effective treatment with sustained cumulative exposure and dose-dense drug delivery.
Methods: From May 2003 to May 2005, 34 pts of TCC who failed MVAC entered to this phase II study. Weekly P (80mg/m2) and C (AUC2) were administered on day 1, 8, 15, 22, 29, 36 and repeated every 7 weeks until progression or intolerable toxicity (maximum 18 cycles). Platinum-free interval (PFI) was defined as the interval from the last MVAC to the start of weekly P plus C.
Results: Pts' characteristics were as follows. Median age was 65.5 (53–80). 13 pts (38%) were 70 y.o. or older. Median PS was 1 (0–3). 25 pts (74%) had visceral metastasis. Median PFI was 4.4 months (1.5–106). Among assessable 31 pts, 2 complete and 8 partial responses were observed (overall response rate 32.3%, 95% CI 15.8–48.7%). The relations between PFI and tumor response were as follows: <6 months; 23.5% (4/17) and ⩾6 months; 42.9% (6/14), respectively (p = 0.43). Median progression-free and overall survivals were 3.7 and 10.3 months, respectively. Elderly pts obtained almost equal response rates (<70 y.o; 31.5% (6/19), ⩾70 y.o; 33.3% (4/12)) and median overall survivals(<70 y.o; 10.2 months, ⩾70 y.o; 17.1 months). One pt whose PS was 3 died from sepsis within 1 month from the last cycle of chemotherapy. Grade 3–4 CTC-toxicities were as follows: anemia; 35%, thrombocytopenia; 0%, neutropenia; 50%, febrile neutropenia: 9%. Most common non-hematological toxicities were alopecia (⩾Grade 1; 72%), neurotoxicity (Grade 1; 59.3%, Grade 2; 9.4%, ⩾ Grade 3; 0%), nausea and vomiting (Grade 1; 34%, Grade 2; 6%, Grade 3; 3%) and diarrhea (Grade 1; 13%, Grade 2; 3%, Grade 3; 3%).
Conclusions: Weekly P plus C was tolerable and active for TCC who failed MVAC. This regimen was less toxic and deserves further evaluation especially for elderly pts with TCC. We are planning the next trial to assess this regimen as the first-line treatment for elderly TCC pts with comprehensive geriatric assessment.

858 POSTER

Alpha and beta CTX urine levels in patients with prostate cancer

S. Ali[1,2], C. Christensen[3], P. Qvist[3], L. Demers[2], L. Engle[2], V. Chinchilli[2], K. Leitzel[2], S. Petrone[4], L. Costa[5], A. Lipton[2]. [1]*Penn State University / Lebanon VAMC, Lebanon, PA, USA;* [2]*Penn State University/Hershey Medical Center, Hershey, PA, USA;* [3]*Nordic Bioscience, Herlev, Denmark;* [4]*Novartis Corp, East Hanover, NJ, USA;* [5]*Hospital Santa Maria, Lisbon, Portugal*

Degradation products of type I collagen can be measured by CrossLaps (CTX) immunoassays, providing an index of bone resorption. The CTX epitope EKAHDGGR comprises a DG-motif susceptible to post-translational modifications. In newly synthesized collagen this motif is in the native form denoted alpha CTX, but converts to an isomerized form (beta CTX) during ageing of bone. Other markers of bone resorption including serum N-telopeptide are elevated in prostate cancer.
For this study, alpha and beta CTX levels were analyzed in serial urines of prostate cancer patients using the respective Nordic Bioscience ELISA. Urines were obtained from patients who participated in a multicenter placebo-controlled trial of pamidronate vs placebo (JCO 21, pp: 4277, 2003). Baseline urine samples were available from 147 patients with advanced disease; 43.5% were terminated early due to disease-related outcomes including death and unsatisfactory therapeutic effect. In this study we correlated urine marker levels with time to skeletal-related events (TTSRE), and also a composite endpoint defined as either TTSRE or early discontinuation from the trial. Serial urine samples were available from a smaller subset of patients due to the early termination.
Median alpha CTX levels were 1.77 (range 0.2–31.9 μg/mmol) and beta CTX levels were 5.26 (range 0.01–86.7 μg/mmol). There was no control data available for males with castrate levels of sex hormones, so control data was used from postmenopausal females. The 95 percentile cutoff (determined for control women who were post-menopausal for less than 5 years) was 2.4 μg/mmol for alpha CTX and 9.62 μg/mmol for beta CTX. Using these cutoffs, 33.1% of patients had elevated alpha CTX levels and 26.5% had elevated beta CTX levels. Patients with elevated baseline urine beta CTX levels had significantly shorter time to the composite end point (Log rank p-value = 0.03), but alpha CTX did not. The change in alpha and beta CTX levels between baseline and 9 weeks after treatment was also analyzed for those patients who had elevated urine marker levels at baseline. Those patients with >50% decrease in alpha CTX urine levels had a significantly longer TTSRE and time to composite endpoint, but no association was seen with change in urine beta CTX.
In conclusion, serial alpha CTX urine levels deserve further evaluation in patients with prostate cancer.

859 POSTER

Bone alkaline phosphatase is predictive of prostate cancer-related outcome in metastatic hormone-refractory prostate cancer

A. Lipton[1], J. Nelson[2], J. Isaacson[3], S. Hulting[3], D. Sleep[3]. [1]*Milton S. Hershey Medical Center, Hershey, PA, USA;* [2]*University of Pittsburgh School of Medicine, Pittsburgh, PA, USA;* [3]*Abbott, Abbott Park, IL, USA*

Background: Bone alkaline phosphatase (BALP), a biochemical marker of osteoblastic activity in metastatic hormone-refractory prostate cancer (HRPC), is associated with sclerotic bone metastases. BALP may be of value as a surrogate for progressive disease in prostate cancer; however, dynamic measures of BALP have not been evaluated as predictors of outcome in men with metastatic HRPC. A large, randomized, double-blind, placebo-controlled study of 10 mg atrasentan (Xinlay™) versus placebo was conducted in patients with metastatic HRPC. Time to disease progression (TTP) was the primary endpoint for the study and was defined by radiographic and clinical events and confirmed by independent radiology and oncology review. In addition, the majority of patients in the study reported new metastatic bone pain, the cardinal symptom of metastatic prostate cancer. The objective of this analysis was to evaluate the predictive value of increasing BALP on disease-related outcome (disease progression and bone pain) in patients receiving placebo.
Material and methods: Data from 369 patients randomized to placebo who had BALP values at both baseline and week 4 were divided into 2 groups: increased or decreased BALP from baseline at week 4. TTP, time to bone pain reported as an adverse event (TTBP), and time to death were compared between the two BALP groups using Kaplan-Meier and Cox proportional hazards methodologies.
Results: At week 4, 64.8% of the patients recorded an increased BALP from baseline and 35.2% a decrease in BALP. TTP and TTBP were significantly shorter for patients with rising BALP (log-rank p < 0.001 and log-rank p = 0.002, respectively). The median TTP was 85 days for those with an increased BALP at week 4 compared to 117 days for those with a decreased BALP. The hazard associated with an event of disease progression or time to the first adverse event of bone pain was decreased by 40% (95%-CI = 0.470, 0.769) and 38% (95%-CI = 0.456, 0.843) for patients with a BALP decrease at week 4. There was no significant difference in survival between the 2 groups.
Conclusions: These data demonstrate that a rising BALP at week 4 in patients with metastatic HRPC is associated with early disease progression and early onset of metastatic bone pain. Prospective trials will be required to determine if serial BALP measurements are predictive of disease-related outcome in HRPC.

860 POSTER

Diagnostic and prognostic value of serum TRACP 5b, MMP-2, MMP-9, and tALP in patients with advanced prostate cancer

E. Salminen[1], M. Kallioinen[1], M. Ala-Houhala[1], S. Alatalo[2], P. Vihinen[1], T. Vahlberg[3]. [1]*Turku University Hospital, Dept of Radiotherapy and Oncology, Turku, Finland;* [2]*Instittue of Biomedicine, Anatomy, Turku, Finland;* [3]*Biostatistics, Biostatistics, Turku, Finland*

Background: Skeletal metastases are a significant problem in prostate cancer (PC) patients. Tartrate-resistant acid phosphatase isoform 5b (TRACP 5b) is a specific parameter of osteoclast activity and bone resorption in cancer patients. Matrix metalloproteinases (MMPs) MMP-2 and MMP-9 are gelatinases, which have been shown to be associated with poor prognosis in patients with cancer. We evaluated TRACP 5b, MMP-2 and MMP-9 in relation to the standard analyte total alkaline phosphatase (tALP) as markers of skeletal metastases and as predictors for survival in advanced PC.
Material and methods: The sera were collected from 35 PC patients with (BM+) diagnosed skeletal metastases and from 49 PC patients without (BM−) radiological evidence of skeletal metastases. Non-fasting serum samples were collected and stored in −70ºC before analysis. Total ALP was determined using a standard laboratory method (Roche Diagnostics). Serum TRACP 5b activity was measured using an in-house immunoassay system. Quantitative analysis of serum MMP-2 and MMP-9 was performed using a commercial ELISA System (Amersham Biosciences, UK). The diagnostic accuracy of the markers was evaluated by ROC curve analysis. The diagnostic sensitivity and specificity were determined at the cut-off level with the highest diagnostic accuracy in the ROC analysis, and these cut-off levels were used in Kaplan-Meier survival analyses for the markers.
Results: Mean values of TRACP 5b and tALP were significantly higher in BM+ group than in BM-group (p < 0.0001), whereas no such difference was observed for MMP-2 or MMP-9. Total ALP showed the highest area under the curve (AUC = 0.98), followed by TRACP 5b (AUC = 0.82) and MMP-9 (AUC = 0.62). The best combination of sensitivity (91%) and specificity (100%) for tALP was reached with cut-off point = 227 U/L, for TRACP

5b the best sensitivity (71%) and specificity (96%) was seen with the cut-off point = 4.98 U/L, and for MMP-9 the best sensitivity (43%) and specificity (82%) with the cut-off point = 96.1 ng/ml. Patients with TRACP 5b ($p = 0.002$) or tALP ($p < 0.001$) levels above determined cut-off values showed significantly shorter survival than patients with low marker levels. MMP-2 and MMP-9 were not associated with survival.
Conclusions: TRACP5b is a novel marker of skeletal metastases and a predictor for survival in advanced PC.

861 POSTER

Retrospective study of inhaled IL-2 as treatment of lung metastasis of renal cell carcinoma. Spanish and Portuguese experience

E. Estéban González[1], A. Jiménez-Lacave[1], J. Vieitez de Prado[1], C. García-Girón[2], P. Maroto Rey[3], A. Canelas[4], R. Andrés Conejero[5], E. Espinosa Arranz[6], A. García García[7], J. Carballido Rodríguez[8]. *[1]Hospital Central de Asturias, Servicio de Oncología, Oviedo, Spain; [2]Hospital General Yagüe, Servicio de Oncología, Burgos, Spain; [3]Hospital Santa Cruz y San Pablo, Servicio de Oncología, Barcelona, Spain; [4]Hospital San Bernardo, Servicio de Urología, Setúbal, Portugal; [5]Hospital Clínico Universitario Lozano Blesa, Servicio de Oncología, Zaragoza, Spain; [6]Hospital Universitario La Paz, Servicio de Oncología, Madrid, Spain; [7]Hospital Reina Sofía, Servicio de Oncología, Córdoba, Spain; [8]Clínica Puerta de Hierro, Servicio de Urología, Madrid, Spain*

Background: Systemic IL-2 has been used for the last decade to treat metastatic renal cell carcinoma (MRCC). Locoregional administration of this cytokine could improve the risk/ benefit ratio of this drug. The objective of this study was to obtain efficacy and safety data on inhaled rIL-2 used in clinical practice in lung metastatic renal cell carcinoma (LMRCC) patients.
Material and Methods: The study was designed as a retrospective chart review in LMRCC patients being treated with inhaled rIL-2. Between September 2000 and April 2005, 32 centres in Spain and 3 in Portugal provided data from 80 LMRCC patients treated with inhaled IL-2. The treatment schedule was: 3 cycles of 36 MIU rIL-2 per day for 5 days/week for 12 weeks (with one week treatment free between cycles) in Spain and for 3 weeks (out of each 4 weeks) for 12 weeks in Portugal. Efficacy was assessed by best response following each treatment cycle and overall. PFS and OS were measured from the time of administration of the first dose of inhaled rIL-2 until progression, last follow up date or death, respectively The Kaplan-Meier method was used to estimate progression free survival (PFS) and overall survival (OS). Safety data were analysed using descriptive statistics, with toxicities expressed as number of toxicity reported weeks, describing grade and cycle.
Results: A total of 1290 treatment weeks were studied. Cough was the most frequent adverse event (reported in 27.8% treatment weeks), tending to be less frequent after the first 12 weeks of treatment. The majority of adverse events were reported to be only grade 1 or 2 in severity. Response rates after 12 weeks treatment were: 2 (2.7%) Complete Response; 10 (13.6%) Partial Response; 21 (28.7%) Stable Disease. At the present moment there were only 48 patients' data for survival calculations. Median PFS and OS were 4.5 (range 0.5–17.3) and 10.7 (range 0.4–42.9) months. At least 10 patients (20.8%) were alive for further than 24 months.
Conclusions: These initial results confirm that IL-2 locoregional administration in LMRCC can improve the risk/ benefit ratio of this drug compared to systemic therapy, maintaining its efficacy with an outstanding toxicity reduction.

862 POSTER

Biochemical response to neoadjuvant hormonoterapy may predict biochemical control rate and distant metastasis free survival after total short term androgen deprivation and conformal radiotherapy in the treatment of prostate adenocarcinoma

F. Akyol[1], G. Ozyigit[1], U. Selek[1], C. Onal[1], E. Karabulut[2], H. Ozen[3]. *[1]Hacettepe University, Faculty of Medicine, Department of Radiation Oncology, Ankara, Turkey; [2]Hacettepe University, Faculty of Medicine, Department of Biostatistics, Ankara, Turkey; [3]Hacettepe University, Faculty of Medicine, Department of Urology, Ankara, Turkey*

Background: We assessed the prognostic factors affecting survival after short term total androgen deprivation (TAD) and radiotherapy in the treatment of localized prostate cancer.
Materials and Method: One hundred twenty-eight patients with T2-T3N0M0 prostate adenocarcinoma patients were treated. Stage T3, PSA $\geqslant$10 ng/dL and Gleason Score (GS) 7 and above were considered as high risk criteria and in case of positivity in one of them the patient was considered as high risk, otherwise treated as low risk. All patients were prescribed neoadjuvant TAD before radiotherapy. In high risk patients, TAD was continued for 6 months after completion of radiotherapy. Total radiotherapy dose was 73.6 Gy at ICRU reference point.
Results: Median follow-up was 48 months. Nineteen patients were in the low and 109 were in the high risk group. Five-year cause specific survival, biochemical control rate (bCR), and distant metastasis free survival rate were 94%, 80%, and 87% respectively. bCR was 87% for patients with PSA $\leqslant$1 ng/dL after 3 months neoadjuvant TAD, and 69% for patients with PSA >1 ng/dL after 3 months neoadjuvant TAD. Multivariate analysis showed that pre-radiotherapy PSA level measured after 3 months neoadjuvant TAD, age and T stage were significant prognostic factors determining bCR, and distant metastasis-free survival.
Conclusions: Response to neoadjuvant TAD may predict biochemical failure and distant metastasis free survival in patients with prostate carcinoma receiving conformal radiotherapy.

863 POSTER

A phase II study of BAY 43–9006 (sorafenib) in patients with androgen-independent prostate cancer (AIPC)

W. Dahut[1], E. Posadas[1], C. Scripture[1], J. Gulley[1], P. Arlen[1], J. Wright[2], N. Harold[1], S. Fioravanti[1], W. Figg[1]. *[1]National Cancer Institute, Cancer for Cancer Research, Bethesda, USA; [2]National Cancer Institute, Cancer Therapy Evaluation Program, Bethesda, USA*

Background: BAY 43–9006 (sorafenib) is a bis-aryl urea and a potent inhibitor of b – and c – Raf kinase, PDGFR and VEGFR-2. Accumulating evidence suggests that the Ras-Raf-MAPK-ERK signaling pathway is dysregulated in the setting of AIPC. Furthermore, published studies have shown a role for anti-angiogenic therapy for AIPC. We have launched a phase II study to determine the clinical and biological activity of BAY 43–9006 in patients with AIPC.
Methods: Patients are enrolled in an open-label, single arm phase II study. The primary objective is to determine if BAY 43–9006 is associated with a 50% 4 month probability of progression free survival as determined by clinical, radiographic, and PSA criteria. Patients must have good performance status and normal end-organ function. Patients with uncontrolled hypertension and those requiring therapeutic anticoagulation are excluded. All patients are treated with orally administered BAY 43–9006 at a dose of 400 mg bid given continuously on 28-day cycles. Clinical assessment occurs every 28 days with radiographic measurements of disease every 2 cycles. Treatment continues until progression.
Results: This study opened in September 2004 and 19 patients (median age 64 years, range 52–74) have been enrolled to date and all have completed at least 1 cycle of therapy. Grade 3 hand–foot syndrome and grade 3 hypertension have each been noted in 1/19 patients. Drug-related rash has been seen in 3/19 patients and has responded to temporary withdrawal of therapy. Other reported grade 1/2 toxicities include fatigue, flatulence, weight loss, anorexia, body aches, bradycardia, and diarrhea. Fifteen patients are off study due to disease progression. Thirteen patients have been treated for at least 4 months; 5 have exhibited stable disease by both PSA and radiographic criteria.
Conclusions: BAY 43–9006 appears to be well-tolerated in patients with AIPC with a reversible skin rash and hypertension as the most prevalent toxicities. Accrual continues, to better assess the activity and the toxicity profile of this agent.

864 POSTER

Phase II study of BAY 43–9006 (sorafenib) in patients with chemo-naïve hormone refractory prostate cancer

K.N. Chi[1], S. Ellard[2], S. Hotte[3], C. Kollmannsberger[1], P. Czaykowski[4], M. Moore[5], E. Winquist[6], J.D. Ruether[7], B. Fisher[8], L. Seymour[8]. *[1]BC Cancer Agency, Medical Oncology, Vancouver, Canada; [2]BC Cancer Agency, Medical Oncology, Kelowna, Canada; [3]Juravinski Cancer Centre, Medical Oncology, Hamilton, Canada; [4]Cancer Care Manitoba, Medical Oncology, Winnipeg, Canada; [5]Princess Margaret Hospital, Medical Oncology, Toronto, Canada; [6]London Regional Cancer Centre, Medical Oncolgoy, London, Canada; [7]Tom Baker Cancer Centre, Medical Oncology, Calgary, Canada; [8]National Cancer Institute of Canada – Clinical Trials Group, Investigational New Drug Program, Kingston, Canada*

Background: BAY 43–9006 (BAY) is an orally bioavailable multikinase inhibitor of raf, VEGFR-2, PDGFR, c-kit and ret which prevents tumor cell proliferation and angiogenesis in pre-clinical models. Activation of the MAPK and VEGF signaling pathways have been implicated with androgen independent progression of prostate cancer, and therefore provides a rationale for evaluating BAY in patients (pts) with prostate cancer who have progressed after castration therapy.
Methods: Multi-centre, phase II study using a two-stage design. Pts with hormone refractory prostate cancer with or without documented