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

G. Arcangeli[1], S. Gomellini[1], B.M. Saracino[1], M.G. Petrongari[1], S. Arcangeli[1], S. Sentinelli[2], S. Canitano[3], A. Marsella[3]. *[1]Regina Elena, Radiotherapy, Roma, Italy; [2]Regina Elena, Hystopatology, Roma, Italy; [3]Regina Elena, Radiology, Roma, Italy*

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

M. Petrongari[1], S. Arcangeli[1], B.M. Saracino[1], S. Gomellini[1], S. Marzi[2], V. Landoni[2], M. Benassi[2], I. Sperduti[3], G. Arcangeli[1]. *[1]Regina Elena, Radiotherapy, Roma, Italy; [2]Regina Elena, Medical Physics, Roma, Italy; [3]Regina Elena, Biostatystics, Roma, Italy*

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

A. Angelucci[1], S. D'Ascenzo[2], D. Millimaggi[2], P. Muzi[2], G.L. Gravina[2], S. Schenone[3], M. Botta[4], V. Dolo[2], C. Vicentini[5], M. Bologna[1]. *[1]University of L'Aquila, Dpt Basic and Applied Biology, L'Aquila, Italy; [2]University of L'Aquila, Dpt Experimental Medicine, L'Aquila, Italy; [3]University of Genova, Dpt Pharmaceutical Science, Genova, Italy; [4]University of Siena, Dpt Farmaco Chimico Tecnologico, Siena, Italy; [5]University of L'Aquila, Dpt Surgery, L'Aquila, Italy*

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

A. Angelucci[1], N. Rucci[2], S. Garofalo[1], S. Speca[1], A. Bovadilla[1], G.L. Gravina[2], P. Muzi[2], A. Teti[2], C. Vicentini[3], M. Bologna[1]. *[1]University of L'Aquila, Department of Basic and Applied Biology, L'Aquila, Italy; [2]University of L'Aquila, Department of Experimental Medicine, L'Aquila, Italy; [3]University of L'Aquila, Department of Surgery, L'Aquila, Italy*

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