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CLINICAL AND EXPERIMENTAL DATA ON CYPROTERONE ACETATE IN THE MANAGEMENT OF BREAST CANCER

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Cyproterone acetate (CPA) is a synthetic steroidal compound with multiple endocrine effects in different types of hormone dependent tissues. CPA was used for the palliative treatment of breast cancer. 34% partial remissions or status of no change were observed in a group of 41 patients as described before (Schulz, K.-D. et al. Verh. Dtsch. Krebs Ges 3, 187, 1982). The present study was designed to investigate the way of action of CPA.
Systemic endocrine effects were monitored under prolonged CPA treatment. Serum levels of cortison (C), androstendione (A), dehydroepiandrosterone (DHEA), dihydrotestosterone (DHT), testosterone (T), estradiol (E_2), prolactin (Prl), FSH and LH were determind. The androgens A, DHEA, DHT and T decreased 30-50% during CPA treatment. Postmenopausally elevated levels of FSH and LH dropped to the range of 20mIU/ml. C, E_2 and Prl were not altered significantly. Permanent cell lines from human mammary carcinomas were incubated with CPA in vitro in a dose range from 1ng/ml to 1µg/ml. At concentrations higher than 100ng/ml the cell proliferation was inhibited significantly. Thus the clinical benefit of CPA-treatment may be the consequence of direct interference with proliferation at the cellular level and of systemic endocrine effects, which in turn may reduce the amount of organotrophic growth factors favouring tumor cell proliferation.

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INFLUENCE OF CYTOTOXIC CHEMOTHERAPY ON SURVIVAL IN PATIENTS WITH METASTATIC BREAST CANCER.

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Because there is no curative treatment modality in patients (pts.) with metastatic breast cancer (b.c.) the therapeutic strategy must be individualized regarding the quality of life under cytostatic treatment on the one hand and the possibility of a prolongation of survival on the other hand. We evaluated the course of the disease in 501 pts. with metastasized b.c. treated according to favourable (p.f.+) or unfavourable (p.f.-) prognostic factors (p.f.: relaps free interval, metastatic site, receptor status). Pts. with p.f.+ and receptor status + or ? were treated primarely with hormonal therapy followed by cytotoxic treatment; pts. with p.f.- were treated with cytotoxic drugs primarely. Pts. with p.f.+ survived significantly longer than pts. with p.f.- ($p < 0{,}05$, p.f.+: median (m)=24 months (M), p.f.-: m: 15 M). Duration of survival was most influenced by the results of the first cytotoxic treatment. Median survival of pts. with p.f.+, who experienced PR (m=26 M) or NC (m=23 M) was not significantly different from pts. with PD (m=24 M). Only p.f.+-pts. with CR survived significantly longer (m=37.5 M). It seems that conventional cytostatic treatment in these pts. (p.f.+) has no particular influence on survival exept in pts. achieving CR! For p.f.--pts. we found completely different results: CR: m=33 M; PR: m=18 M; NC: m=16 M; PD: m=8 M. Pts. with PD lived significantly shorter than pts. with CR, PR, or NC ($p < 0{,}05$). Neither in remission rates nor in remission duration we found any difference between VAC (Vincristine, Adriamycin, Cyclophosphamide) and CMF (Cyclophosphamide, Methotrexate, 5-Fluorouracil) chemotherapy regimens.

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SECOND-LINE TREATMENT IN PATIENTS WITH ADVANCED METASTASIZING BREAST CANCER WITH 4'-EPIDOXORUBICIN, VINCRISTINE AND CYCLOPHOSPHAMID.

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4'- Epidoxorubicin (4'-Epi-DX) is a new epimerized analog of adriamycin. Preclinical tests and initial clinical trials demonstrated that 4'-Epi-DX has the same antitumour activity as doxorubicin but does so with less systemic toxicity and less cardiotoxicity than the parent compound. The lack of serious acute and subacute toxicity together with its possible reduction of cardiomyopathy justifies a clinical study of combined 4'-Epi-DX, Vincristine and Cyclophosphamide as second-line chemotherapy following CMF treatment in patients with advanced metastatic breast cancer. **Treatment plan:** day 1: 4'-Epi-DX: 40 mg/m^2 i.v., Vincristine: 1 mg/m^2 i.v.; day 3-6: Cyclophosphamide: 200 mg/m^2 p.o.; drug administration is repeated every 3-4 weeks. **Eligibility criteria:** age between 18-75 years, performance status $\leq$ grade 3 (WHO-scale), no signs of congestive heart failure, no history of myocardial infarction during the last 6 months, tumour progression or relapse following CMF treatment. 25 patients (pts.) entered the study. 23 pts. are now evaluable for response (UICC-criteria). **Response:** Partial remission was observed in 6 of the 23 pts. (no complete remission). Stable disease occured in 11 pts.. 6 pts. experienced progressive disease. Remission duration: median: 7 months (range: 3-13 months); duration of stable disease: median: 6 months (range: 3-11$^+$). **Toxicity:** WBC-toxicity (WHO-scale): m: grade (g) 2, range (r): 0-4; platelet toxicity: m: (g) 0, r: 0-3; nausea/vomiting: m: (g) 2, r: 0-3; alopecia: m: (g) 3, r: 2-3; adverse cardiac effects have not been observed. The study will continue until a total of 30 patients have been enrolled.

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INFLUENCE OF MASTECTOMY AND HIGH-DOSE GESTAGEN THERAPY ON THE BLOOD COAGULATION SYSTEM OF PATIENTS WITH METASTATIC BREAST CANCER

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Many experimental and clinical investigations in cancer patients (pts) indicate that an interaction exists between the cancer cells and the blood coagulation system.Therefore,the blood coagulation system of 16 evaluable patients with metastatic breast cancer (mbc) without signs of metastases was tested before and 10 days after mastectomy. Clinical investigations have shown that high-dose gestagen therapy leads to clinical thrombosis and hypercoagulability.The blood coagulation system of 35 pts treated with high-dose medroxyprogesterone acetate (MPA) (1000 - 1500 mg o.p. daily) was controlled.The same experiments were performed an 16 pts with mbc under megestrol acetate (MA) therapy (200-800 mg).Blood coagulation tests were carried out at intervals of 2 and 6 weeks,3 months and 4-15 months of those under MPA therapy.It was generally noticed that the results after mastectomy did not differ significantly from those prior to mastectomy.
The fibrinopeptide A and the fibrin monomers under high-dose MPA therapy increased in comparison to the data before therapy,and the PTT was shorter.The results of the thrombin generation test,which shows the dynamic development of the blood coagulation,showed a clear state of hyper-coagulability under MPA therapy.The pts on MA showed similar results which,however,were not quite as clear as those on MPA.
Thisstudy shows that important changes in the blood coagulation system 10 days after mastectomy,compared with the date before mastectomy,did not occur.The development of hypercoagulability mostly under MPA therapy was related to high levels of fibrin monomers and fibrinopeptide A and deficiency of Antithrombin III.The results show an increased of hypercoagulability under high-dose gestagen therapy, which might explain thromboembolic and cardivascular complications which have been observed in cancer pts.

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