Poster Discussion Presentations (Sun, 25 Sep, 11:00−12:00)

Genitourinary Malignancies − Other

7105 POSTER DISCUSSION

Belinostat in Combination With Carboplatin and Paclitaxel (BelCaP) for Treatment of Bladder Cancer − A Pharmacokinetic Study of Exposure to Belinostat and Its Metabolites

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Background: Belinostat (Bel, PXD101) is a class I and II Histone DeACetylase (HDAC) inhibitor. A single arm Ph II study was conducted to evaluate the safety and activity of Belinostat, Carboplatin and Paclitaxel (BelCaP) in patients (pts) with Transitional Cell Carcinoma of the Bladder (TCCB) (n = 15). A part of the study was a pharmacokinetic study of plasma exposure to Bel and its metabolites. The *in vitro* efficacy of belinostat and its metabolites were compared and related to plasma exposure in pts.
Materials and Methods: Pts with TCCB were treated with BelCaP every third week; Bel was given as a 1000 mg/m^2 30-min i.v. inf. on days 1−5 with P (175 mg/m^2) and subsequently Ca (AUC5) administered 2−3 hrs after Bel on day 3. The plasma exposure (AUC) of Bel and its metabolites were determined. The *in vitro* pharmacological effect of Bel and its five major metabolites: belinostat glucuronide (BelGlcU), 3-(Anilinosulfonyl)benzene carboxylic acid (3-ASBA), methylated belinostat (Metbel), belinostat amide (Belam) and belinostat acid (Belac) were examined in a HeLa HDAC enzyme inhibition assay (HDAC-i), in WST proliferation assays and in clonogenic assays (CA). Fold differences in exposure of metabolites and belinostat (10 pts on day 3) and fold differences in *in vitro* efficacy of belinostat and metabolites were compared.
Results: The exposure of each metabolite relative to Bel was evaluated. The increases (molar $AUC_{0-\infty}$) relative to Bel were 16- (BelGlcU), 3- (3-ASBA), 1- (Metbel), 1- (Belam) and 0.5-fold (Belac).
Bel metabolites did not inhibit HDAC-i activity or cell WST proliferation *in vitro*. In the CAs the IC_{50} for Bel were 0.4 to 1.3 μM. Three metabolites had weak effect relative to Bel. The fold increase in IC_{50} relative to Bel was: >65 (BelGlcU), >42 (Metbel) and >114 (Belam).
Conclusions: Five major human Bel metabolites (BelGlcU, 3-ASBA, Metbel, Belam and Belac) were identified in a Ph II study of BelCaP in pts with TCCB.
Bel metabolites were inactive in HDAC-i assays and in WST assays and had weak activity in CA. The metabolite with highest fold exposure compared to Bel was BelGlcU (16-fold), which was 65 fold less effective *in vitro* than Bel. The present study finds that Bel metabolites do not have significant biological effect at therapeutic relevant plasma exposure in cancer pts.

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The Proteasome-inhibitor Bortezomib is Active in Human Urothelial Cancer Cell Lines in Combination With the Tyrosine-kinase Inhibitor Sunitinib or Cisplatinum

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Background: The outcome of advanced muscle-invasive urothelial cell carcinoma (UCC) is generally modest. Cisplatinum-based chemotherapy is considered the standard of care, but novel strategies are urgently required. The proteasome-inhibitor bortezomib has shown activity in UCC in vitro and in vivo by inducing apoptosis through the tumour-necrosis-factor-related apoptosis-inducing-ligand (TRAIL). The aim of this study was to investigate whether induction of apoptosis and/or cytotoxicity can be enhanced by combining bortezomib with cisplatinum or the tyrosine-kinase inhibitor sunitinib.
Materials and Methods: HTB-2, HTB-3 (squamous) and HTB-5 cell lines were treated with increasing concentrations of bortezomib alone and in combination with sunitinib or cisplatinum for 72 hours. Cytotoxicity was determined by an MTT-based vitality assay (EZ4U, Biomedica). Apoptosis was detected by flow cytometry (PI-staining) using FACS calibur (Becton Dickinson). Protein analysis was performed using Western blots.
Results: In all three urothelial carcinoma cell lines bortezomib showed a significant reduction in cell-proliferation with an IC50 of 5 to 8 nanomolar (nM). Bortezomib alone induced significant DNA-fragmentation in up to 50% of viable cells in all cell lines, mostly at concentrations below 10 nM. This led to a consecutive reduction of cells in the G2/M and S-Phase. On the protein basis bortezomib induced apoptosis through down-regulation of pSTAT3, PARP and pS6 at concentrations starting at 5nM. The combination of bortezomib and sunitinib mainly induced an anti-proliferative effect through cell cycle arrest in the G0/G1 phase. P-ERK, PARP and pS6 were significantly downregulated when the two drugs were combined. Bortezomib (5, 10 nM) and sunitinib (5 μM) showed synergistic activity at low concentrations that are achievable in vivo, while cisplatinum and bortezomib showed additive activity through induction of apoptosis.
Conclusions: At concentrations feasible in vivo, bortezomib induced apoptosis in urothelial cancer cell lines. Sunitinib and cisplatinum enhanced the cytotoxic and apoptotic effects of bortezomib. These combinations warrant further clinical investigation.

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Prognostic Impact of the Expression of Putative Cancer Stem Cell Markers ALDH1 and SOX2 in Urothelial Cancer of the Upper Urinary Tract

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Background: The aim of this study was to elucidate the prognostic impact of the putative cancer stem cell markers aldehyde dehydrogenase 1 (ALDH1) and sex determining region-Y (SRY)-related high mobility group box 2 (SOX2) in urothelial cancer of the upper urinary tract.
Material and Methods: Immunohistochemical staining for ALDH1 and SOX2 was carried out on archival specimens from 125 patients with urothelial cancer of the upper urinary tract who underwent radical nephroureterectomy from April 1995 to August 2010. The expression of ALDH1 and SOX2 was compared with clinicopathologic features, cancer-specific survival (CSS) and recurrence-free survival (RFS).
Results: In univariate analysis, grade, T stage, N stage, lymphovascular invasion, ALDH1 and SOX2 were associated with a poor prognosis and disease recurrence. In multivariate analysis, the independent factors of prognosis and recurrence were grade ($p = 0.0378$; $p = 0.0029$), pN ($p = 0.0276$; N.S.), and ALDH1 expression ($p = 0.0005$; $p = 0.0377$). When using subgroup analysis, the subgroups with two positive, one positive, or no positive immunohistochemistry in ALDH1 and SOX2 expression had estimated 5-year CSS of 79.7%, 46.6%, and 22.2%, respectively ($p < 0.0001$).
Conclusions: Expression of ALDH1 and SOX2 correlates with patient survival and recurrence in urothelial cancer of the upper urinary tract. ALDH1 expression is an especially strong independent predictive factor. The data suggest that cancer stem cells may play an important role in the progression of urothelial cancer.

7108 POSTER DISCUSSION

Surveillance in Stage I Testicular Cancer − Safety of Low Dose CT Scans

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Background: Surveillance is accepted as the optimal management strategy for stage I testicular seminoma and is an accepted option for stage I non-seminoma. However, there is concern that the cumulative radiation exposure associated with multiple CT scans of the abdomen and pelvis (CT A/P) used in follow-up may result in an increased risk of second malignancy. The purpose of this study was to assess the safety of using low-dose CT scans in detecting retroperitoneal nodal relapse.
Methods: Between 2005 and 2011, 244 patients (198 seminoma, 46 non-seminoma) with stage I testicular germ cell tumours were enrolled into a phase II study. All patients initially underwent standard dose CT A/P and low dose CT A/P (40−60% dose reduction) and those with acceptable image quality continued with low dose CT alone. Relapse in the retroperitoneum detected on low dose CT was confirmed with standard dose CT. A single radiologist prospectively compared nodal size between the 2 imaging techniques.
Results: One patient had images unsuitable for surveillance with low dose CT. At a median follow up of 26 months there were 34 relapses: 32 in retroperitoneal lymph nodes and 2 with raised serum tumour markers. Of the 32 nodal relapses, 30 pairs of CT images were assessed for nodal size. Mean size of retroperitoneal nodal relapse (short axis) was 16.7 mm and 16.6 mm for standard and low dose CT, respectively ($p = 0.48$). The

difference in short axis of the measured nodes between the two imaging techniques was <2 mm in all cases.
Conclusion: The quality of low dose CT images is adequate for retroperitoneal nodal surveillance in stage I testicular germ cell tumours and allows a reduction in cumulative radiation exposure. This technique may be safely adopted in surveillance schedules.

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An Individualized Dose/Schedule Strategy for Sunitinib in Metastatic Renal Cell Cancer (mRCC) May Improve Progression Free Survival (PFS) − Correlation With Dynamic Microbubble Ultrasound (DCE-US) Data

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Background: Sunitinib area under the curve (AUC) correlates with response and PFS (Houk et al). Current recommendations for dose modification do not take this into account.
Material and Methods: A single center retrospective review identified mRCC patients (pts) where individualized (individ) sunitinib dose/schedule modifications (DSM) were used to maximize dose and minimize time off therapy (Rx). Pts were started on 50 mg 28 days (d) on/14d off. DSM were done to keep toxicity (fatigue, skin, GI) at $\leqslant$ grade-2. DSM-1 was 50 mg 14d/7d with individ increases in d on Rx based on toxicity. DSM-2 was 50 mg 7d/7d with individ increases in d on Rx. DSM-3 was 37.5 mg continuously with individ 7d breaks. DSM-4 was 25 mg continuously with individ 7d breaks.
Results: In 172 pts; median age was 60 y; 20% good, 60% intermediate, 20% poor prognosis by Heng criteria; 80% had nephrectomy; 79% clear cell histology; 60% were previously untreated. At a median follow-up of 12.9 months (mo), overall median PFS was 8.9 mo. All 20 pts still on therapy are on a DSM Rx. Pts were allocated to three groups based on the dose/schedule used for the longest time. The PFS/response% (PR+SD) for each group was 4.9 mo/64.1% (standard 50 mg 28d/14d; 39 pts), 10.4 mo/77.5% (DSM-1/DSM-2; 71pts) and 11.9 mo/82.3% (DSM-3/DSM-4; 62 pts) with improved PFS (p = 0.0002) in both DSM groups vs. the standard schedule but no difference in response. In 20 responding pts studied by DCE-US at baseline, and after 7d and 14d on Rx or after 14d and 28d on Rx, tumour blood volume decreased at d7 and again at d14 vs. baseline but was stable or increased at d28 vs. d14. A rebound was seen after 14d off Rx.
Conclusions: Based on the US data, previous pharmacokinetic data (steady state at 10−14d) and this clinical data, starting pts on 50 mg 14d/7d followed by individ DSM may be safe and active. This DSM strategy was associated with a favorable toxicity profile, apparent improvement in PFS and a good PR+SD rate in a group of unselected mRCC pts, warranting confirmation in a prospective trial. Pts that tolerate 50 mg 28d/14d with minimum toxicity may need dose escalation and/or less time off therapy to optimize PFS.

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A Phase II Trial of Docetaxel, Cisplatin, 5-Fluorouracil (TPF) in Locally Advanced and Metastatic Carcinoma of the Penis (CRUK/09/001)

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Background: Chemotherapy for penis cancer is used mainly as palliation of metastatic disease. It also has a role in treatment for locally-advanced disease but the rarity of the disease has hampered attempts to define an evidence base for this. The combination of cisplatin (P) and 5-fluorouracil (F) has been used for treatment of squamous cell carcinoma (SCC) of the penis since 1990. Pathological similarities to head and neck SCC suggest that the addition of docetaxel (T) to an established platinum-based regimen may enhance therapeutic benefits.
Materials and Methods: A single-stage, single-arm academically-sponsored phase II trial was conducted. Eligible patients (pts) had histologically proven SCC of the penis staged as M1; or T4, any N, M0; or any T, N3/inoperable N2, M0; or any T, N1, M0 where chemotherapy was offered as first-line therapy after MDT discussion. All pts had measurable disease. Treatment consisted of three 21-day cycles of: T 75 mg/m^2 day 1, P 60 mg/m^2 day 1, F 750 mg/m^2/day (days 1−5). The recruitment target was 26 evaluable pts. Fourteen or more responses were required to conclude a response rate of 60% or more (p0=0.35, p1=0.60, α=0.1, β=0.2; Fleming-A'Hern exact methods). The primary endpoint was overall response rate at completion/discontinuation of trial treatment. Secondary endpoints included safety, tolerability, progression-free and overall survival.
Results: 29 pts were recruited from 9 UK centres between September 2009 and December 2010. Median age was 61 years; 19 pts had performance status (PS) 0, 10 PS1, 1 PS2. Three pts discontinued treatment early for reasons other than progression. Dose reductions or delays were reported for 13 pts. With a median follow-up of 7 months, 19 pts remain in follow-up and 10 pts have died. Toxicity data are available for 28 patients: 19 (68%) experienced toxicity at grade 3/4, with neutropenia most common (n = 13, 46%). 8 pts (29%) experienced febrile neutropenia and/or sepsis.
Central independent review of response will be completed in April 2011. Full analysis of the primary endpoint, overall response rate, will be presented.
Conclusions: UK clinicians successfully recruited to a multi-centre trial in penis cancer. A network of centres has been established for future studies. Toxic effects of TPF were common but within acceptable limits. Response data are awaited.

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High-dose Chemotherapy With Autologous Stem-cell Support in Patients With Metastatic Non-seminomatous Testicular Cancer − a Report From the Swedish Norwegian Testicular Cancer Group (SWENOTECA)

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Background: Within the SWENOTECA IV study on patients with metastatic non-seminomatous testicular cancer, 55 men were treated with high-dose chemotherapy (HDCT) in three clinical situations: A) insufficient response to standard-dose intensified chemotherapy (BEP with addition of iphosphamide), B) histologically vital cancer at surgery following intensified chemotherapy, C) relapse after intensified chemotherapy. In situation A and C two HDCT cycles and in situation B one HDCT cycle was recommended. This study presents survival and toxicity data for these patients.
Material and Methods: From 1995 to 2007 situation A was the reason for HDCT in 36 patients, B in 7 patients and C in 12 patients. The first HDCT cycle consisted of carboplatin 28x(GFR+25) mg, cyclophosphamide 6000 mg/m^2 and etoposide 1750 mg/m^2, all divided in four daily doses. For the second cycle etoposide was replaced by tiotepa 480 mg/m^2.
Results: In total 33 men (59%) received two high-dose cycles, of whom 27/36 (75%) in situation A and 4/12 (33%) in situation C received two cycles. The main reasons for only one HDCT cycle was serious toxicity (n = 7, 32%), according to protocol (n = 5, 23%), and progressive disease (n = 4, 18%). After a median follow-up of 7.5 years, overall survival in situation A, B and C were 72%, 100% and 58%, respectively, whereas failure-free survival was 64%, 71% and 42%, respectively. In Cox regression analysis stratified for treatment indication, increasing age (HR 1.09, 95% CI 1.03–1.15) and being marker positive prior to HDCT (HR 2.47, 95% CI 1.20–5.11) was associated with increased risks for death due to any cause, while having received only one HDCT cycle (HR 2.84, 95% CI 0.83–9.77) tended to be associated. Three patients (5.5%) died during HDCT of renal failure or intracerebral hemorrhage, all treated before 2000. Nephrotoxicity was the most common non-hematological grade 4 toxicity, affecting 5 (9%). The time interval between cycle one and cycle two was median 55 days (range 30−84). Hematological toxicity was not more pronounced during the second vs. the first HDCT cycle. The hospitalization