1379 ORAL

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.

1380 ORAL

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.

1381 ORAL

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.

1382 ORAL

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.

1383 ORAL

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

significantly higher relapse rate compared to ctx ± rtx, but those pts were salvaged by effective ctx.

1384 POSTER DISCUSSION

Radiotherapy for stage I testicular seminoma – A prospective trial

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Purpose: With high cure rates of 95–98% for radiotherapy (XRT) of stage I (CS I) testicular seminoma it is the aim of modern treatment strategies to reduce the intensity of adjuvant XRT without compromising locoregional tumour control. We therefore conducted a multicenter prospective trial for limited XRT of CS I seminoma with reduced treatment portals and small total doses. Data on the "per protocol" population have been reported previously. We now present updated results including data of those patients with protocol violations.

Method: Patients with histologically proven pure CS I seminoma received adjuvant XRT to the paraaortic lymph nodes only. Treatment portals stretched from the upper border of thoracic vertebra 11 (T11) to the lower border of lumbar vertebra 4. The total dose was 26 Gy in 2 Gy daily fractions. Acute and late side effects of treatment were prospectively scored using the EORTC score.

Results: Between 4/91 and 3/94 721 patients were enrolled for the trial. 670 patients were eligible for an interim analysis in 1/99. 483 patients were treated strictly per protocol (PP), 187 patients showed protocol violations (PV). Mean follow up was 55 months. There have been 24 cases of relapse, 18 (3.7%) in the PP and 6 (3.2%) in the PV group. There was no in-field recurrence. 22/24 patients were salvaged with two cases of disease-realted death. Statistical analysis showed no differences in relapse rate nor survival between the study populations. Acute side effects of adjuvant XRT were moderate.

Conclusions: Limited volume XRT for CS I seminoma yields high cure rates with moderate acute side effects.

1385 POSTER DISCUSSION

$E_{400}P$ in good prognosis advanced seminoma. The Spanish germ-cell cancer group experience

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Objective: To analyse response, toxicity, time to treatment failure (TTF) and survival (OS) in patients (p) with IGCCG good-prognosis advanced seminoma treated with $E_{400}P$ (cisplatin 25 mg/m^2/d and etoposide 100 mg/m^2/d × 4 d).

Methods: Since 1994 63 p with were included, 48 p with advanced disease at diagnosis (76%) and 15 p who relapsed after stage I (13 p follow-up, 1 p RT and 1 p carboplatin × 2 after orchiectomy). Mean age was 38 y (19–83), Metastatic sites were retroperitoneum (89%), mediastinum (10%), other lymph nodes (19%) and lung (2%). Royal Marsden stages were II: 84%, III: 14% and IV: 2%. Sixteen p (25%) had high BHCG levels, 16 p had LDH > 2 × N, and 61 p (97%) were classified as MIRC good-prognosis (*Fosse et al, Eur J Cancer 33: 1380–87*). Number of cycles administered were 3 (7%), 4 (80%), 5 (10%) or 6 (3%); 3 p are still on treatment.

Results: Grade 3–4 toxicities were anemia (3%), thrombocytopenia (3%), neutropenia (32%), mucositis (3%), neurotoxicity (2%), alopecia (96%) and emesis (4%). Twenty-one p (33%) received prophylactic filgastrim and 53/60 p (85%) received ≥80% of the maximum dose intensity. All p responded (72% CR, 28% residual disease). After a median follow-up of 26 m, treatment failed in 4 p (6%). Failure was defined as viable tumor after CT (1 p), regrowth of a residual mass (0 p), relapse (3 p) or unacceptable toxicity (0 p). These 4 p had MRC good-prognosis and normal BHCG; 3 of them were IIa–b. One p is on 2nd CT, the other 3 p achieved a 2nd CR (1RT, 2CT). One p died after a 2nd relapse. Median TTF and OS have not been reached. Three-year TTF and OS are 92.5% (95%CI: 85.4–99.6%) and 97% (95%CI: 91–100%) respectively. All IIc–IV p are alive and their 3-year TTF is 96%.

Conclusion: In our experience, $E_{400}P$ is a safe regimen for patients with good prognosis advanced seminoma. This regimen could reduce acute and late toxicities observed with the more standard $E_{500}P$ or BEP regimens.

1386 POSTER DISCUSSION

Identification of prognostic subgroups in patients (PTS) with poor risk germ cell cancer (GCT): A cart analysis

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Purpose: Only a few data exist about prognostic criteria within the group of pts who exhibit poor prognostic criteria according to the IGCCCG classification.

Methods: We retrospectively analyzed the data of 332 pts with 'IGCCCG' poor risk GCT using the classification-and-regression-tree model (CART). The following variables were included: primary localization, presence of visceral or lung metastases (met.), presence of an abdominal tumor, number of metastatic sites, levels of β-HCG, AFP and LDH. All patients had been treated with cisplatin/etoposide-based CTx within randomized clinical trials.

Results: Patient characteristics: gonadal/retroperitoneal (G/R) primary tumor 260 pts (78%), mediastinal primary, tumor 72 pts (22%), visceral met. 205 pts (62%), lung met. 247 pts (74%), abdominal tumor 241 pts (73%), elevated AFP, β-HCG or LDH levels 235 (71%), 253 (76%) and 275 (83%) of pts, respectively. Pts with primary, mediastinal disease and lung met. exhibited the worst 3-year PFS (28%), whereas pts with primary G/R disease and without visceral met. showed the longest 3-year PFS (75%). Pts without visceral met and primary G/R tumor had the most favourable 3-year OS (79%). In contrast, pts exhibiting visceral met. from a primary mediastinal tumor displayed the worst 3-year OS (40%).

Conclusion: Different prognostic subgroups can be identified within the group of poor risk GCT. These data may help to estimate detailed individual prognoses and to identify subgroups of high risk pts that may, in turn, be included in new treatment strategies.

1387 POSTER DISCUSSION

Acute and late sequelae in conventionally fractionated and hyperfractionated conformal radiotherapy in prostate cancer. Preliminary evaluation

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Purpose: To evaluate acute and late toxicities in patients affected by prostate cancer treated with conformal radiotherapy using conventional (STD) or pure hyperfractionated (HFX) regimens.

Method: One hundred patients (pts) were treated with 5-field conformal radiotherapy to prostate and seminal vesicles; 85 were evaluable for this analysis. Forty-two pts were treated with STD-CRT at a total dose (ICRU p.p.) of 73.5–75.5 Gy (median: 75.5 Gy; mean: 74.7 Gy); 43 were treated with HFX-CRT at a total dose of 78.3–82 Gy (median: 80.7 Gy; mean: 80.2 Gy). Acute and late toxicities according to RTOG-EORTC criteria were evaluated weekly during CRT, one month after CRT and 3–4 times yearly afterwards.

Results: No significant worsening of acute toxicities was observed using HFX-CRT (grade 2 max. incidence with HFX vs STD: G.I.: 56% vs 62%; G.U.: 33% vs 31%; grade 3 max. incidence with HFX vs STD: G.I.: 0% vs 0%; G.U.: 9% vs 17%). Actuarial probability at 20 months of grade 2 G.U. toxicity was 13% with HFX and 23% with STD, while grade 2 G.I. toxicity was 20% with HFX and 19% with STD. Only one pt, belonging to the STD-CRT group, experienced a grade 3 toxicity (G.U.). Erectile function in pre-radiotehrapy potent patients was maintained at one year in 86% of HFX and 69% of STD pts.

Conclusion: HFX-CRT seems to favourably compare with lower dose STD-CRT with respect to treatment feasibility and acute/late sequelae.

1388 POSTER DISCUSSION

Immunotherapy with the bispecific antibody MDX-H210 (anti-HER2 × anti-CD64) combined with GM-CSF in HER2 positive hormone resistant prostatic cancer

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Purpose: Treatment of hormone resistant cancer is palliative in nature and new therapies are urgently needed. We report results following treatment with the bispecific antibody MDX-H210 (anti-HER2 × anti-CD64)