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TREOSULFAN IN ADVANCED OVARIAN CARCINOMA: A PHASE III STUDY

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In 10/87 a randomized phase III multicenter trial was inaugurated in order to compare PT (70/5000/m2 i.v. 6xq.4wks) with a standard PC regimen (70/1000/m2 i.v. 6xq.4wks) in advanced ovarian carcinoma (FIGO IIb-IV). About 500 patients (pts.) have been enregistered. Interim evaluation in 8/92 included 270 pts.(PT 136/PC 134). Tumour residuals after primary surgery were nil (R0) in 71 pts. (PT 41/PC 30), 2cm (R1) in 87 pts. (43/44) and <2cm (R2) in 103 pts.(47/56). Final judgement after completion of therapy was accrued in 207 pts.(107/100) showing 35 NED (23/12), 45 CR (24/21), 40 PR (21/19), 30 NC (9/21), 47 PD (23/24) and 10 missing data. Leucocytopenia, thrombocytopenia and gastro-intestinal complaints were equal. Differences in alopecia rates (WHO>1, forcing pts. to wear a wig) were statistically significant: PT 5-20%, PC 18-71%. Data are correlated to psychosomatic observations during therapy. The study hypotheses seem to be well approvable regarding equal rates of primary progression under therapy, comparable hematologic side effects and a large benefit for PT in respect of alopecia. Supported by medac.

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TREOSULFAN/CARBOPLATINUM IN OVARIAN CARCINOMA THERAPY

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Regarding the well-known lower toxicity of carboplatinum in comparison to cis-platinum, a combination schedule of carboplatinum/treosulfan (CpT) should be less toxic than the investigated cis-platinum/treosulfan (PT) protocol. Between 12/89 and 1/93 thirty two patients with ovarian carcinoma have been treated with 300 mg/m2 Cp and 4 g/m2 T combined with ondansetron for antiemetic prophylaxis, 11 of them in an adjuvant and 21 of them in a palliative attempt.
Updating at January 31, 1993 all of them have been evaluable regarding response, showing eleven NEDs (adjuvant) and not more than six primary progresses in 21 palliative situations. Side effects never caused a therapy dropping during the first three cycles, after four and five cycles respectively five patients had to be taken from the protocol due to persisting leucocytopenia, three others due to thrombocytopenia. Based on the experiences up to now, CpT may be recommended as induction therapy (less than four cycles), if the therapy shall be continued, one has to be carefull regarding myelotoxicity. Myelotoxicity may be reduced by halfening the dosis and 2-weekly application.

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D-TRP-6-LHRH (DECAPEPTYL) IN ADVANCED OVARIAN CANCER

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Gonadotrophins have been implicated in ovarian carcinogenesis and tumour progression. LHRH agonist therapy suppress gonadotrophins. Therefore GnRH agonists should have some beneficial effects in ovarian tumours. We treated 65 patients in the UK and 67 in Germany (mainly FIGO stage III or IV) who had relapsed following conventional treatment. The patients were given the long acting depot formulation of D-Trp-6-LHRH once a month. There were no exclusion criteria and patients of any age or performance status were eligible. In Erlangen the patients were started on the therapy at the earliest sign of relapse and were continued on the drug until death (average 60 weeks). In London the patients were started later in the course of the illness and the drug was stopped on tumour progression (average 27 weeks). Tumour response was not assessed in Erlangen but survival data is available. Eleven patients (17%) achieved a partial remission in the UK and some of these were maintained for up to 60 months and longer. Eight patients (12%) remained stable on the drug and were maintained on the drug for periods of 3-14 months. The average survival was 63 weeks in Germany and 44 weeks in the UK. These data indicate there is a need to treat these patients earlier rather than later and randomised studies of combination therapy have been started.

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NO CORRELATION BETWEEN CHEMOTHERAPY DOSE AND TREATMENT OUTCOME IN ADVANCED OVARIAN CANCER

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From January 1981 until Octobre 1992 34 patients with advanced stage epithelial ovarian cancer were treated with polychemotherapy after optimal cytoreductive surgery. The overall response rate was 67%, CR's 44%. The overall 3(4)-year survival was 19% (8%), the progression free survival 8% (4%). Seven out of 15 patients in CR who had stopped therapy after 4 cycles of chemotherapy showed a median survival of 21.4 months, whereas 8 patients completing 6 cycles lived for 36 months (p=0.03).
The normalized dose intensity (nDI), defined as the ratio of the actual DI to the designed DI, was not influenced by the number of chemotherapy cycles.
In deceased patients (n=22) the fit between nDI and survival time is statistically not significant. In the remaining alive patients (n=12) an even inverted correlation between nDI and survival was found.
In conclusion: retrospectively no influence of dose intensity on treatment outcome could be demonstrated.

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LONG TERM SURVIVAL OF PATIENTS WITH EPITHELIAL OVARIAN CARCINOMA TREATED WITH MULTIMODAL THERAPY.

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From December 1979 to December 1987, 150 pts. with stage IC-IV ovarian carcinoma were treated by multimodal therapy. Debulking surgery was followed by Cis-Platinum-Adriamycin combination (50 mg/m2 each,6-9 cycles). Whole abdominal irradiation, (3000 cGy), was administred as consolidation therapy to pts. with no clinical evidence of disease. In a retrospective analysis pts were devided into two groups: those who died within 5 years from diagnosis,(Group I,103 pts,67%) and those who had longer survival (Group II, 47 pts, 31%). The distribution of prognostic factors was:

	Group I	Group II	Significance
Stage III-IV	90 pts. 87%	25 pts. 53%	p<0.001
Grade III	69 pts. 67%	16 pts. 34%	p<0.001
Res. tu.> 2cm.	66 pts. 65%	4 pts. 9%	p<0.001

In the long survival group median survival was 94 months (60-144) and median time to relapse 67 months (24-125). We conclude that long term survival occured in 31% of pts. with ovarian carcinoma treated by multimodal approach. Stage, grade and residual tumor correlate with survival.Late relapses up to 125 months were observed.

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EOSTROGEN PRODUCTION BY EPITHELIAL OVARIAN TUMOURS IN ELDERLY WOMEN: A POTENTIALLY USEFUL MARKER OF AN EARLY STAGE DISEASE

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The diagnosis (Dx) of early stage epithelial ovarian tumours is a clinical challenge; most reach stage III when detected. We report 4 elderly (>78y) women at stage Ia who presented with hypereostrogenemia; 3/4 had clinical symptoms and/or signs (vaginal, uterine and mammary). Serum estradiol (E2) was >230 pmol/L pre-operatively in all cases. An elevation of progesterone and testosterone was found as well. This hormone profile disappeared shortly after ovarian extirpation, along with regression of the target tissue manifestations. The tumours removed were: mucinous cystadenocarcinoma (2), endometrioid carcinoma (1) and a mucinous cystadenoma with a contralateral Brenner tumour (1). At Dx, CA 125 was elevated in the endometrioid case only. E2 excess has primarily been linked to stromal neoplasms (e.g., granulosa cell type). However, hypereostrogenemia may also accompany epithelial tumours, possibly by stromal stimulation. We advise clinicians to be alert to this phenomenon.