Conclusion: These data suggest safety and promising efficacy of oxaliplatin and pemetrexed for 2nd and 3rd line treatment of CRPC, with a majority of patients achieving stable disease or better.

7028 POSTER

Dasatinib and docetaxel combination treatment for patients with metastatic castration-resistant prostate cancer (CRPC): analysis of Study CA180−086

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Background: SRC and SRC-family kinases (SFK) play a key role in proliferative, invasive, and bone-metastatic processes in solid tumors. Dasatinib (Bristol-Myers Squibb) is a potent SRC and SFK inhibitor that inhibits prostate cancer cell proliferation and migration *in vitro*. In clinical studies, dasatinib treatment was associated with downregulation of osteoclast activity and bone turnover. Following preliminary reports from Study CA180−086 (ASCO 2009, abs. 5061), we report an intent-to-treat analysis for dasatinib and docetaxel combination treatment 5 months after completion of accrual.
Methods: CA180−086 is a phase 1/2 study in men with CRPC progressing despite castrate levels of testosterone (⩽50 ng/dL) and requiring chemotherapy. Patients (pts) (phase 1) received dasatinib 50–120 mg once daily (QD) and docetaxel 60−75 mg/m^2 every 21 days (Q21D), with selected doses of dasatinib 100 mg QD plus docetaxel 75 mg/m^2 Q21D and prednisone 5 mg twice daily administered to all pts enrolled in phase 2. Bisphosphonate continuation was permitted but anti-androgens were discontinued. Responses were determined according to PSWG2 criteria. To assess bone turnover, urinary N-telopeptide (uNTX) and serum bone alkaline phosphatase (BAP) levels were measured.
Results: At the time of analysis, median treatment duration was 4.8 mos (range 0.1−9.6) and 18/46 treated pts remain on therapy. The most common grade 1/2 adverse events (AEs) were fatigue, dysgeusia, and GI and skin disorders. A grade 3 AE was reported in 9 pts and a grade 4 AE in 2 pts. A prostate-specific antigen (PSA) response was observed in 21/43 evaluable pts (49%). Bone scans showed reduction in size and number of lesions in 11/39 (28%) pts and stable lesions in 27 (69%) pts (n = 8 at ≈6 wks; n = 6 at ≈12 wks; n = 6 at ≈18 wks; n = 5 at ≈24 wks; n = 2 at ≈30 wks). Of 31 pts with RECIST-evaluable lesions, best response was: partial response (PR) in 14; unconfirmed PR in 4 (still on study); stable disease in 12 (6−21 wks); and progressive disease in 1 pt. Of pts evaluated for bone markers, 17/34 (50%) had a ⩾35% uNTx decrease (2 received bisphosphonates) and 24/32 (75%) had a BAP decrease from baseline (9 received bisphosphonates).
Conclusions: Dasatinib and docetaxel treatment is well tolerated. These promising data, showing modulation of bone markers and PSA at a higher-than-expected rate, support combined anti-tumor and anti-osteoclast targeting and serve as the basis for the ongoing phase 3 study of this combination.

7029 POSTER

CYP17 gene polymorphism in prostate cancer

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Background: The cytochrome P450c17a mediates both steroid 17a-hydroxylase and 17, 20-lyase activities and functions at key steps in the genesis of human sex steroid hormones. The 5′-untranslated promoter region of the *CYP17* gene contains a polymorphic T-to-C substitution that gives rise to *A1* (T) and *A2* (C) alleles. The *CYP17* polymorphism may play a crucial role in the etiology of hormone-related cancers such as prostate cancer and breast cancer. The aim of our study was to investigate the distribution of the *CYP17* genotype between a control group and prostate cancer patients.
Material and Methods: Blood samples from 200 subjects (mean age 59.5±7.4 years, range 50 - 78 years) were obtained from healthy, unrelated subjects. A total of 195 prostate cancer patients (mean age 67.0±8.2 years, range 50−85 years) with histologically verified prostate cancer were invited to participate in the project. Both patients and controls were interviewed regarding age, smoking habits, drinking habits, possible chemical exposure, previous and/or current prostate diseases, incidence of cancer and chronic diseases. PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism analysis) was used to detect *CYP17* polymorphisms. The χ^2 method was used to test frequencies of genotypes/allele in prostate cancer patients and controls.
Results: The frequency of the *A2* allele was similar in cases and controls. Compared with men with the *A1*/*A1* genotype, the adjusted odds ratio was 1.06 (95% CI = 0.68 to 1.64) for the *A1*/*A2* and 0.66 (95% CI = 0.37 to 1.20) for the *A2*/*A2* genotype. The multivariate analysis confirmed the association between PSA levels and *CYP17* genotypes (*A1*/*A1 vs. A1*/*A2; A2*/*A2*). Prostate cancer patients with PSA levels (4−10 ng/ml) and *A1*/*A2; A2*/*A2* genotypes had an excess risk to develop prostate cancer (OR = 2.84, 95% CI = 1.06 to 7.62; OR = 3.15, 95% CI = 0.75 to 13.3, respectively).
Conclusions: These results suggest that the *CYP17 A1*/*A2* and *A2*/*A2* genotypes predict susceptibility to prostate cancer in men with serum PSA levels above 4 ng/ml. It is also possible that *CYP17* interacts with other genes that influence risk of prostate cancer.
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7030 POSTER

Dose finding and safety analysis of inecalcitol in combination with docetaxel-prednisone regimen in hormone-refractory prostate cancer (HRPC) patients (pts)

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Introduction: Inecalcitol is a novel synthetic vitamin D3 analogue with potent antiproliferative effects in human cancer cell lines and a 100-fold lower hypercalcemic activity than calcitriol in animal models.
Methods: In this study, escalating dosages of inecalcitol was combined to chemotherapy in naive HRPC pts. Safety and efficacy were evaluated in groups of 3−6 patients receiving inecalcitol daily or every other day on a 21-day cycle in combination with docetaxel (75 mg/m^2 q3w) and oral prednisone (5 mg bid). Biphosphonates were prohibited during the first cycle. Patients received up to six cycles unless unacceptable toxicity or disease progression. Primary endpoint was dose limiting toxicity (DLT) defined as grade 3 hypercalcemia within the first cycle. Calcemia, creatininemia and CBC were assessed weekly; biochemistry, ECG and PSA every 3 weeks. Efficacy endpoint was PSA response defined as ⩾30% decline within 3 months.
Results: Five dose levels: 40, 80, 160, 300, 600 μg have been evaluated in 34 pts; 9 pts are still being treated at 600 μg; 25 pts have completed 6 cycles (13 bone metastases; 3 extrasqueletic metastasis, 8 bone and extrasqueletic metastases; 1 PSA-only disease). Median age was 72 years [range 53−87], median Gleason score (Gs) 7 [36% Gs 10−8, 64% Gs 7−6] and median PSA 41.5 ng/mL [range 0.9−962.4]. No increased calcemia was reported. Most adverse events (AE) were G1−2, asthenia (19pts), constipation (14pts), diarrhea (13pts). G3−4 AEs were neutropenia (11pts) lymphopenia (9pts), asthenia (3pts), arrhythmia (2 pts), general health deterioration (2pts) and diarrhea (1pt). None of these AEs was considered related to inecalcitol. Of the 23 evaluable pts for PSA response, 20 (87%) had ⩾30% PSA decline.
Conclusion: Results from this ongoing study show the safe toxicity profile of inecalcitol when given daily in HRPC pts. PSA responses with this combination are encouraging. As DLT was not reached, higher dose of inecalcitol (1000 μg/day) are being tested.

7031 POSTER

The impact of neoadjuvant and concurrent MAB for intermediate & high risk localized prostate cancer treated with IMRT

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Background: The sensitivity to hormonal therapy in Japanese prostate cancer patients is though to be much higher than that in other countries.

The purpose of this study is to evaluate the impact of neoadjuvant & concurrent MAB for intermediate & high risk prostate cancer patients.
Materials and Methods: Between Sep 2000 and Sep 2007, 163 localized prostate carcinomas (T1-T3, N0M0) were treated with neoadjuvant (3−6 months) and concurrent (2months) hormonal therapy. Maximum androgen blockade (MAB) was used as hormonal therapy. There were 101 high risk and 62 intermediate risk group patients. Initial PSA level was ranging 4.0−246 ng/ml (median: 26.5 ng/ml) and Gleason score was ranging 4−10 (median: 7). IMRT was delivered with SMLC-IMRT technique using a 2 Gy/fraction to a total dose of 76 Gy. GTV was defined as prostate and CTV was defined as GTV+ seminal vesicles. PTV margin 7 mm around the CTV except for posterior direction. Posterior margin was 5−6 mm. We used 3-gold markers for localization. After radiation therapy, no further hormonal therapy was used until PSA failure. The PSA failure definition was done according to Phoenix criteria. The follow-up interval was every 3months. We evaluate the PSA failure free (PFF) survival rate, Overall survival rate (OS) and acute and late sequelae by NCI/CTV (version 3.0).
Results: The PFF at 5years of intermediate and high risk group were 100%, 92.3%, respectively. The OS at 5 years of each group were 100%, 95.4%, respectively. The cause of death was another cancer (lung, esophagus, stomach). Acute Grade 1−2 urogenital and gastrointesitinal sequelae was observed in 70%, 5.2%, respectively. No grade 3 acute sequelae was observed. Late Grade 1 urogenital and gastrointestinal sequelae were observed in 11%, 3.3%, respectively. Grade 3 urethral stricture was observed in 2 patients. All of them recovered after bougie. No grade 2 or higher rectal complication was observed.
Conclusion: In Japan, according to our 5 year results of short course (5−9 months) neoadjuvant and concurrent MAB with 76 Gy irradiation would be effective for intermediate & high risk prostate cancer patients at 5 years. Longer follow-up might be necessary.

7032 POSTER

The effects of high-dose-rate brachytherapy combined with external beam radiation therapy in patients with prostate cancer

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Purpose: To determine the effects of high dose rate brachytherapy (HDR-BT) combined with external beam radiation therapy (EBRT), and to evaluate the early and late sequelae.
Patients and Methods: From April 2002 to December 2008, 92 patients with prostate cancer were treated with HDR-BT combined with EBRT. Patients were stratified into three groups: low-risk [20 patients (pts.)](GS: 2−6, PSA $\leqslant$ 10, T1c-T2a), intermediate-risk [24 pts.] (GS: 7, PSA 10−20, T2b-T2c), and high-risk [48 pts.] (GS: 8−10, PSA$\geqslant$20, T3). In all patients EBRT was performed before HDR-BT. Patients in low-risk group, intermediate-risk, and high-risk group were delivered 40 Gy/20 fractions/4 weeks, 46 Gy/23 fractions/4.6 weeks, and 50.4 Gy/28 fractions/5.6 weeks respectively, using a four field technique with a 10 MV photon beam. One to six days after the completion of EBRT, HDR-BT was performed with 18−19.5 Gy/3 fractions/2 days. Clinical Target Volume (CTV) was determined 3−5mm outside the periphery of the prostate. Proximal part of the seminal vesicle was also included in the CTV in patients with T3. More than 95% of the prescription dose was delivered to the CTV.
Results: The median follow-up was 43 months. Biochemical failure (PSA failure) according to the Phoenix definition (nadir + 2 ng/ml) was 0 (0%), 2 (8.3%), and 4 (8.3%) in low-, intermediate- and high-risk group, respectively. Overall survival rate was 96.7% and cause specific survival rate was 100%. Early sequelae were evaluated according to the Common Toxicity Criteria (CTC)-ver 3.0. Early genitourinary toxicity of grade 1, grade 2, and grade 3 was observed in eight, two and one patient, respectively. All the patients recovered from early toxicity within 12 months. Only one patient who had been previously undertaken TURP suffered from late toxicity (urinary tract stricture), and the patient had urinary tract dilatation. There was no early and late rectal damage.
Conclusions: HDR-BT combined with EBRT is also applicable to intermediate- and high-risk group patients in addition to low-risk group patients with prostate cancer. Biochemical failure and early and late sequelae were acceptable. Especially, HDR-BT had the advantage of avoiding rectal toxicity.

7033 POSTER

Five-year results of disease control and quality of life analysis of a combined hypofractionated radiation and hormone therapy regimen for intermediate-risk prostate cancer

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Background: The aim of this analysis is to evaluate the chronic toxicity, efficacy and quality of life associated with a treatment of hypofractionated radiation combined with a short course of hormone therapy for intermediate-risk prostate cancer in a phase II trial.
Materials and Methods: Forty two patients with intermediate-risk prostate cancer were recruited. Patients received neoadjuvant and concomitant hormonal therapy consisting of a single injection of an LHRH agonist together with an oral non-steroidal anti-androgen medication for the first month. The radiation regimen of 57 Gy in 19 fractions over 4 weeks started 8 weeks after the injection. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0 toxicity scale. Quality of life was assessed yearly from the second year onward using a French version of the Expanded Prostate Cancer Index Composite (EPIC) questionnaire.
Results: The 60-month biochemical progression free survival obtained by Kaplan-Meier analysis was 80.5%. No grade 3 or more toxicity was reported. Grade 1 and 2 urinary and gastro-intestinal toxicities were each present in 10% of cases. Erectile dysfunction was present in 76% of patients; however, the problem was present before initiation of therapy in 41% of them. Other hormonal/sexual toxicities were reported by 10% of patients. At a median follow-up of 72 months the mean scores for all domain summaries of the EPIC questionnaire were excellent, above 95, except for the sexual summary score which was 33.2. Of the patients who had a normal level of testosterone at the start of the study, 40% did not recover a normal level of testosterone at a median follow-up of 72 months.
Conclusions: Hypofractionated radiotherapy associated with a short course of hormonal therapy is a well tolerated and effective treatment for intermediate-risk prostate cancer. Moreover, this approach allows for an excellent long term quality of life, except for the presence of erectile dysfunction. Upcoming phase III trials will enlighten us further on the treatment of choice for these patients.

7034 POSTER

IORT and radical prostatectomy for high-risk prostate cancer: a feasibility study

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Background: To explore the feasibility of intra-operative radiotherapy (IORT) in patients affected by high-risk prostate cancer and candidates for radical prostatectomy.
Material and Methods: Thirty eight patients with locally advanced prostate cancer were enrolled. No patients had evidence of lymph node or distant metastases, probability of organ-confined disease >25%, and risk of lymph node involvement >15% according to the Memorial Sloan Kettering Cancer Center Nomogram. IORT was delivered after exposure of the prostate by a dedicated linear accelerator with beveled collimators using electrons of 9−12 MeV to a total dose of 10−12 Gy. Rectal dose was measured *in vivo* by radio-chromic films placed on a rectal probe. IORT was followed by completion of radical prostatectomy and regional lymph node dissection. All cases with extracapsular extension and/or positive margins were scheduled for postoperative radiotherapy. Patients with pT3−4 disease or positive nodes received adjuvant hormone therapy.
Results: Mean dose detected by radio-chromic films was 3.9 Gy (range 0.4−8.9 Gy) to the anterior rectal wall. IORT procedure lasted 31 minutes on average (range 15−45 minutes). No major intra- or post-operative complications occurred. Minor complications were observed in 10/33 (30%) of cases. In the 27/31 patients who completed the postoperative external beam radiotherapy, 3/27 experienced grade 2 rectal and 1/27 grade 2 urinary toxicity.
Conclusions: IORT during radical prostatectomy is a feasible procedure and allowed to safely deliver postoperative external beam radiotherapy to a total dose of 50 Gy to the tumor bed without relevant acute rectal toxicity.