somatuline administration. Our preliminary findings suggest that the combination of Tamoxifen and Somatuline is a safe and effective regimen for breast cancer pts, which is able to achieve a significant reduction in circulating IGF-1 levels.

294 FADROZOLE HYDROCHLORIDE (CGS 16 949 A), A DOUBLE-BLIND DOSE-FINDING STUDY IN POSTMENOPAUSAL PATIENTS WITH ADVANCED BREAST CANCER.

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for the AI/BC2 INTERNATIONAL STUDY GROUP

To determine the optimal daily dose of fadrozole, a new potent oral non-steroidal aromatase inhibitor, a multicentre, randomised, double-blind, dose-finding study was performed in postmenopausal patients with advanced breast cancer after failure of tamoxifen. The doses tested were 0.5, 1 and 2 mg twice daily. UICC criteria were used to assess tumour response. The study was approved by local Ethical Committees and Informed Consent was obtained from all patients (pts). Records of pts with CR, PR or NC were peer reviewed. From June '88 to Jan. '90, 423 pts were enrolled in 49 centres, in Argentina, Belgium, Canada, Denmark, Finland, France, Germany, Netherlands, Norway and Spain. Patient characteristics (intent-to-treat) were: median age 65 yrs, PS 0: 159 pts, 1: 165 pts, 2: 95 pts, 3: 2 pts; median time since menopause: 14 yrs; median DFI: 26 mths. Receptor status was positive in 56% of pts, unknown in 43.3%, negative in 0.7%. Ninety-five percent of pts had had treatment with tamoxifen for advanced disease and 4.7% had had progression of disease under adjuvant tamoxifen. Sixty-six pts (15.6%) had had additional treatment for advanced disease. Seventy-three pts were not evaluable for tumour response because of non-evaluable/measurable lesions (16), lack of documentation (37), stopping treatment before assessment (17) or concomitant anti-cancer therapy (3). The objective response rate (CR+PR) of the remaining 350 pts was: 17.5% for 1mg/d (95% CI: 10.9 - 24.1%), 18.2% for 2mg/d (11 - 25.4%) and 13.1% for 4mg/d (6.9 - 19.3%)(NS). NC was 33.3%, 30% and 26.3%, and PD was 49.2%, 51.8% and 60.5% for 1, 2 and 4mg daily. The median overall duration of objective response was 15.4, 18 and 15.4 mths (NS) and TTF was 5, 5 and 3.4 mths, respectively (p=0.04). The main adverse events reported, independent of causal relationship, were (intent-to-treat) nausea/vomiting: 11.3% of pts, hot flushes 5.4%, fatigue 4.5%, dyspnea 3.1%, dyspepsia 3.1%, diarrhoea 3.1%, constipation 2.8%, headache 2.4%, skin rash 1.9%, anorexia 1.7%, dizziness 1.7%, hyperhidrosis 1.7%, coughing 1.7%, vertigo 1.2%, leg cramps 1.2%, lethargy 1%. In conclusion, the overall objective response rate was 16.1% (12.2-20%) with no difference between doses, and fadrozole appeared well tolerated.

295 ALTERATIONS IN PLASMA AND URINE ESTROGENS IN BREAST CANCER PATIENTS TREATED WITH AMINOGLUTETHIMIDE OR 4-HYDROXY-ANDROSTENEDIONE.

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Aminoglutethimide (AG) and 4-hydroxyandrostenedione (4-OHA, Lentaron) is the two aromatase inhibitors most extensively used for treatment of breast cancer. Tracer studies have shown both drugs to inhibit *in vivo* aromatisation of androstenedione (A) into estrone (E_1) by >90%. On the other hand, several studies have reported plasma estrogens to be sustained at levels 30-50% of their control values. Whether this finding may be due to technical artefacts or it suggests alternative estrogen sources is not known. To study this phenomenon we measured urinary estrogen metabolite excretion using a specific GC-MS method to compare alterations in plasma and urinary estrogens in patients treated with AG or 4-OHA. The mean values of total estrogens (tot E), major urinary estrogen metabolites and plasma estrogens during treatment expressed as % of their control values were

	Plasma			Urine					
Treatment	E_2	E_1	E_1S	tot E_1	E_1	E_2	E_3	16OHE$_1$	2OHE$_1$
AG (n=7)	21%	36%	30%	39%	36%	29%	52%	33%	37%
4OHA (n=9)	36%	30%	33%	36%	32%	25%	25%	21%	24%

Conclusions: Our results show an internal consistency between the relative suppression of plasma estrogens (measured by a RIA technique) and the relative suppression of urinary estrogen metabolites in patients treated with AG or 4OHA. The findings provide indirect support to the hypothesis that there may be alternative estrogen sources in patients treated with aromatase inhibitors.

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296 MODULATION OF ESTROGEN AND PROGESTERONE RECEPTORS BEFORE AND AFTER TREATMENT WITH INTERFERON-ALPHA 2A (IFN) IN PATIENTS WITH BREAST CANCER

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Whether interferons induce a positive or negative effect on the expression of hormonal receptors in breast cancer is still a debated question. Twelve breast cancer patients with local recurrence or accessible soft tissue metastasis, without any concurrent treatment, were included in our study. Using an immunocytochemical assay (ICA) with monoclonal antibodies to estrogen (ER) and progesterone (PgR) receptors , we have evaluated hormone receptors status on fine needle aspiration performed before and after administration of IFN at the dose of 3.0 MU/IM, three times a week for two weeks.

The aspirated cells were immediately suspended in a buffered saline solution, cytocentrifuged onto glass slides and processed for ICA staining according to the Abbott ER-ICA and PgR-ICA kit. Smears were randomly evaluated by two observers, without any information about patients and sample succession. Results of ICA were expressed as percentage of stained cells calculated on a minimum 400 cancer cells. A calculation of the mean percentages of positive cells before and after IFN and a t-test for paired data were performed. The results are presented below:

	Before IFN mean +/- SE	After IFN mean +/- SE	p-value
ER-ICA	72.4±8.9	50.3±12.9	0.05
PgR-ICA	51.4±11.7	48.6±12.4	0.60

The percentage of ER-ICA positive cells decreases after IFN treatment and the value of the t-test is of borderline significance (P=0.05). The expression of PgR is not significantly influenced by the IFN administration.

Our results suggest that IFN-ALPHA 2A decreases the expression of ER in breast cancer patients. Whether this phenomenon is the result of a biologic modulation or not, will be further investigated.

297 TAMOXIFEN AND INTERFERON BETA IN THE TREATMENT OF METASTATIC BREAST CANCER: A PHASE II STUDY.

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In vitro studies indicate that Interferon (IFN) Beta has direct antiproliferative activity and can determine an increase in ER content in breast cancer cell lines (Golstein, Cancer Res.49, 2698,1989).A phase II study was conducted in 26 metastatic breast cancer patients (pts) to evaluate the efficacy and ttoxicity of a combination of IFN Beta 6x10 IU im every 2 days for 2 weeks followed by Tamoxifen 20 mg/die plus IFN Beta 3x10 UI im every 2 days untill progression. Patient characteristics were: median age 60 (range 42-73); PS 0 (range 0-1); ER status: positive 6 pts, unknown 20; prior adjuvant treatment 15 pts (chemotherapy 13; Hormonotherapy 2); prior palliative chemotherapy 8 pts. Sites of metastases were: bone 8, soft tissue 10, viscera 2, bone-soft tissue 3, viscera-soft tissue 1, bone-viscera 1, bone-viscera-soft tissue 1. One complete response and 5 partial response were observed (response rate 23%), stable disease in 46.3% and progression in 30.7%. Median duration of response was 3 months (range 1-7) and median time to progression was 2 months (range 1-2). Toxicities were mild: grade 1-2 fever plus grade 1-2 fatigue in 13 pts, flu-like syndrome in 3 pts. The study is ongoing and a randomized comparison with Tamoxifen is planned.

298 CHANGES IN SERUM LIPIDS LEVEL AND LIPOPROTEIN PROFILE IN BREAST CANCER WOMEN TREATED WITH TAMOXIFEN.

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Estrogens play a significant role in the regulation of lipid metabolism and have a protective function in coronary heart disease development.The aim of this study was to evaluate the influence of antiestrogen therapy with tamoxifen on lipid metabolism.

The serum lipids: total, free cholesterol,HDL,LDL, triacyloglicerols and lipoprotein profile were estimated in a group of patients and in a control group. The former included 43 postmenopausal breast cancer women,the mean age 68,3 years,treated with tamoxifen from 6 to 54 months.The control group comprised 43 healthy women,the mean age 65,5 years.

We observed statistically significant difference between patients' total cholesterol mean value 237,3 mg/dl and control total cholesterol - 268,8 mg/dl ($p<0,05$) as well as LDL 156,0 mg/dl vs 190,4 mg/dl ($p<0,05$),also LDL:HDL ratio 2,89 vs 3,53 ($p<0,05$). Dysproteinemia was more frequent in the control group 55,9% vs 37,2% ($p<0,05$).In neither group statistically significant difference was noticed in triacyloglicerols and HDL levels.

Significant differences in serum lipids levels in breast cancer women show that tamoxifen therapy is a protective factor against coronary heart disease. We conclude that it is due to an estrogen-like activity of the drug.Tamoxifen is a mixed agonist/antagonist drug.

299 DROLOXIFENE, A NEW ANTIESTROGEN IN ADVANCED BREAST CANCER, A DOUBLE BLIND DOSE FINDING PHASE II TRIAL

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Droloxifene (3-OH-tamoxifen) is a new antiestrogen with interesting preclinical and clinical characteristics:

- High affinity to estrogen-receptors (more than ten-fold higher than tamoxifen)
- Higher antiestrogen/estrogen ratio than tamoxifen
- Lack of carcinogenicity in animal models and in vitro testing
- Rapid pharmacokinetics
  - achieves peak serum concentrations within hours and steady-state serum concentrations within days
  - cleared rapidly: serum elimination half life of less than 24 hours

The objective of the study was to determine the optimal daily dose of droloxifene in the treatment of postmenopausal patients with advanced breast cancer. Between June 15, 1988 and March 31, 1991, 369 women with hormone receptor positive or unknown metastatic or locally unresectable breast cancer were entered in 42 Canadian, Brazilian and European Centers Droloxifene was administered in a double-blind randomized design with oral doses of either 20, 40 or 100 mg once a day as first-line systemic therapy with the exception of adjuvant chemotherapy if terminated at least one year before recruitment. An interim analysis of the 331 patients included until Oct. 30, 1990 is presented The records of all patients were peer reviewed at adjustification meetings. Twentytwo patients were ineligible because they had surgically operable breast cancer, 40 patients were ineligible because of violation of various eligibility criteria, while 20 were inevaluable because of protocol violations. Fourteen patients remained open. The overall response rate (CR + PR) was 23/74 (31 %) for 20 mg, 33/74 (45 %) for 40 mg and 36/86 (42 %) for 100 mg. Median time to disease progression was 5 + months (range 0 to 31 +), 8 + months (range 0 to 28 +), and 5 + months (range 0 to 28 +) for 20, 40 and 100 mg respectively. Toxicity was minimal at all doses and droloxifene appears to be well tolerated.

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300 TOXICITY OF LONG-TERM TREATMENT WITH TAMOXIFEN IN BREAST CANCER PATIENTS.

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Toxicity of Tamoxifen is generally considered more or less negligible. This permits long-term administration of this drug, with positive effect in a good percentage of advanced breast cancer patietns as well as an adjuvant treatment of post-menopausal patients in particular. In the present study we reviewed the side effects of a longer than two years treatment of Tamoxifen in breast cancer patients. 246 patients were reviewed. Their characteristics were: median age 54 (34-88), women 243 patients, men 3, premenopausal 64, post menopausal 179. 216 patients got Tamoxifen as adjuvant and 30 as treatment of metastatic disease. The dose of Tamoxifen was 20-40 mgs per day and the duration was from 2 to 13 years with a median of 4 years. The follow-up of the patients was 2 to 19 years with a median of 4.8 years. No patient ceased the treatment because of serious side effects. Several minor reactions were observed. The toxicity was grouped as follow: Myelotoxicity: Anaemia, leukopenia, thrombocytopenia in total 17 patients (6.9%). Metabolic side effects: Hypercalcemia 8 patients (3.25%), Hypocalcemia 3 patients (1.2%), serum cholesterol decrease in 5 patients (2%) and in 3 increase. Uric acid increase in 2 patients, blood urea and serum creatinine increase in 3 patients. Liver toxicity by increase of γ-Glutamic transpeptidase in 3 patients. Face flashing, headaches and skin rash in 18 patients (7.32%). Decrease of sight (1 patient) decrease of nail growth (2 patients). One patient had metrorhagia, another 3 years after Tamoxifen presented with TBC lymphodenopathy, 7 patients (2.8%) presented second malignancy 2-8 years after they started treatmetn. Two ovarian cancers, 1 endometrial, 1 cervical, 1 bladder and gastric, one carcinoma, and one lyngohoma.

Conclusion: Tamoxifen long term treatment two-thirteen years is well tolerated. 7 second malignancies that were observed in different sites can not be, necessarity attributed to Tamoxifen.

301 Prognostic value of positive Tamoxifen response in subsequent hormonal manipulation in patients with advanced breast cancer.

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Twenty six patients with advanced breast cancer were started on Medroxyprogesterone acetate (MPA). Group A included 14 patients who were ER/PgR positive and Group B included 12 patients- ER/PgR negative. Histological grades were comparable but only 21% of receptor positive patients while 50% of receptor negative patients were Grade III.

The pattern of metastatic disease, local recurrence/axillary nodes, metastatic nodes, bone metastases and soft tissue/visceral metastases were similar in both groups.

Prior tamoxifen responses were not dissimilar, 78% in group A and 67% in group B but the average duration of response was 25 months in group A and 12 months in group B.

Positive MPA response was 50% in both groups but the average duration of response was 11 months in group A and 6 months in group B.

In conclusion although the presence of hormone receptors in breast cancer patients is predictive for a positive tamoxifen response neither hormone receptor positivity or previous positive tamoxifen response is predictive for subsequent response to MPA. The duration of response to both tamoxifen and MPA is significantly longer in those patients with ER and PgR receptors.

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GnRH AGONISTIC ANALOGUE (Decapeptyl^{R}) AS A FIRST LINE ENDOCRINE TREATMENT IN PREMENOPAUSAL ADVANCED BREAST CANCER PATIENTS

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Endocrine manipulation have been employed in the treatment of metastatic breast carcinoma with response rate of 15-40%. Twelve premenopausal patients(pts) with advanced breast cancer were entered into pilot phase II trial to assess efficacy, toxicity and influence on the pts hormonal status of synthetic GnRH analogue D-Trp^{6}-GnRH (Decapeptyl). The pts, aged from 33-50 yrs, with newly diagnosed stage IV breast cancer (3 pts) or with recurrent disease (9 pts), were not previously treated by any kind of hormonal therapy. Steroid receptor status (ER and PR) was known in 9/12 pts. Decapeptyl was applied monthly at a dosage of 3.75 mg i.m. until progression. Serum LH, FSH and estradiol levels were determined prior each administration of Decapeptyl. The therapeutic response was evaluated in 11/12 pts. Five pts achieved partial remissions lasting 7,9,9+,4+,4+, 3 pts showed stabilization of their disease and 3 pts showed progressive disease. Objective remission was seen in 3/4 pts with pleuropulmonal, and in 4/6 pts with soft tissue involvement, while the optimal response of bone metastases was stabilization(4/6 pts).The best therapeutic response was found in pts aged from 41-45 yrs, even in pts with incomplete ovarian suppression and regardless of steroid receptor status. The significant suppression of mean serum LH and estradiol levels, and partial suppression of mean FSH levels, were followed by amenorrhoea in all treated pts. The therapy was free of any side effect, except hot flushed in 7 pts. The modest side effects of this treatment modality makes Decapeptyl attractive alternative to oophorectomy in treating premenopausal women with metastatic breast cancer.

303 TREATMENT OF THE ADVANCED BREAST CANCER IN PREMENOPAUSAL WOMEN WITH LHRH AGONISTS AND MEGESTROL ACETATE

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We have treated thirty premenopausal women with advanced low risk breast cancer (bone metastases:20 pts., skin:8 pts., nodes:8 pts. and lung-pleural:3 pts) with an hormonal association of Leuprolide Acetate and Megestrol Acetate continously.

Patiens characteristics: median age 40,5 y(33-49).Initial clinical stage: I 2, IIA 5, IIB 6, IIIA 7, IIIB 3,IV 6. Previous treatment: none 2, surgery 5, surgery+radiotherapy 2, surgery+chemotherapy 16, chemotherapy+surgery+radiotherapy 3, surgery+radiotherapy+hormonotherapy 2. Hormonal receptors : negatives 7 pts., positives 3pts., unknows 20 pts.. Relapse free survival median: 10,5 m(0-50).

Results: overall objetive response 9/30(30%),complet responses 1(3,3%), partial responses 8/30(26.6%); stabilitation 14/30(46.6%) with subjetive response in 10 cases(33,3%); progresion 7/30(23,3%). Objetive response site: skin 5, bone 3, nodes 2, lung 1, pleural 1. The median of the duration of objetive responses was 19 m(7-42+) with a time for the response of 3 m(1-9) median; for the subjetive response was of 7 m (2-23+) and 1 m(1-4) respectively. The treatment duration median was 7 m(1-42+). The median of the overall survival was 65 m(1-96+). The most important toxicitys were amenorrea (16/30), gain of body weight (7/30) and initial pain increment (6/30).

Conclusions:in premenopausal women with low risk advanced breast cancer the efficacity of LHRH-agonists is similar to the surgical or phisical castration with minor toxicity. The hormonal association with Megestrol Acetate induce a medical estrogenic complete blockade that may improve the therapeutic benefits.

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305 A PILOT STUDY OF r-ALPHA-INTERFERON-2B (IFN) PLUS MEDOXYPROGESTERONACETATE (MPA) IN HORMONAL REFRACTORY METASTATIC BREAST CANCER

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Preclinical investigations showed that r-alpha-IFN-2b may have an influence on cell differentiation and steroid receptor expression in human mammarian carcinoma cells. Based on these results we designed a phase-II-trial with a combination of MPA + IFN in patients (pts) with ER/PR-positive advanced breast cancer and progression under hormonal treatment. Treatment protocol: IFN 5 Mio IU s.c. 3x/week (wk), wk 1 + 2, from day 15 MPA 1000 mg/day p.o., while IFN was continued 3x/wk. Response was evaluated after 12 wks. In case of CR/PR/MR/NC the therapy was continued until progression. Steroid receptor expression was investigated in punctable skin or lymph node lesions before and 2 wks after the IFN treatment. Patient characteristics: 9 pts are at present evaluable, median age 70 (51-79), mastectomy 9/9, all pts with irradiation and > 2 hormonal treatments, documented progression. Metastatic sites: locoregional lymph nodes (5), bone (5), lung (3), skin (1), other sites (1). Results: The median treatment duration was 28 wks (8-48 wks). 1/9 CR (11%), for 40 wks, PR 2 (22%) (24/52+ wks), MR 4, PD 2: Determination of steroid receptors showed significant increase in oestrogen and particularly ER receptor expression after IFN treatment in 2/3 pts. Conclusion: The change of steroid receptor expression under IFN in breast cancer is an highly interesting concept for the improvement of hormonal treatment in hormone receptor positive breast cancer. The reinstitution of hormonal treatment modulated by IFN seems to be interesting in terms of particularly low toxicity.

305 ACETATE (MPA) THERAPY FOR ADVANCED BREAST CANCER.

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5 years ago, an MPA (Farlutal) effective level service was instituted in the Federal Republic of Germany in order to be able to perform an effective level adapted high-dose progestin therapy in advanced breast cancer with the help of MPA serum level measurements. The objectives of the trial were to optimise MPA therapy by ensuring effective levels of a minimum of 100 ng/ml. Up to now more than 2000 patients with histologically proven advanced breast cancer entered this study, but up to now 846 of all patients have been evaluated. Treatment schedule: initially 1,500 mg MPA were given per os as a loading dose for a period of at least 6 weeks and then the daily dosis was reduced down to 1,000 mg. Serum samples would be taken in three monthly intervals until progression or unacceptable toxicity. If the MPA serum levels were lower than 100 ng/ml the daily dosis of MPA was increased within the initial phase of MPA therapy from 1,500 to 2,000 mg or later on from 1,000 to 1,500 mg. Two weeks later the MPA serum levels would be determined again. CONCLUSIONS: The investigation clearly indicates that the MPA serum level is an important prognostic factor for the response to high-dose MPA therapy in metastasizing breast cancer. In progressive tumor patients with low MPA serum levels renewed remission can be achieved by means of dose increase. Steroid hormone receptors rich breast cancer is more likely to respond to high-dose MPA therapy than receptor negative tumors. Differences in the incidence of adverse effects in high-dose MPA therapy cannot be found in a wide range of serum concentrations. It can be said that its effectiveness in metastasizing breast cancer justifies the use of high-dose MPA therapy as a second line therapy second to tamoxifen - due to its wide range of action so far unsurpassed by any other endocrine treatment concept.

306 BETA-INTERFERON (B-IFN) AND MEDROXYPROGESTERONE ACETATE (MAP) IN ADVANCED BREAST CANCER (ABC) REFRACTORY TO MAP.

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Natural B-IFN enhances the content of estrogen and progesterone receptors (ER,PR) in breast cancer cell cultures, both in hormone-responsive and in hormone-insensitive cell lines. In vivo low doses of B-IFN increase ER and PR in primary breast cancer and in skin metastases. MAP is usually employed in ABC after a disease progression with Tamoxifen. Its efficacy is related to the content of ER and PR and it could be theoretically enhanced by an increase of ER and PR level obtained by B-IFN. Aim of our study was to verify the possibility to increase or to restore the responsiveness to MAP in patients (pts) affected by ABC refractory to MAP administered for at least 4 months (m.). Up to date 19 pts are evaluable for response and toxicity. 8 pts had stable disease (SD) and 11 progressed with MAP alone. 17 were post and 2 pre menopausal. Median age was 63 years. ER and PR status was unknown in 17 pts, ER+PR+ in 1 pt, ER-PR+ in 1 pt. Regimen consisted of: wash-out therapy for 1 week, B-IFN 3MU/die i.m. for 1 week, then 2MU/alternate-days and MAP 1.5 g/die p.o. until progression. Median duration of treatment was 4 m. Considering the disease sites we obtained 2 complete responses (CR) (bone, skin), 6 partial responses (PR) (3 skin, 1 pleura, 1 nodes, 1 primary breast cancer), 11 SD (4 bone, 2 pleura, 3 lung, 2 nodes), 12 progressive diseases (PD) (7 bone, 1 skin, 3 lung, 1 liver). Considering total patient's response we obtained: 0 CR, 3 PR, 6 SD, 10 PD. PR were obtained in 2 pts with SD and in 1 pt with PD with MAP alone. Response duration was 8+, 2+ and 4 m. respectively. We didn't register any toxicity. Our data seem to suggest a possible role of B-IFN in the strategy of breast cancer treatment.

307 COMPARISON OF CONTINUOUS AND DISCONTINUOUS CHEMOTHERAPY IN PATIENTS (pts) WITH METASTATIC BREAST CANCER. FINAL ANALYSIS OF A PHASE III RANDOMIZED STUDY.

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Although metastatic breast cancer (MBC) is considered the most sensitive of all solid tumors to chemotherapy, it remains incurable with current therapeutic approaches.
The objective of the present study was to compare two treatment strategies in women under 70 years presenting a cytologically or histologically confirmed MBC which was hormone-resistant (hormone receptors negative or relapse after hormonal manipulation). Pts who had previously received chemotherapy were excluded, with the exception of those who had received adjuvant chemotherapy (doxorubicin was allowed if the dose was less than 300 mg/m2). After 3 monthly courses of F.E.C. (4 Epi-doxorubicin 50 mg/m2), the tumor response was evaluated. Pts with at least stable disease were randomized to receive either continuous chemotherapy (monthly FEC up to 12 cycles, then CMF until relapse). or discontinuous chemotherapy (3 months rest, 3 courses of FEC, 3 months rest... up to 12 cycles, then discontinuous CMF until relapse). Tumor response was assessed every 3 months. Pt quality of life was indirectly evaluated using treatment-related toxicity, Karnofsky index and time spent in hospital.
Between jan. 86 and jan. 91, 309 pts entered the study. The pts' characteristics were the following : mean age 53.9 years (range 27-69) ; previous adjuvant chemotherapy : 52.7 % ; previous adjuvant hormonotherapy 52 % ; metastatic sites were bone (61.9 %), liver (45.5 %), lung (35.6 %) and loco-regional soft tissue (35.6 %). 62.7 % of the pts had 2 or more metastatic sites. At the end of the preselection phase, 181 (62.2 %) of the 291 evaluable pts had non progressive disease and 176 pts were randomized : 86 to continuous therapy and 90 to discontinuous therapy.
The final analysis has shown no statistically significant difference between continuous and discontinuous arm in terms of time to disease progression (median 7 months (m.) vs 9 m.), survival (median 17 m. vs 15 m.) or quality of life. However, pts in the discontinuous treatment group received an average of 6.4 chemotherapy courses (range 3-14) whereas those in the continuous treatment group received an average of 9.5 courses (range 3-24).
We conclude that discontinuous chemotherapy is as effective as continuous chemotherapy in MBC, and represents a real alternative to conventional approaches.
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