The most frequently occurring (>10%) grade 3−4 adverse events for pts receiving temsirolimus were anemia (20%), asthenia (11%), and hyperglycemia (11%). A greater proportion of pts receiving IFN (79%) experienced grade 3−4 adverse events compared with temsirolimus (69%, p = 0.024).
Conclusions: Temsirolimus increased OS and PFS when used as first-line treatment for pts with advanced RCC and poor prognostic features, compared with IFN, with an acceptable safety profile.

4012 POSTER

Preliminary results of the 2-year prostate re-biopsy in a phase II randomized study of conventional fractionation vs. hypofractionation on patients with high risk prostate cancer

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Background: Several recent studies suggested a great sensitivity of prostate cancer to high dose fractions, due to a low α/β ratio of this tumor. To test this hypothesis we designed a randomized study comparing conventional fractionation with a biologically equivalent hypofractionated regimen, based on an α/β value of 1.5, as suggested by Fowler et al. (Int J Radiat Oncol Biol Phys 2003; 56: 1093). This is a preliminary report on histologic results from biopsies taken 2 years after the end of radiotherapy.
Material and Methods: From January 2003 to March 2007, 144 patients with histologically proven high risk prostate cancer were recruited to this study. High risk were patients with PSA > 20 ng/ml or with at least 2 of the following characteristics: PSA of 11 to 20, Gleason Score >6, T > 2b. All patients received hormonal therapy for 9 months. Seventy four patients were randomized to receive 80 Gy in 40 fractions in 8 weeks (control arm), and 73 were allocated to receive 62 Gy in 20 fractions in 5 weeks, 4 fractions per week, (hypofractionated arm). All patients were treated with 3D conformal radiation therapy (3DCRT). The median follow-up (FU) is 25 months (range 2−47). Of the 71 patients with a >2 year FU, 48 patients, 23 in the control and 25 in the hypofractionated arm, underwent a 2-yr prostate re-biopsy with, at least, 6 specimens for each lobe, depending on the size of the residual prostate.
Results: In 43 of the 48 patients (89.5%) undergone prostate re-biopsy, the histological examination showed only extended post-XRT modifications. Residual atypic cells were found in the remaining 5 patients (10%), 1 in the control and 4 in the hypofractionation arm. Only 1 of the 5 patients with positive biopsies is presently showing a PSA rise due to pelvic node metastases, while the remaining 4 are still b-NED with a PSA < 0.5 ng/ml.
Conclusions: Despite all patients in this study had a poor prognosis, only few patients, 5/48 (10%) showed a local tumour persistence. Since 4 of these 5 patients with a positive biopsy are showing no biochemical progression, a longer FU is necessary to explain the meaning of this finding.

4013 POSTER

Hypofractionation versus standard fraction in prostate cancer: analysis of the acute toxicity

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Background: The aim of this study is to evaluate the tolerance and the acute toxicity of a hypofractionation in comparison to a conventional fractionation regimen in the radiotherapy of prostate cancer.
Material and Methods: From January 2003 to March 2007, 144 patients with histologically proven, high risk prostate cancer were recruited to this study. All patients received a total androgen deprivation (AD) for 9 months. After 2 months of AD, all patients underwent a 3D conformal radiotherapy to the prostate and seminal vesicles. Patients were randomized to receive a conventional fractionation of 80 Gy in 40 fractions in 8 weeks, or 62 Gy in 20 fractions in 5 weeks, (4 fractions per week). Acute hematological, gastrointestinal (GI) and genitourinary (GU) toxicities were weekly evaluated according to the RTOG/EORTC score system.
Results: No patient experienced acute hematological toxicity or grade 3 gastrointestinal (GI) or genitourinary (GU) toxicity.
The acute grade 2 GI and GU toxicities were observed in the 20% and 34% of patients, respectively, in the control arm and in 33% and 41%, of patients, respectively, in the hypofractionation arm (p = 0.02 for GI and 0.04 for GU toxicity). The actuarial analysis showed an earlier appearence of both toxicities in the hypofractionation arm in comparison to the standard arm. However, when both toxicities were analyzed as a function of the normalized total dose in 2 Gy fraction equivalents (NTD2) using α/β value of 10 for acute reactions, the statistical significance disappeared for both toxicities, suggesting that the acute toxicity is simply anticipated in the hypofractionation with respect to conventional fractionation. This observation was confirmed by the evaluation of the Mucositis Index which did not result in a significant difference between the 2 arms, analyzed either as a function of time or of NTD2.
Conclusions: These preliminary results suggest that the hypofractionation schedule is well tolerated although the acute G2 toxicity in this group, was observed earlier than in conventional fractionation.

4014 POSTER

A new inhibitor of EGFR/SRC activation is able to block several key molecular events in prostate cancer progression

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Background: The encouraging results obtained in the last years by molecular therapy have induced researchers to intensify their efforts in developing new drugs with higher anticancer potency. One of the more promising targets of anticancer agents is the class of tyrosine kinases, including several growth factor receptors and signal transducing molecules.
Materials and Methods: Starting from the scaffold of pyrazolo[3,4-d]-pyrimidine c-Src kinase inhibitors we have synthesized new compounds that demonstrated an effective antiproliferative activity against different tumor cell lines. After a preliminary screening of their kinase inhibition capacity we selected the molecule SI35 that demonstrated a submicromolar inhibitory activity against EGFR and c-SRC.
Results: SI35 demonstrated in vitro to block the proliferation of prostate carcinoma cells PC3 and LnCaP (IC50 is about 30uM), while it had no effect in modulating vitality/proliferation of normal human fibroblasts, Hs27, and of primary human endothelial cells, HUVEC. Moreover we observed a strong inhibition by SI35 in modulating PC3 cells migration and invasion. In fact PC3 cells responded to the presence of EGF by increasing their migratory ability and this effect was strongly reduced by the addition of SI35 at concentrations below its IC50. Further observations demonstrated that SI35 molecule modulated PC3 cells morphology and their adhesive capacity on different physiological substrates. At the same time SI35 blocked invasive and sprouting capabilities of endothelial cells when seeded in Matrigel, inhibiting the formation of lamellipodia and of actin stress fibers. The action of SI35 molecule appeared to involve, in parallel with c-Src and EGFR inhibition, the downmodulation of the active forms FAK/paxillin and ERK.
Conclusions: These data suggest that pharmacological use of pyrazolo-[3,4-d]pyrimidines EGFR/Src inhibitors is potentially able to block several aspects of tumor progression including tumor growth, migratory/invasive capacity and angiogenesis by interference with transduction pathways emanating from EGFR and involving c-Src and FAK activation.

4015 POSTER

Arachidonic acid sustains prostate tumor growth in bone metastasis through the COX-2-mediated production of TNF-α

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Background: Diets high in n-6 fatty acids are associated with an increased risk of bone metastasis from prostate carcinoma (PCa). Although the bone represents, mainly in elderly, a rich repository of fatty acids, the molecular mechanism underlying this phenomenon is largely unknown. Arachidonic acid (AA) can be metabolized through lypoxigenase and cyclooxygenase (COX) pathways producing pro-inflammatory cytokines and mitogenic factors that act as autocrine and paracrine regulators of cancer behaviour. We and other Authors have previously reported that factors released by PCa cells play a key role in inducing an aberrant response in bone cells and favouring PCa cells growth. The aim of this study was to investigate how exogenous AA may modulate in vitro the interaction between PCa cells and bone cells.
Results: First we observed that exogenous AA is in PCa cells an effective inducer of gene transcription. In particular COX-2 activity stimulates the production of pro-inflammatory cytokines, including TNF-α and IL-1β. The blockade of COX-2 activity through a specific inhibitor is sufficient to repress

AA-induced gene transcription. In an animal model the production of TNF-α by PCa cells was responsible of the maintenance of a chronic inflammatory status in metastatic bone marrow, evidentiated by the presence of mature T-cells. Moreover the over-expression of TNF-α by AA-primed PCa cells resulted particularly effective in modifying cell behaviour of cultured bone stromal cells (BMSCs) and osteoclasts. In fact we observed an increment in the number of osteoblasts and in the production of RANKL by BMSCs, and a concomitant activation of osteoclasts. These cross-talks may contribute to the osteolytic appearance of bone lesions observed in vivo in PCa metastasis models.
Conclusions: These findings provide a possible molecular mechanism by which dietary n-6 fatty acids accumulating in bone marrow may influence the formation of PCa-derived metastatic lesions and indicate new molecular targets for therapy of metastatic PCa.

4016 POSTER

MR-guided prostate brachytherapy in a low-field open MR system: canine and in vitro dosimetry study

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Background: MRI provides excellent visualization of the prostate, its substructure and surrounding tissues, making it the modality of choice for guiding and monitoring interventions like brachytherapy and biopsy. Our objective was to demonstrate the feasibility of transperineal MR-guided prostate interventions in an open-MR unit focusing on needle-placement accuracy and rectal dosimetry.
Materials and Methods: The procedures were performed on 6 canines in an open-configuration 0.35T MR scanner. For interventions an MR compatible custom-made device was used consisting of 3 major parts: template-obturator rod, immobilization arm and patient tray. The canines were placed feet first in the right lateral decubitus position. Template reconstruction, trajectory planning, target and OAR delineation were based on T2 FSE images. For image guidance and target confirmation, fast gradient spoiled echo (FSPGR) sequence was used. MR compatible coaxial needles were inserted through the perineum to the base of the prostate. After satisfactory position was confirmed, brachytherapy catheters were placed through the coaxial needles, which were then removed. For the imitation of our 5-channel rectal dosimeter an MR compatible model was designed, inserted into the obturator and tested in gel phantom.
Results: MRI allowed clear definition of the prostate, periprostatic tissues, needles and catheters. Mean and standard deviation was 2.1 mm$\pm$1.2 mm, with a median of 1.9 mm. 97% of the errors were less than 4.0 mm; maximum error measured was 4.5 mm. The average time needed for each step was: setup and positioning – 20 min, initial imaging – 15 min, template registration and trajectory planning – 15 min, insertion of 10 needles – 45 min The five separated detector within the obturator was clearly visualized on the MR images. In gel phantom study the planned and measured doses at the different levels of the detectors was favorably and adequately matched.
Conclusions: A system for transperineal MR-guided prostate intervention has been developed and applied successfully on canines. This method seems to be a promising approach for performing feasible, accurate, reliable and high-quality image guidance within a reasonable time span. MR modeling of rectal dosimeter seems to be promising device to provide a more accurate prediction about the rectal doses. Our results facilitate us to introduce MR guided high-dose-rate (HDR) brachytherapy into the daily clinical practice in the near future.

4017 POSTER

Mutation of epidermal growth factor receptor in hormone sensitive and refractory prostate cancers

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Background: Hormone refractory prostate cancer (HRPC) is a significant cause of morbidity and mortality. Androgen receptor mutations and amplifications may explain relapse in some patients, but in approximately 70% of cases, alternative mechanisms must be invoked and type I receptor tyrosine kinases may play a role in mediating HRPC. In this study, EGFR and ERBB2 gene amplification and alteration were analyzed in HRPC.
Materials and Methods: EGFR were analyzed by fluorescence in situ hybridization in prostate cancer. We sequenced exons 18−24 of the EGFR and exons 19, 20 of the ERBB2 from genomic DNA isolated from matched tumor pairs (one taken in hormone sensitive and one in hormone refractory) from 10 prostate cancer patients. Amplification and mutation was compared with clinicopathologic features.
Results: EGFR amplifications were observed in 6 (30%) out of 20 specimens. A total of 9 EGFR mutation were detected in 3 (30%) of the 10 prostate cancer patients. EGFR mutation were not associated with ductal type but acinar type in adenocarcinoma prostate cancer. The EGFR mutations were in exon 18 (2 cases), exon 19 (5 cases), and in exon 23 (2 cases). Of them, 6 mutations showed aminoacid change and these aminoacid changes occurred in both hormone sensitive and hormone refractory specimens. No significant correlation was found in shifting of mutation between hormone sensitive and refractory status. Meanwhile, ERBB2 mutations were absent in prostate cancers.
Conclusions: EGFR may represent one of independent routes to metastatic and advanced prostatec cancer. EGFR deletion mutation and gene amplification may be occurred in far advanced prostate cancer, but which do not appear to play a significant role in the hormonal refractory pathway but is associated with prognosis.

4018 POSTER

Post-treatment prostate biopsies in the era of three-dimensional conformal radiotherapy. What can they teach us?

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Background: The vast majority of studies indicating a dose–response relationship are based on biochemical control as the primary end point. However, post-radiotherapy prostate biopsies are useful in evaluating innovations such as dose escalation protocols, or combined modality treatments. The present study was undertaken to correlate post-treatment biopsy results with PSA and clinical outcome in prostate cancer patients treated with three-dimensional conformal radiotherapy (3DCRT) in a dose escalation trial.
Materials and Methods: This study included 129 patients with localized prostate cancer treated with 3DCRT to a median isocenter dose of 73.1 Gy that consented and underwent a trans-rectal ultrasound (TRUS) guided prostate biopsy 24−36 months after radiotherapy. Thirty seven per cent (48/129) of biopsies were performed in patients under PSA failure conditions and the remaining 63% (81/129) in patients with PSA control. Risk-adapted short-term and long-term androgen deprivation (STAD and LTAD) was associated in 22 and 82 of patients respectively. The median follow-up was 66 months (range 26–147).
Results: Seventeen percent (22/129) of patients had post-treatment positive biopsies (PB), 35% (17/48) with prior PSA relapse and 6% (5/81) with prior PSA control. Patients receiving higher radiation dose experienced a lower incidence of PB after treatment ($p = 0.051$). The 6-year biochemical disease-free survival (bDFS) was 81%, 63% and 86% for the whole series, PB and negative biopsies (NB) patients respectively ($p = 0.044$). In multivariate analysis, only biopsy status at 24–36 months ($p = 0.043$) was independent predictor of clinical failure-free survival (cFFS).
Conclusion: The results of the present study show a strong correlation between a post-treatment PB and the 5-year probability of cFFS and suggest a relationship between radiation dose and histological response.

Results of multivariate analysis of potential factors affecting bDFS

Variable	Beta	Hazard ratio	P value	95% CI
PSA nadir $\leqslant 1$	−1.285	0.284	0.044	0.083−0.967
Post-treatment positive biopsy	0.771	2.163	0.014	1.166−4.011
Radiation dose (continuous)	0.185	1.203	<0.001	1.097−1.320