1 = number of abstract – I’ll ask to have CRP added to my monthly bloodtest
2 – I’ll ask to have LDH added to my monthly bloodtest
3 and 4 – Taxotere (docetaxel) + estramustine (3x280 mg/day) better than Taxotere alone
5 – same as 3 and 4, but 3x140 mg/day estramustine equally effective as 3x280 mg, and less toxic
6 – Thalidomide + bevacizumab (Avastin) + Taxotere: works!
7 – Taxotere + Carboplatin works after Taxotere alone stopped working
8 – weekly Taxotere + capecitabine (Xeloda + oral drug) is effective and well-tolerated
9 – Carboplatin + Avastin + Xeloda worked in one patient who did not respond to Taxotere alone
10 – Satraplatin + prednisone is barely better than placebo + prednisone: “at 12 mos, 16% (S+P) and 7% (P) had not progressed”
11 – Decadron (dexamethasone) has synergency with Taxotere, at least in the Petri dish. I don’t take daily prednisone while on chemo, but 2x0.5 mg Decadron. Should I take more?
12 – biweekly Taxotere + 800 mg Celebrex/day works
13 – some patients, not responding to Taxotere, will respond to four estradiol patches – with comments by Dr. Charles Myers (3/3/07)
14 – 8 of 74 patients on Taxotere + estramustine had a PSA ‘flare-up”; did not impact survival
13, 14 & 15: androgen receptor and androgens continue to play a role after patients become hormone-refractory!

1 - C-reactive protein as a prognostic marker for men with androgen-independent prostate cancer (AIPC): Results from the ASCENT trial.
T. M. Beer, et al.

Introduction: Concentrations of blood proteins such as PSA, hemoglobin (HGB), and LDH are associated with survival in men with AIPC. We sought to identify additional blood proteins associated with prognosis in chemotherapy-treated AIPC patients. Methods: Baseline plasma samples were stored (-80°C) from 160 patients enrolled in the ASCENT trial, a randomized placebo-controlled phase 2 trial comparing weekly docetaxel plus DN-101, an oral high-dose formulation of calcitriol, to weekly docetaxel. Multiplex immunoassays measured 16 cytokine/chemokine or cardiovascular/inflammation markers including IL-1a, IL-1ß, IL-2, IL-6, IL-8, IL-10, TNFa, MCP-1, EGF, VEGF, PAI-1, MMP-9, sE-Selectin, sICAM-1, sVCAM-1, and C-reactive protein (CRP). Cox’s proportional hazard model was used to assess association between baseline biomarkers and survival or skeletal-related event (SRE)-free survival, and logistic regression for PSA Working Group Criteria response. Results: Baseline characteristics were similar to those of the 90 patients without samples, except for age (mean 68.0 vs. 70.6 yrs) and HGB (12.8 vs. 12.2 g/dL). CRP was the only biomarker that significantly predicted shorter overall survival (HR 1.41, 95% CI 1.20-1.65, p < 0.0001). When CRP (continuous) was entered into a multivariate model using 13 baseline variables (including PSA, LDH, alkaline phosphatase, HGB, ECOG Performance Status, age) only elevated CRP remained a significant predictor (p < 0.0001) of shorter survival. When categorized as normal (< 8 mg/L) or abnormal (> 8 mg/L), elevated CRP was a significant predictor of shorter survival (HR 2.96 95% CI 1.52-5.77, p = 0.001) as was HGB (p = 0.007). Elevated CRP was also associated with a lower probability of PSA response (OR 0.74, 95% CI 0.60-0.92, p = 0.007) and a shorter SRE-free survival (HR 1.30, 95% CI 1.15-1.48, p < 0.0001).

Conclusions: Elevated levels of plasma CRP appear to be a strong predictor of poor survival and development of SREs in AIPC patients receiving docetaxel-based therapy. The use of CRP as a risk marker and its potential as a surrogate marker of treatment effect should be prospectively evaluated in future clinical trials in advanced prostate cancer.
2 - The prognostic value of change in hemoglobin (HGB), LDH and PSA levels at 3 months from baseline in men with castrate recurrent prostate cancer.
S. Halabi et al.

Introduction: A recent report by Beer et al reported that decrease in hemoglobin (HGB) levels at 3 months was associated with worse clinical outcomes in men with castrate recurrent prostate cancer (CRPC). We asked the question whether changes in HGB, PSA and LDH at 3 months from baseline are associated with shorter survival duration in men with CRPC. Methods: Data from two randomized phase III trials conducted by the Cancer and Leukemia Group B were pooled. Eligible patients had progressive adenocarcinoma of the prostate during androgen ablation (with castrate testosterone levels), an ECOG performance status of 0-2, and adequate hematologic, renal and hepatic function. The primary endpoint for this analysis was overall survival (OS). The proportional hazards model was used to explore the prognostic significance of changes in HGB, LDH and PSA Levels at 3-months from baseline in predicting OS adjusting on treatment arm. Results: The median baseline HGB, LDH and PSA levels were 12.6, 203, and 115. The median change at 3-months from baseline in HGB, LDH and PSA levels were -0.60, -21, and -15.9, respectively. In multivariable analysis, a decrease in HGB levels at 3-months from baseline was statistically associated with an increased risk of death. The hazard ratio (HR) was 1.15 (95% confidence interval (CI)=1.06-1.26, p-value <0.001) for one unit decrease in HGB levels. Moreover, increases in LDH and PSA levels at 3-months from baseline were statistically significant predictors of a poorer OS with HR=1.03 (95% CI=1.01-1.04, p-value= p-value<0.001) and HR=1.08 (95%CI=1.03-1.13, p-value=0.003), respectively.

Conclusions: This multi-center study confirms the data of Beer et al that decreased levels of HGB at 3 months from baseline are associated with shorter survival duration in men with CRPC. We extend those observations and show that increased levels of LDH and PSA are also associated with shortened survival. These results suggest the importance of monitoring changes in HGB, PSA and LDH during treatment as early predictors of survival. Finding other markers with even greater predictive power is a research priority.

3 - Docetaxel (D) ± estramustine (E) as first line chemotherapy for patients (pts) with hormone-refractory advanced prostate cancer (HRPC): Results of a multicentric phase II randomized trial.
O. Caffo et al.

Introduction: D is presently considered a standard treatment for HRPC pts. E has shown a synergistic activity with D in vitro, however the role of D+E combination remains to be defined in the clinical practice. Purpose of this study was to evaluate the activity, in terms of PSA decline (PSA?), the safety and quality of life (QoL) of D±E in HRPC pts. Methods: Eligibility criteria included: HRPC diagnosis, hormone-refractory advanced disease (PSA progression after at least two hormonal therapy), ECOG PS <2, adequate renal, hepatic and hematological functions, no prior chemotherapy. Pts were randomized to D 70 mg/m2 IV d1 q3w (arm A) or D 70 mg/m2 IV d1 q3w + E 280 mg/TID PO starting 1 day prior to D, for 5 consecutive days (arm B). The treatments were planned until best PSA response achievement or PSA progression. Toxicity was recorded according to NCIC criteria. QoL was assessed by self-filled questionnaires during the treatment. Results: Between 04/2003 and 09/2005, 95 pts (median age 69 years, range 48-86, median PSA 80 ng/ml, range 5-2166 and measurable disease in 45) were randomized to arm A (49) or arm B (46). To date, 1 pt is still on treatment in arm A. In arm A, pts received 319 cycles (median 6, range 0-26) with only 13 (4%) delays > 7 days. In arm B, pts received 338 cycles (median 7, range 0-20) with only 16 (4.7%) delays. Median follow-up was 87 weeks. Grade 3-4 hematological toxicities consisted of neutropenia, 4% in arm A and 6% in B. One pt in arm B had febrile neutropenia and grade 3 diarrhea. Grade 3-4 non-hematologic toxicities were vomiting (1 pt in both arms), stomatitis (1 pt in arm A and 2 pts in B) and diarrhoea (1 pt in arm B). Two cases of stroke were reported in arm A. No treatment related death was recorded. Responses, in terms of PSA? >50% were: 40% in arm A and 75% in arm B with PSA normalization in 5% and 32% respectively. Progression free survival (biochemical) was 20 weeks in arm A and 30 in B.

Conclusions: D-based regimens are active in HRPC with a manageable toxicity profile. From this preliminary data, DE combination appears promising, in terms of activity and tolerability so, front-to-front formal comparison in a phase III trial can be recommended.
4 - Does adding estramustine to chemotherapy improve survival in patients with castration-refractory prostate cancer (CRPC)? Results from a meta-analysis on individual data of randomized trials assessing chemotherapy with and without estramustine.

K. Fizazi et al.

Introduction: Estramustine is a mustard-estradiol conjugate, with hormonal and non-hormonal effects. In phase II trials, the response rates of microtubule inhibitors are increased when combined to estramustine. Whether adding estramustine to chemotherapy increases survival in CRPC is still controversial.

Methods: Data from published and unpublished prospective randomized trials assessing chemotherapy + estramustine versus the same chemotherapy alone in CRPC was sought using electronic database searching and hand searching. The primary endpoint was overall survival (OS). The analysis was performed on an intention-to-treat basis. The stratified log-rank test was used. The hazard ratio (HR) for individual trials and for overall comparison was computed using fixed effect model. $\chi^2$ heterogeneity tests were used to test for gross statistical heterogeneity. All p-values are two-sided.

Results: Individual data were obtained from all 5 identified randomized trials conducted in the PSA era having completed accrual before 2004 (n = 605). Chemotherapy (with or without estramustine) consisted of docetaxel (1), paclitaxel (1), ixabepilone (1), and vinblastine (2). With a median follow-up of 2.8 years, 512 deaths had occurred. Time to progression (TTP) was significantly improved in the chemotherapy + estramustine arm (HR = 0.74; 95% CI [0.58-0.94]; p = 0.01). OS was also significantly better in the chemotherapy + estramustine arm (HR = 0.81; [0.68-0.97]; p = 0.02). The estimated 18 month OS rates were 43% and 35% in the chemotherapy + estramustine arm and in the chemotherapy alone arm, respectively. In multivariate analysis, hemoglobin (p = 0.0001), chemotherapy + estramustine (p = 0.008), performance status (p = 0.002), and serum PSA (p = 0.04) were independently associated with OS.

Conclusions: Adding estramustine to chemotherapy significantly improves both TTP and OS as compared to chemotherapy alone in patients with CRPC.

5 - Randomized study of docetaxel (D) and dexamethasone (DX) with low- or high-dose estramustine (E) for patients with advanced hormone-refractory prostate cancer (HRPC).

F. Reiher et al.

Introduction: D-based chemotherapy is a burgeoning option for men with advanced HRPC. Alone or in combination with E, D has been shown to improve median survival. Here we tested the combination of D with two different doses of E in pts. with HRPC to improve response rates and to lower side effects.

Methods: 72 metastatic HRPC pts were assigned to receive D (70mg/m2 IV, d2, q3w) and E (3 × 280 mg/d PO starting 1 day prior to D, for 5 consecutive days) for arm A or E (3 × 140 mg/d PO starting 1 day prior to D, for 3 consecutive days) for arm B. Initially, 6 cycles were administered. Chemotherapy was restarted after significant PSA rise. Patients were monitored for measurable PSA response, time to progression, survival and toxicity.

Results: PSA declines of >75%, >50% and <50% were 36.8%, 55.3% and 44.7% in arm A and 38.2%, 67.6% and 32.4% in arm B, respectively (P=.442). TTP in arm A and arm B were 11 months (95% CI, 7-14) versus 14 months (95% CI, 8-19), P=.6911) and overall survival 21 months (95% CI, 6-35) versus 22 months (95% CI, 18-27), respectively, (P=.4149). The primary treatment-related side effects observed in arm A and arm B were granulocytopenia (34% and 29%, P=.663) and thrombotic complications caused by E (four pts (11%) and one pt (3%), respectively, P=.206). Associated baseline factors with overall survival in univariate analysis were ECOG performance status (P<.001), hemoglobin level (P<.001), bone pain (P<.001), and PSA (P<.097) and in multivariate analysis ECOG performance status (95% CI, 2.9-13.9) and bone pain (95% CI, 3.2-20.1), (P<.001).

Conclusions: The combination of docetaxel and estramustine had substantial activity in patients with HRPC. No statistically significant difference exists between high and low dose estramustine in combination with docetaxel regarding PSA response, time to progression and survival. Tendency of higher toxicity in the high dose estramustine arm. In patients with ECOG performance status 2 high dose estramustine leads to a shorter survival compared to the low dose group. Independent prognostic factors in multivariate analysis were ECOG performance status and bone pain at presentation.
6 - Phase II trial of thalidomide, bevacizumab, and docetaxel in patients (pts) with metastatic androgen-independent prostate cancer (AIPC). 
Y. M. Ning et al.

Introduction: Angiogenesis plays a vital role in the progression of prostate cancer. Antiangiogenic agents thalidomide (T) and bevacizumab (Bv) may enhance docetaxel (Doc) activity in metastatic AIPC. However, T and Bv have different antiangiogenic mechanisms. Since tumor angiogenesis is a complex interplay of multiple angiogenic factors, we reasoned that combination of mechanistically different antiangiogenic agents T and Bv with Doc might be associated with an adequately high and durable PSA response to merit further study. Methods: Pts are required to have progressive metastatic AIPC and no prior chemotherapy for AIPC. Treatment consists of Doc 75 mg/m2 plus Bv 15 mg/kg days 1, q 21 days as a cycle (C), plus T 200 mg qhs and prednisone 10 mg qd. Enoxaparin is used for thrombosis prevention and pegfilgrastim initiated after detection of grade >3 neutropenia. PSA is assayed q C and staging studies are done at C 0, C 2, & then q 3 Cs. Results: 33 pts were enrolled, median age 67 [54-79], Gleason score 8 [76% Gs 10~8, 24% Gs 7~6], on-study PSA 87 ng/ml [7.7-4,399] and pre-study PSA doubling time 1.6 months [0.7-18.2, 88% <3 month]. Median treatment Cs is 17 [3-25]. 28 pts (85%) had PSA declines of >50%, with median >50% PSA duration 12 Cs [0~23]. 3 pts have PSA declines around 40% and 2 stable. 23 pts (70%) had >80% PSA declines. 14 pts with measurable disease were evaluable: 1 CR, 8 PR, & 5 SD, with 64% ORR. Significant toxicities: febrile neutropenia (4/33), syncope (3/33), colon perforation or fistula (2/33), grade 3 bleeding (2/33), thrombosis (2/33).

Conclusions: This trial is the first study to combine antiangiogenic agents of different mechanisms with Doc in metastatic AIPC. Most of the accrued patients have unfavorable characteristics as evidenced by a high Gleason score and a rapid PSA doubling time. However, the combination of T and Bv with Doc appears to result in both a high durable PSA decline rate (85%) and a high response in measurable disease (64%) with acceptable toxicities. The trial has proceeded to the second stage of the study to better delineate the activity and toxicity of this combination.

7 - A phase II trial of docetaxel plus carboplatin in hormone refractory prostate cancer (HRPC) patients who have progressed after prior docetaxel chemotherapy.
W. K. Oh et al.

Introduction: Treatment options for HRPC patients who progress after docetaxel chemotherapy are limited. Carboplatin may enhance the efficacy of docetaxel chemotherapy. Methods: We prospectively treated HRPC patients with documented PSA or radiographic progression during a minimum of 2 cycles of docetaxel-based chemotherapy or within 45 days of completing therapy. No prior platinum was allowed. Patients received docetaxel 60 mg/m2 and carboplatin AUC (4) every 21 days until progression or unacceptable toxicity. Measurable response was assessed by RECIST criteria. PSA declines were assessed per PSA Working Group. 5 patients were not evaluable for PSA response as they received only 1 cycle but are included in the denominator. Results: Thirty-four patients were treated. Median age was 68 years (range 47-81), 94% white. Baseline performance status was 0 or 1 in 85%. Prior therapies included antiandrogens (30%) and ketoconazole (52%); docetaxel was used alone (64%), with estramustine (36%) or another agent (0%). Median PSA at baseline was 189 ng/ml (range 12-4,466). Patients received a median of 4 cycles of docetaxel/carboplatin (range 1-12). PSA declines of >50% were noted in 6 of 34 patients (18%, 95% C.I. 7-35%). Median duration of PSA response was 7.4 months (95% C.I. 2.8-7.4 months). In addition, 10 patients had SD for a minimum of 2 months, suggesting an overall clinical benefit (PR+SD) in 47% (95% C.I. 30-65%). Of 21 patients with measurable disease at baseline, 3 (14%; 95% C.I. 3-36%) had confirmed PR. Therapy was well tolerated, with no treatment-related deaths and mostly mild to moderate toxicities, including anemia, leukopenia and hyperglycemia. Median time to progression was 4.3 months (95% C.I. 2.3-5.6 months); median survival was 12.4 months (95% C.I. 7.0-17.0).

Conclusions: Docetaxel plus carboplatin demonstrated clinical activity in patients who definitively progressed after docetaxel-based therapy. PSA declines >50% were seen in 18%; measurable responses in 14%. Analysis of response to serum markers of neuroendocrine differentiation (CGA, NSE) is ongoing and will be presented.
8 - Phase II trial of docetaxel and capecitabine combination in metastatic androgen independent prostate cancer (AIPC).
U. N. Vaishampayan et al.
Introduction: Docetaxel-based chemotherapy has demonstrated survival benefit in metastatic AIPC. Combination of docetaxel- capecitabine demonstrated synergistic anti-tumor effect attributable to docetaxel-mediated up-regulation of thymidine phosphorylase (TP). A phase II trial was conducted to assess efficacy and tolerability of weekly docetaxel and capecitabine in metastatic AIPC. Methods: Patients with metastatic AIPC with no prior chemotherapy for metastatic disease were treated with docetaxel 36 mg/m2/week IV on days 1,8, and 15 and capecitabine 1,250 mg/m2/day in two divided doses on days 5-18 in 28-day cycle. Response assessed every 2 cycles. Primary end point was response rate. Results: 30 patients (28 r-e) have been accrued to complete the trial. Patient characteristics included median age of 69 years (range 47-80 years); 10 patients of African American ethnicity, 19 Caucasians, and 1 Hispanic. Median performance status was 1, and median PSA at study entry of 60.6 ng/ml (range 1.2-3,716.9); Of the 30 patients, 20 had bone pain pretherapy; Gleason score > 8 in 18; 12 had measurable disease; 18 had progression of bone metastases; and all patients had PSA progression.132 cycles have been administered (median 4, range 1-10 cycles); 6 patients continue on therapy. All patients are assessable for toxicity, and 27 of 28 are r-e. Severe toxicities noted were Grade 4 neutropenia in 1 patient and Grade 3 hand-foot syndrome in 2 patients. There were no treatment related deaths. A PSA partial response (PR) defined as > 50% decline sustained for at least 4 weeks was observed in 19/27 (71%) with >90% PSA decline in 8/27 (30%) patients. PR per RECIST noted in 5/10 (50%) evaluable measurable-disease patients. Follow up for survival and progression is ongoing and will be reported. Studies are being conducted to evaluate TP overexpression and correlate with response and outcome.
Conclusions: Capecitabine with weekly docetaxel is well tolerated and demonstrated favorable efficacy in metastatic AIPC. TP overexpression induced by docetaxel could be utilized as a potential therapeutic target in advanced prostate cancer.

9 - Durable response to the combination of carboplatin/capecitabine with bevacizumab in a patient with metastatic hormone refractory prostate cancer resistant to docetaxel-based chemotherapy.
S. Wu, S. Madajewicz
Introduction: Docetaxel in combination with prednisone every three weeks is the current standard therapy for patients with metastatic androgen-independent prostate cancer (AIPC). When these patients are not responsive to the taxane-based chemotherapy, very limited treatment options are available. Methods: One patient with metastatic AIPC to bone and lung lymphangio-carcinomatosis following progression after a docetaxane-based chemotherapy was treated with carboplatin (area under the curve of 5) plus capecitabine (875 mg/m2 orally twice daily 2 weeks on/one week off) and bevacizumab (10 mg/kg) every three weeks. Results: Prostate-specific antigen levels decreased by > 95% (from 243.16 to 9.77 ng/ml) over a 12 month period, and were associated with decreasing level of alkaline phosphotase. Chest X-ray and CT scan were also normalized. The treatment was well tolerated. Noticeable treatment related side effect includes anemia, which responded to darbopoietin injection. The patient received a total of 12 cycles of the combination, and currently is treated with bevacizumab as a single agent. Conclusions: This case has demonstrated a durable response with carboplatin plus capecitabine in combination with bevacizumab for a patient with disease progression after the taxane-based chemotherapy. A clinical trial to evaluate this regimen is warranted.

10 - A phase III, randomized, double-blind trial of satraplatin and prednisone vs placebo and prednisone for patients with hormone refractory prostate cancer (HRPC).
D. P. Petrylak et al.
Introduction: Satraplatin (S) is a novel oral platinum compound that has demonstrated antitumor activity in a variety of tumors, including HRPC. We recently completed enrollment to a randomized phase III trial (SPARC) which evaluated S as second-line therapy for HRPC. Methods: The primary objective of this double-blind randomized trial was to compare progression-free survival (PFS) in patients (pts) with HRPC receiving either S + prednisone (S+P) or placebo + P, after failure of 1 prior chemotherapy regimen. Eligible pts included men > 18 years with stage D2 HRPC. After stratification by
performance status, pain index (PPI), and type of progression (PSA only vs. others), pts were randomized 2:1 to S (80 mg/m² qd × 5 q5w) + P (5 mg BID qd) or to placebo + P (same schedule). Progression was based on either radiologic progression, symptomatic progression, skeletal events or death. All disease progression events were adjudicated by an independent review committee. All analyses were conducted on an intent-to-treat basis. The results of SPARC can be compared to the previous randomized trial conducted by the EORTC comparing (S+P) to prednisone alone as first-line therapy in HRPC. Fifty patients were accrued prior to its early termination. The median PFS was longer in the (S+P) arm than in the P alone arm (p = 0.023) (Sternberg, Oncology 2005; 68: 2-9).

Results: 950 pts were accrued to the SPARC study over a period of 28 mos. Pts in the S arm had a 40% reduction in the risk of disease progression (HR = 0.6; 95% CI: 0.5-0.7) compared with pts in the Placebo arm. Improvement seen in PFS by S+P pts increased over time. At the median, S+P pts had a 13% improvement in PFS compared to the P group (11 vs 9.7 weeks). At the 75th percentile, there was an 89% improvement in PFS (36 vs 19 wks). At 6 months, 30% (S+P) and 17% (P) of pts had not progressed; at 12 mos, 16% (S+P) and 7% (P) had not progressed. The most common toxicities were myelosuppression (thrombocytopenia, neutropenia) and GI (nausea/vomiting, diarrhea), which were generally mild to moderate.

Conclusions: Satraplatin is a highly effective oral agent, with a favorable safety profile, which could be a valuable treatment option for pts with advanced HRPC.

11 - Dexamethasone enhances the anti-angiogenic activity of docetaxel in prostate cancer cell lines.

P. Scullin et al.

Background: Two randomised clinical trials have demonstrated improved median survival in men with metastatic hormone refractory prostate cancer (HRPC) treated with docetaxel + prednisolone compared to mitoxantrone + prednisolone. Interestingly, patients in the docetaxel arms of both studies received additional glucocorticoids when compared to those treated with mitoxantrone (24 mg additional dexamethasone per cycle of treatment). Recently, dexamethasone has been shown to inhibit angiogenesis and decrease the expression of the pro-angiogenic chemokine interleukin-8 (IL-8) in a prostate cancer xenograft model. Therefore, we hypothesize that the clinical benefit of docetaxel therapy may be in part explained by the ability of dexamethasone to enhance the established anti-angiogenic effects of taxanes. Methods: All work was carried out in the PC-3 and LNCaP cell lines. NFκB transcriptional activity was assessed by luciferase assay and IL-8 expression by real time PCR. Cell viability was determined using a MTT assay. Angiogenesis was assessed using the Angiokit assay. Results: We have shown that dexamethasone (10nM) suppresses NFκB transcriptional activity in the AIPC cell line PC3 and IL-8 synthesis by these cells. We looked at the effect of dexamethasone on proliferation of PC-3 and LNCaP cells and showed no effect. Similarly dexamethasone had no effect on the cytotoxicity of docetaxel in PC-3 and LNCaP cells. While dexamethasone alone had no anti-angiogenic activity at a concentration of 10nM, co-administration of docetaxel 1nM plus dexamethasone 10nM significantly decreased mean vessel area (p=0.0077) and mean vessel length (p=0.0038) when compared to docetaxel 1nM treatment alone.

Conclusion: Dexamethasone enhances the anti-angiogenic activity of docetaxel possibly through suppression of NFκB and IL-8 activity. Further study of the role of corticosteroids in conjunction with docetaxel is required.

12 - Preliminary results of biweekly docetaxel in combination with celecoxib in hormone refractory prostate cancer.

C. Pfister et al.

Background: The aim of this phase II open, multi-center study was to assess the efficacy and tolerance of docetaxel administered every 15 days, in combination with celecoxib, in patients with hormonal refractory prostate cancer (HRPC). Material and Methods: 48 patients were included in the study, mean age 70.4 years with an average Gleason score of 7.5, satisfactory Karnofsky performance-status score of 90% and a metastatic bone site measurable in 80% of cases. The mean delay between initial diagnosis and first administration of docetaxel was 45 months, with a mean total PSA progression of 54.8 ng/ml. The therapeutic schedule was docetaxel 50 mg/m² administration every 15 days, one cycle
corresponding to 2 injections at a 2-week interval (D1 = D28) with a total of six cycles and simultaneously a daily oral fixed dose of celecoxib 800 mg.

Results: 237 cycles of docetaxel were administrated with dose reduction observed: 23 cases at D1, 36 cases at D15. The hematological toxicity was grade 1-2 for anemia, only 10% of grade 3-4 for neutropenia. As regards clinical benefit, 13.5% of positive effects on pain intensity was observed. The response rate for total PSA was 45.5% (30.4%–61.1%), with a mean time to progression estimated at 9.5 months and a tumor response rate estimated at 26.3%. A total of 75% of patients had a global survival estimated at higher than 14.6 months.

Conclusions: Our results confirm the usefulness of docetaxel in the treatment of HRPC and suggest significant impact of celecoxib in combination with biweekly docetaxel chemotherapy schedule on safety and efficacy tumor response.

13 - Clinical activity of transdermal estradiol in patients with hormone and chemotherapy refractory prostate cancer.

M. N. Stein et al.

Background: Oral estrogens are an effective treatment for metastatic hormone refractory prostate cancer but are not used because of an increased cardiovascular risk, particularly thromboembolism. Use of alternative formulations that bypass first pass metabolism may be safer and more effective. Therefore, we evaluated the anticancer safety and efficacy of transdermal estradiol (TDE) in patients with hormone refractory prostate cancer. Materials and Methods: Patients with metastatic prostate cancer who had progressed on hormonal therapy and at least one chemotherapy regimen that included docetaxel (median of 2 prior regimens, range 1-5) were treated with four TDE 0.1 mg/24 hour patches which were changed every 7 days until disease progression or unacceptable toxicity occurred. Serum prostate-specific antigen (PSA) levels were followed at regular intervals. End-points included PSA response, measurable disease response, time-to-progression (TTP), toxicity and quality of life. Results: In this ongoing trial, two patients out of eleven had a PSA response (confirmed PSA decline by > 50%). In five of the nine patients who did not have a > 50% biochemical response to therapy, the PSA level declined between 2.1% and 25.4%, with a median of 19.9%. Two of the eleven patients have continued on study and are on week 9 and week 14, respectively. For the remaining nine patients who are now of study, the TTP ranged from 4 to 19 weeks, with a median duration of 8 weeks. Treatment toxicity included grade 1 nausea, breast enlargement/ tenderness and/or leg edema in six patients. No thromboembolic or cardiovascular events occurred.

Conclusions: Early analysis of this ongoing study reveals modest antitumor activity of TDE with minimal toxicity in heavily pretreated patients with hormone refractory prostate cancer.

Dr. Myers commented in the HRPCa mailing list as follows:

“Based on what I have seen, it is pure idiocy to use a fix number of patches when there is such a huge range in estradiol bioavailability between patients and even in each patient over time. Also, they have severely under dosed. Poorly done study, especially when Ockrim's initial study already specified the target blood level concept. This study should never have received IRB approval, should never have been funded and should never have been accepted for publication. Sloppy.” (3/3/07).

Dr. Myers had a similar criticism two years earlier, on another abstract, also in the HRPCa mailing list:

“The dose they used is far too low to see much activity. I have been following the protocol as per the Ockrim paper, adjusting the number of patches needed to attain 900 estradiol level. It takes at least 4 patches and may take 8-12. Each patch is 0.1 mg per day. These folks just used two 0.1 mg patches.

This is one of my favorite beefs about the literature. Ockrim published a clear formula for success. Now others proprot to try and duplicate it, but really do not. They modify doses, etc. Then when they do not get the same results, rather than see the error of their ways, they say the original paper is bogus. Just crazy.

What Ockrim did was really quite unusual and I wonder what was behind their decision to go so high in dose? In any case, it is clearly needed for success.” (4/26/05)
14 - Impact of PSA flare-up under the combined treatment with docetaxel and estramustine in patients with hormone-refractory prostate cancer.

T. Nelius et al.

Introduction: The intention of this study is to describe the impact and underlying potential basis of the PSA flare-up phenomenon in patients with hormone-refractory prostate cancer (HRPC) treated with docetaxel-based chemotherapy. Methods: We retrospectively identified 74 consecutive patients who received docetaxel/estramustine-based chemotherapy at our institution. Patients were evaluated based on modified criteria from the Prostate-Specific Antigen Working Group regarding survival and toxicity. Additionally, 2 androgen receptor mutations derived from patients with advanced disease were analyzed for promiscuous transactivation activity. Results: The 74 patients were stratified into 4 groups: Response, Partial Response, Flare-up-initial PSA elevation, Progression. Median survival in the flare-up group (n=8) was 20 months and did not differ from the response group (p=0.564). The flare-up group showed a maximum PSA elevation from baseline between 3.4% and 28.3% (between 3 and 6 weeks) followed by PSA decline >50% from the baseline level in 7 of 8 patients. The androgen receptor mutations AR877 and AR715 displayed a 37.5- and 5.2-fold increase in transactivation activity by progesterone and a 12.6- and 5.4-fold increase by estrogen compared to the ARWT, respectively. Conclusions: A considerable portion of HRPC patients experience an initial PSA flare-up under systemic chemotherapy. In this study, occurrence of flare-up phenomenon did not impact survival. Chemotherapy should be continued a minimum of 6 weeks before removing patients from a docetaxel-based regimen. We showed evidence that the co-medication with dexamethasone/prednisolone and/or estramustine itself can induce an initial PSA flare-up via androgen receptor mutations.

15 - Activity of dutasteride plus ketoconazole in hormone-refractory prostate cancer (HRPC) after progression on ketoconazole alone.

A. O. Sartor et al.

Introduction: Ketoconazole is commonly used as a secondary hormonal therapy in patients with hormone-refractory prostate cancer (HRPC), but disease progression typically occurs after a median of 3-4 months. In patients with HRPC, both prostatic (Titus et al., Clin Cancer Res 11:4365) and metastatic (Stanbrough et al., Cancer Res 66:2815) lesions are known to over-express type I but not type II 5-alpha reductase (SRDA5). Knowing that many cancer cells derived from HRPC patients are actually hypersensitive to androgen stimulation, we hypothesized that inhibition of SRDA5 enzymes in combination with ketoconazole would mitigate progression after treatment with ketoconazole alone. Methods: Ten HRPC patients with PSA progression after 600-1,200 mg/day ketoconazole treatment were treated with the same dose of ketoconazole plus dutasteride (0.5 mg po q day). Results: All patients had previously received and continued to receive medical or surgical castration; median age was 69.8 years (range 49-81); 7/10 patients had radiographically and/or pathologically documented metastatic disease; median duration of prior ketoconazole treatment was 7.7 months (range 3.7-24.2); median PSA at dutasteride initiation was 5.3 ng/ml (range 0.5-80.7). After dutasteride addition, eight patients (80%) achieved various degrees of PSA decline. Though the median PSA decline was only 16.5% (range 0-39.8%), median progression-free survival was 4.9 months (range 2.7+ to 9.8 months). Progression in all but one patient was manifested by a rising PSA. One patient had radiographic progressive disease. No dutasteride-treated patient achieved a 50% decline in PSA. No radiographic responses were recorded. No significant adverse events were encountered. Conclusions: Dutasteride in combination with ketoconazole is associated with delays in PSA progression in HRPC patients experiencing PSA progression after ketoconazole alone. Additional studies using a combination of ketoconazole and dutasteride are ongoing in a prospective multicenter phase II trial.