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Randomized phase II trial assessing estramustine and vinblastine combination chemotherapy vs. estramustine alone in patients with hormone escaped prostate cancer

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Purpose: Based on the results of combined data of similar Phase II studies obtained at three american centers using combination chemotherapy of EMP and VBL in hormone refractory prostate cancer demonstrating a decrease in serum PSA of greater than 50% in 46 out of 83 patients (55.4%) a randomized Phase II study in the same patient population was performed.

Patients and Methods: 92 patients were treated either with oral EMP or oral EMP in combination with VBL infusion. Aim of the study was assessement of toxicity and PSA response rate in both groups with the option to continue the trial as a Phase III study with time to progression and survival as endpoints.

Results: Treatment duration was 70 (EMP/VBL) and 72 days (EMP). Toxicity was comparably high in both groups. Nausea, constipation and edema was most frequently seen within the EMP alone group, while nausea and 2 cardiovascular deaths had to be noticed in the EMP/VBL arm. In 51% the reason for stopping treatment was either toxicity or refusal by the patients, in 63% of these during the first cycle. Time to PSA-progression was 27 and 31 weeks, survival time was 44 and 51 weeks. PSA response rate was only 32.4% and 31.6%.

Conclusion: Based on these results a Phase III trial was not justifiable. A toxicity rate which is clearly exceeding the response rate is not accaptable in a noncurative chemotherapy. Neither monotherapy with EMP nor its combination with VBL therefore can be recommended in the tested patient population.

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Regulation of protease-inhibitor maspin in prostate epithelial- and prostate carcinoma-cells

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Purpose: Maspin (Mammary serpin) is a novel serine protease inhibitor with tumor suppressor activity in human prostate epithelial cells. The maspin gen is expressed in normal prostate epithelial cell lines but down regulated in a series of tumor derived prostate cell lines. The loss of maspin expression during tumor progression is regulated at the transcriptional level and results most likely from the absence of transactivation through the DNA binding motive Ets and the presence of transactivation repression through the negative hormonal responsive element (HRE).

Methods and Results: We have cloned and sequenced the maspin promoter region to investigate its regulation in normal and tumor cells. By CAT (Chloramphenicol-Transferase) Assays and Deletions Analysis we have identified a Ets- and HRE (Hormonal Responsive Element) motiv within the maspin promoter sequence. The Ets element is active in regulating maspin expression in normal prostate epithelial cells but inactive in prostate tumor cells. The HRE is a negative element that is active in both cell types.

Conclusions: Our data demonstrate that the loss of maspin expression during tumor progression is regulated at the transcriptional level and results from the absence of transactivation through the Ets element and the presence of transcription repression through the HRE element.

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A trial of accelerated fractionation (AF) in T2/3 bladder cancer

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Purpose/Objective: To evaluate the efficacy and toxicity of an accelerated fractionation regimen in locally advanced bladder cancer.

Materials & Methods: A prospective randomised trial in 229 patients registered between 1988 and 1998 comparing AF (mainly 60.8 Gy in 32 F in 26 days) treating twice per day (1.8 and 2.0 Gy) with a 1 week gap after the first 12 F, with standard F (64 Gy in 32 F in 45 days). All except 3 patients were treated in 4 UK centres, The Royal Marsden Hospital (n = 100), The Bristol Oncology Centre (n = 67), Nottingham City Hospital (n = 38), Velindre Hospital, Cardiff (n = 20).

Results: AF (n = 118) and SF (n = 92) patients were well matched for initial haemoglobin, CT staging, T stage, histological grade and initial ureteric obstruction. Initial analysis on 199 patients evaluable revealed grade 2/3 bowel toxicity in 41%/4% of AF patients compared to 26%/0% on SF, and grade 2/3 bladder toxicity in 18%/20% of AF patients compared to 18%/17% on SF. There was no significant difference between AF and SF tumour outcomes of local control, time to metastasis and overall survival.

Conclusion: This AF schedule did not improve on efficacy of SF in T2 and T3 bladder cancer and caused increased bowel toxicity.

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The three-month recurrence as a prognostic factor for the long term outcome in TaT1 bladder cancer

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Objectives: In stage TaT1 bladder cancer treated by transurethral resection, prognostic factors have a more important influence on a patient's prognosis than the choice of adjuvant prophylactic intravesical treatment. A combined analysis of individual patient data from EORTC and Medical Research Council (MRC) phase III trials has been carried out to determine the prognostic importance of early recurrences or tumour regrowth (within 3 months of transurethral resection (TUR)) on a patient's time to progression, progression-free survival and overall survival.

Methods: Eight EORTC and two MRC randomized trials of prophylactic treatment totalling over 3400 patients were included. The relative prognostic importance of recurrences at the first follow-up cystostcopy at 3 months has been evaluated in multivariate Cox proportional hazards regression models which included the most important baseline prognostic factors (tumour and patient characteristics).

Results: A recurrence at any site in the bladder within 3 months of TUR was the most important prognostic factor for time to progression and progression-free survival. It was also an important factor for survival ($P = 0.001$).

Conclusion: Recurrence within 3 months after TUR should be used in deciding on the further treatment of patients with TaT1 bladder cancer and should be taken into account when planning randomized clinical trials in this disease.

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Management of extragonadal seminoma (EG-SEM) – Results of a multicenter analysis of 104 patients (PTS)

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Purpose: (1) To evaluate the outcome of pts with primary mediastinal (med) and retroperitoneal (rp) EG-sem, (2) to identify prognostic variables for survival and recurrence, (3) to access the efficacy of different treatment modalities.

Methods: 635 EGGCT-pts treated at 11 centers in the US and Europe during the cisplatin-based chemotherapy era (ctx) were retrospectively evaluated (1975–96).

Results: 52 pts with primary rp (50%) and 51 with med EG-sem (49%) were identified [cervical LN n = 1 (1%)] representing 16.4% of 635 EGGCT-pts. Pts characteristics: median age 37 yrs (18–70), treatment: ctx ± secondary surgery (sr) in 77 pts (76%), radiotherapy (rtx) in 9 (9%), ctx + rtx in 18 (17%); sites of metastases: abdominal LN 20 (19%), bone 6 (6%), cervial LN 17 (16%), liver 4 (4%), lung 5 (5%), paratracheal LN 6 (6%), no. of metastatic sites <2 = 93 (89%), ≤2 11 (11%); elevated β-HCG 35 (34%) [median: 5 (1–90 ng/ml)], elevated LDH 51 (49%), [median: 539 (158–8555 U/l)]. Ctx regimens: DDP-based 81 (80%), CP-based 11 (11%), other 2 (2%). 92% of pts responded favorable to treatment. 18 pts (17%) relapsed after initial treatment, 14% after ctx and 67% after rtx (ctx + rtx 6%) [$p < 0.0001$]. 2-yr-DFS was 92.1% for pts treated with ctx and 55.6% for the rtx subgroup ($p = 0.041$). 2-yr-OS was equal for both groups [92.1 vs. 100%, (ns)]. 2-yr OS and DFS for rp and med EG-sem were 96% vs. 92% and 92% vs. 88% (ns).

Conclusion: In contrast to NS-EGGCT this analysis revealed no difference in the outcome of rp and med-EG-sem. Rtx was associated with a