CRPC by patient subgroups (ClinicalTrials.gov; NCT00286091; Sponsored by Amgen Inc).
Methods: Men with non-metastatic CRPC at high-risk for bone metastasis (PSA value ⩾8.0 ng/mL and/or PSA doubling time ⩽10.0 months) were randomized 1:1 to receive either monthly subcutaneous denosumab 120 mg or placebo. Calcium and vitamin D supplements were encouraged. Enrollment began February 2006; primary analysis cut-off was July 2010, when >660 men had bone metastasis or died. The primary endpoint was time to first bone metastasis or death from any cause, i.e. bone metastasis-free survival. Here we assessed time to bone metastasis-free survival by patient subgroup including baseline PSA risk group (a) dual risk factors: PSA ⩾8.0 ng/mL + PSA doubling time ⩽10.0 months vs (b) single risk factor: PSA <8.0 ng/mL + ⩽10.0 months or ⩾8.0 ng/mL + >10.0 months, Gleason score (2−7 or 8−10), age (<75 years old or ⩾75 years), ethnicity (white or other), and geographic location (North America, Europe, or rest of world).
Results: 1432 men were enrolled; 716 in each arm. Denosumab significantly increased median bone metastasis-free survival by 4.2 months compared with placebo (29.5 and 25.2 months, respectively; Hazard Ratio [HR] 0.85 [0.73–0.98], $P = 0.03$). This benefit on bone metastasis-free survival was consistently observed among all patient subgroups (range of HRs 0.79–0.95). Denosumab also delayed time to symptomatic bone metastasis (0.67 [0.49–0.92]; $P = 0.01$). Primary results including efficacy and safety have been presented previously (Smith et al, AUA 2011).
Conclusion: Denosumab significantly prolonged bone metastasis-free survival compared with placebo among all men, with consistent results observed among subgroups of disease and demographic variables. This is the first large, clinical trial to demonstrate that targeting of the bone microenvironment significantly delays onset of bone metastases.

7004 ORAL

Pain Outcomes in a Randomized Phase 3 Clinical Trial of Denosumab Vs Zoledronic Acid (ZA) in Patients With Solid Tumours and Bone Metastases

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Background: Bone metastases in patients with advanced cancer commonly cause pain and can lead to skeletal-related events (SREs). Denosumab is a fully human monoclonal antibody against RANK Ligand that delayed or prevented SREs more effectively than ZA in patients with solid tumours and bone metastases in a randomized phase 3 clinical trial (Henry D et al, *J Clin Oncol*. 2010. Abstr 9133). We present here the pain outcomes for patients with solid tumours. Patients with breast or prostate tumours were not enrolled in the trial (sponsored by Amgen Inc., ClinicalTrials.gov identifier NCT00330759).
Methods: Eligible patients received 120 mg of denosumab SC or 4 mg of ZA IV every 4 weeks in a randomized, multinational, double-blind, double-dummy trial. Patient-reported pain was assessed with the Brief Pain Inventory (0: no pain-10: pain as bad as can be imagined) at baseline (BL), day 8, and before each monthly visit. Analgesic use was assessed by the 8-point Analgesic Quantification Algorithm (AQA). Analyses included time to moderate/severe pain (>4 points), proportion of patients with no/mild pain (0−4) at BL reporting moderate/severe pain by visit, time to clinically significant worsening of pain (⩾2-point increase from BL), time to clinically significant improvement in pain (⩾2 point decrease from BL), and proportion of patients shifting from no or low analgesic use (AQA ⩽ 2) at BL to strong opioid use (AQA ⩾ 3) by visit.
Results: At BL, mean worst pain scores were 4.9 points (SD=2.8) for the denosumab group (N = 799) and 5.2 points (SD=2.9) for the ZA group (N = 797). Patients with no/mild pain at BL (n = 596) experienced a delay in median time to moderate/severe pain with denosumab treatment (144 days) compared with ZA treatment (112 days) (HR 0.81, CI: 0.66−1.0, $P = 0.0499$). The proportion of patients with no/mild pain at BL reporting moderate/severe pain on study was lower at each visit with denosumab treatment than with ZA treatment. Denosumab-treated patients also experienced a delay in clinically significant worsening of pain compared with ZA-treated patients (median: denosumab 143 days, ZA 119 days; HR 0.86, CI: 0.74–0.99, $P = 0.0392$). The time to clinically significant improvement in pain was similar between treatment groups. Compared with ZA, a lower proportion of patients receiving denosumab shifted from low or no analgesic use to strong opioid use at each visit.
Conclusion: In patients with solid tumours, denosumab delayed the time to increased pain severity compared with ZA. Also, a lower proportion of patients receiving denosumab required increased analgesic use over time.

Poster Discussion Presentations (Mon, 26 Sep, 11:00−12:00)

Genitourinary Malignancies − Prostate Cancer

7005 POSTER DISCUSSION

PSA Measurement at the Fifth Week of Radiotherapy Is an Independent Predictor of Failure in Intermediate Risk Prostate Cancer Patients

R. de Crevoisier[1], T. Messai[2], P. Wibault[2], A. Bridier[2], P. Blanchard[2], J.D. Ospina[3], M. Bakkour[2], A. Bossi[2]. *[1]Centre Eugène Marquis INSERM642, Ille et vilaine, Rennes, France; [2]Gustave-Roussy, Ile de France, Villejuif, France; [3]INSERM 642, Ile et Vilaine, Rennes, France*

Background: The objective was to identify early predictor of recurrence during exclusive radiotherapy for intermediate risk prostate cancer patients.
Material and Methods: A total of 240 patients of median age 71 years (range: 50−83 years) received exclusive external beam radiotherapy (EBRT) for intermediate prognostic group prostate cancer (D'Amico classification). T stages were: stage 1 (45%) and stage 2 (55%). Gleason scores were: scores ⩽6 (57%) and score 7 (43%). Mean pre-treatment PSA (PSA0) value was 11 ng (range: 1.4−20). All the patients received a total dose of 70 Gy in 7 weeks, either in 2.0 Gy/fraction, 5 fr/week (n = 53) or 2.5 Gy/fr, 2.0 Gy/ week (n = 187). PSA was also measured at the fifth week after treatment started (PSA5). Cox regression and log-rank test were used to analyze the impact of the following variables on biochemical failure (BF: nadir + 2 ng/ml) and clinical failure (CF) (metastases): T stage, Gleason score, PSA0, PSA5, PSA ratio (PSA5/PSA0) and dose/fraction.
Results: Median follow-up was: 58 months (range: 6–235). Five year BF and CF rates were 28% (95% CI: 23%-33%) and 5.5% (95% CI: 2%-9%), respectively. Median PSA5 was 8 ng (range: 0.8−30) and median PSA ratio was 0.72 (range: 0.14−3.7).
In univariate analysis, PSA5 was found significant on BF ($p < 0.01$; odds ratio =1.13). Neither the PSA0, PSA ratio as continuous variable, T stage, the Gleason score and the dose/fr were found as predictors for BF. PSA ratio >0.8 increased significantly the risk of BF($p = 0.01$; odds ratio =2.0). In multivariate analysis, PSA ratio >0.8 remained the only predictor of BF ($p = 0.03$; odds ratio =2.3).
As there are only 13 events of CF, multivariate analysis was not feasible. In univariate analysis, neither the PSA0, PSA ratio as continuous variable, T stage nor the Gleason score were found as predictors for CF. However, PSA5 ($p = 0.01$; odds ratio =1.13) as well as PSA ratio >0.8 had a significant impact on CF (logrank test: $p = 0.04$).
Conclusions: PSA measured at 5th week of radiotherapy and PSA ratio (PSA5/PSA0) can be use as simple early predictor of recurrence among intermediate risk prostate cancer patients receiving exclusive radiotherapy. "Bad responders" (PSA ratio >0.8) could receive "intensified" treatment like androgen deprivation combined with high dose radiotherapy.

7006 POSTER DISCUSSION

Predictive Models of Rectum Toxicity in Prostate Cancer Radiotherapy

R. De Crevoisier[1], J. Zhu[2], J.D. Ospina[2], E. Le Prisé[3], A. Bossi[4], T. Messai[4], K. Gnep[3], V. Beckendorf[5], F. Polet[5], A. Simon[2]. *[1]Centre Eugène Marquis Inserm U642, Département de Radiothérapie, Rennes, France; [2]Inserm U642, Laboratoire Traitement du Signal et de l'Image, Rennes, France; [3]Centre Eugène Marquis, Département de Radiothérapie, Rennes, France; [4]Institut Gustave Roussy, Département de Radiothérapie, Villejuif, France; [5]Centre Alexis Vautrin, Département de Radiothérapie, Nancy, France*

Background: In case of prostate 3D conformal radiotherapy (3DCRT): - To identify patients and treatment predictors of rectal toxicity; - To compare the performance of different Normal Tissue Complication Probability (NTCP) models for predicting rectal toxicity.
Materials and Methods: A total of 439 patients (pts) received 3DCRT for localized prostate cancer to a median total dose of 78 Gy (range: 70 to 80 Gy), 2 Gy/fraction. Pts were selected based on the availabilityof dose-volume histograms (DVH). Median age was 67 years (45−78). History of abdominal or pelvic surgery, anticoagulant therapy (ACT) and diabetes were observed in 30%, 15% and 6% of pts, respectively. Tumour prognostic groups (D'Amico classification) were: good (7%),medium (65%)

and bad (28%). The data were collected prospectively for 42% of patients. Rectal toxicity was analyzed according to the SOMALENT classification (> Grade 2) and rectal bleeding (at least once episode) at 2, 3, 4 and 5 years. The effects of pts characteristics, DVH (including mean dose) and NTCP models on rectal toxicity at the different follow-ups were assessed using logistic regression (univariate and multivariate analysis). A total of 6 NTCP models were tested: Lyman Kutcher Burman (LKB), logit EUD, Poisson EUD, Kallman, Schultheiss and Parallel models. The parameters of the models were identified using the MATLAB Genetic Algorithm Toolbox and constrained optimization. The performance for predicting toxicity of the models was performed using Efron's pseudo R squared.

Results: Median follow-up was 60 months (range: 6 to 154). Two-, 3-, 4- and 5-year grade >2 toxicity rates were: 15%, 21%, 25% and 30%, respectively. Two-, 3-, 4- and 5-year rectal bleeding rates were: 21%, 28%, 32% and 38%, respectively. Univariate analysis shown following parameters as significant predictor of 4-year grade >2 toxicity: total prescription dose, V_{71} to V_{73} and maximal rectal dose. In multivariate analysis, the remaining factors were total dose, V_{72} and V_{73}. The table shows the parameters of the NTCP models. The NTCP models which probability values are significantly related with bladder toxicities are: LKB, Logit EUD and Poisson EUD models. The model having the better predictive capability is Poisson EUD model.

Conclusions: Both, some DVH parameters and three NTCP models (Poisson EUD model being the most predictive) are useful to assess rectal toxicity and could be used as constrains in IMRT planning.

Table: NTCP of 4 Year rectal toxicity (grade $\geqslant$2)

Model	TD_{50} (Gy)	Volume Effective Factor	Slope Factor	Log-Likelihood (p value)
LKB	79.14	n = 0.0025	m = 0.2705	159.05 (0.0022)
LogitEUD	80.57	n = 0.0063	k = 9.5959	159.08 (0.0022)
PoissonEUD	81.50	n = 0.0063	γ = 2.1618	158.95 (0.0018)

7007 POSTER DISCUSSION

Predictive Models of Bladder Toxicity in Prostate Cancer Radiotherapy

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Background: In case of prostate 3D conformal radiotherapy (3DCRT), the objectives were:

– To identify patients and treatment predictors of bladder toxicity;
– To compare the performance of different Normal Tissue Complication Probability (NTCP) models for predicting bladder toxicity.

Materials and Methods: A total of 436 patients (pts) received 3DCRT for localized prostate cancer to a median total dose of 78 Gy (range: 70 to 80 Gy), 2 Gy/fraction. Pts were selected based on the availability of dose-volume histogram (DVH). Median age was 67 years (45−78). History of abdominal or pelvic surgery, anticoagulant therapy (ACT) and diabetes were observed in 30%, 15% and 6% of pts, respectively. Tumour prognostic groups (D'Amico classification) were: good (7%), medium (65%) and bad (28%). The data were collected prospectively for 42% of patients. Bladder toxicity was analyzed according to the SOMALENT classification ($\geqslant$ Grade 2) and bladder bleeding (at least once episode) at 2, 3, 4 and 5 years. The effects of pts characteristics, DVH (including mean dose) and NTCP models on bladder toxicity at the different follow-ups were assessed using logistic regression (univariate and multivariate analysis). A total of 6 NTCP models were tested: Lyman Kutcher Burman (LKB), logit EUD, Poisson EUD, Kallman, Schultheiss and Parallel models. The parameters of the models were using the MATLAB Genetic Algorithm Toolbox and constrained optimization. The performance for predicting toxicity of the models was performed using Efron's pseudo R squared.

Results: Median follow-up was 60 months (range: 6 to 154). Two-, 3-, 4- and 5-year grade $\geqslant$2 toxicity rates were: 15%, 19%, 24% and 30%, respectively. Two-, 3-, 4- and 5-year bladder bleeding rates were: 6%, 9%, 11% and 16%, respectively. Univariate analysis shown following parameters as significant predictor of 4-year grade $\geqslant$2 toxicity: diabetes, total prescription dose and maximal bladder dose (none of the DVH values). In multivariate analysis, the remaining factor was the total dose. The table shows the parameters of the significant NTCP models.

The NTCP models which probability values are significantly related with rectal toxicities are: LKB, Logit EUD, Poisson EUD and Schultheiss models. The model having the better predictive capability is LKB model.

Conclusions: NTCP models (LKB model being the most predictive) are useful to assess bladder toxicity and could be used as constrains in IMRT planning.

NTCP of 4 Year bladder toxicity (grade $\geqslant$2)

Model	TD_{50} (Gy)	Volume Effective Factor	Slope Factor	Log-Likelihood (p value)
LKB	80.56	n = 0.0920	m = 0.3641	158.12 (0.0038)
LogitEUD	81.00	n = 0.0431	k = 7.6206	157.91 (0.0049)
PoissonEUD	82.19	n = 0.0409	γ = 1.7510	157.88 (0.0045)
Schultheiss	71.38	–	k = 8.2548	160.69 (0.0089)

7008 POSTER DISCUSSION

Twenty-four-month Safety Data From Phase II Studies of Radium-223 Chloride, a First-in-class Alpha-pharmaceutical With a Highly Favorable Safety Profile for Patients With Castration-resistant Prostate Cancer (CRPC) and Bone Metastases

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Background: Radium-223 chloride (^{223}Ra; Alpharadin™) is a first-in-class alpha-pharmaceutical with a potent, highly targeted antitumour effect on bone metastases. Phase II trials assessed the safety and efficacy of ^{223}Ra in patients (pts) with CRPC and bone metastases. Here we report long-term safety data from the end of the treatment period until 24 months after the first injection of ^{223}Ra.

Methods: Two double-blind, dose-response phase II trials (BC1−03 [NCT00667199], BC1−04 [NCT00337155]) and 1 double-blind, placebo-controlled phase II trial (BC1−02 [NCT00459654]) of ^{223}Ra were conducted in 286 pts with CRPC and bone metastases (255 pts received ^{223}Ra;100, 122, and 33 pts in BC1−03, BC1−04 and BC1−02, respectively). Doses varied from 5 to 100 kBq/kg (single [BC1−03] and repeated injections [BC1−02 and BC1−04]). Follow-up safety assessments were performed at months 6, 9, 12, 18, and 24 and included treatment-related adverse events (AEs), hematology, clinical chemistry, potential long-term toxicity, and death. Twenty-four month safety data are available for all 3 studies.

Results: A total of 159 pts were included in this analysis. No pts reported any treatment-related serious AEs during follow-up to 24 months. One patient had mild diarrhea 2 days after receiving an optional second injection of 50 kBq/kg ^{223}Ra at the start of follow-up; it was reported as probably related to the last ^{223}Ra injection. One patient reported lumbar pain after 24 weeks (only treatment-related AEs were reported during follow-up). CTC grade 4 hematologic toxicity was seen in 1 patient each for platelets, neutrophils, WBC, and hemoglobin. Across all studies, 7 pts experienced CTC grade 3 anemia, 5 pts grade 3 thrombocytopenia, and 3 pts grade 3 neutropenia. The BC1−02 study showed no statistically significant difference in hematologic parameters between the ^{223}Ra and placebo groups during follow-up. No patient reported a secondary diagnosis of acute myelogenous leukemia, myelodysplastic syndrome, aplastic anemia, or primary bone cancer. No signs of renal or hepatic toxicity were observed. The frequency and cause of death during follow-up were as anticipated for pts with metastatic CRPC.

Conclusion: Safety data from the 24-month follow-up period support previous findings of the highly favorable safety profile of ^{223}Ra in pts with CRPC and bone metastases. A randomized phase III study, ALSYMPCA, is ongoing worldwide with overall survival as the primary endpoint.

7009 POSTER DISCUSSION

Sensitivity and Specifity to Detect Local Recurrent Prostate Cancer Using Dynamic Contrast Enhanced (DCE) MRI Without Endorectal Coil and MRI Patterns of Post-prostatectomy Recurrence and of Its Response to Salvage Radiotherapy

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Purpose: To determine sensitivity and specifity of dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) without endorectal coil