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

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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

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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

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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