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Results from intermittent and continuous dosing schedules with sunitinib (SU) in previously treated, advanced non–small-cell lung cancer (NSCLC)

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Background In NSCLC, VEGF expression correlates with increased tumor angiogenesis and shortened survival. SU is an oral multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, RET, FLT3 and CSF-1R being evaluated in NSCLC as second-line therapy. The minimum plasma concentration of SU that inhibits the phosphorylation of VEGFR and PDGFR is ≥50 ng/mL (Mendel et al. Clin Cancer Res 2003;9:327-37). Single-agent activity of SU given via intermittent and continuous dosing schedules was assessed in advanced NSCLC. Methods This phase II study evaluated the efficacy, safety and pharmacokinetics (PK) of SU given in 2 patient (pt) cohorts: 50 mg/day for 4 wks followed by 2 wks off treatment (Schedule 4/2; 6-wk cycles) or 37.5 mg/day continuous daily dosing (CDD; 4-wk cycles). The primary endpoint was objective response rate. Eligible pts had stage IIIB/IV NSCLC and were ineligible or failed prior platinum-based chemotherapy. Results 110 pts were treated: 63 on Schedule 4/2 and 47 on Schedule CDD. Most pts (89%) had stage IV disease and adenocarcinoma (64% 4/2; 53% CDD). On Schedule 4/2, 7 pts (11%) had PRs, 18 pts (29%) had SD of ≥8 wks, median PFS was 12 wks and median OS was 23.4 wks. On Schedule CDD, 1 pt (2%) had a PR, 9 pts (19%) had SD of ≥8 wks, median PFS was 12.3 wks and median OS was 38.1 wks. Both regimens were generally well tolerated. Non-hematological grade 3/4 adverse events (AEs) of all causality included fatigue/asthenia (29% 4/2; 17% CDD), pain/myalgia (17% 4/2; 2% CDD), dyspnea (11% both) and nausea/vomiting (10% 4/2; 2% CDD). Hematological grade 3/4 AEs included thrombocytopenia (5% 4/2; 0% CDD) and neutropenia (5% 4/2; 9% CDD). At steady state, Schedule 4/2 median total drug trough concentrations (C_{trough}) were >80 ng/mL (nadir $_{trough}$ was ~50 ng/mL (44.4–65.3 ng/ml); both within the targeted range. Conclusions In heavily pretreated NSCLC pts, intermittent and continuous SU regimens showed promising single-agent antitumor activity with manageable toxicities, and achieved SU plasma concentrations predicted to inhibit VEGFR and PDGFR. Further evaluation of SU in NSCLC is ongoing in SU1087, a Ph III trial of SU 37.5 mg CDD plus erlotinib versus erlotinib alone.

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HL-91 uptake and its correlation with molecular alterations in colon cancer cells. In vivo and in vitro studies

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Background: Colorectal adenocarcinoma is one of the main mortality causes by cancer. The decrease of oxygen concentration (hypoxia) constitutes a characteristic of solid tumors and has an important role in radiotherapy and in chemotherapy with some cytotoxic drugs. However, its quantification is only achieved by invasive methodologies which are difficult to use in routine basis. The nuclear medicine is able to give functional information after labeling specific molecules with gamma emitting radionuclides. The aim of this work is to correlate in vivo and in vitro hypoxia imaging with 99mTc- HL-91 homemade synthesized and molecular hypoxia alterations.

Material and Methods: A pharmaceutical formulation of HL-91 homemade synthesized was prepared in order to be labeled with 99mTc. Colon cancer cell cultures were incubated under hypoxic and normoxic conditions during 60 min. The 99mTc-HL-91 uptake was carried out during 120 min. The molecular analysis of tumoral cells was performed using flow cytometry in order to find out reactive oxygen species (ROS) (2,7-dichlorodihydrofluorescein diacetate), apoptosis (Annexin-V), and protein adducts reductively-activated by pimonidazole (Hypoxiprobe). Nude mice were injected with colon cancer cells. After three weeks, the animals were injected with pimonidazol. In order to perform a two phase dynamic acquisition the animals were injected with 37 MBq of 99mTc-HL-91. It was also performed the acquisition of static images until 240 min after radiopharmaceutical administration. The animals were sacrificed and several organs including tumor were excised and counted in a well count. The tumors were homogenized mechanically and chemically by collagenase IV in order to isolate tumoral cells. The isolated cells were submitted to the same molecular protocol referred above. Statistical analysis was made by a Spearman correlation.

Results: In vitro results show that 99mTc-HL-91 uptake is statistically different ($p<0.01$) at normoxic and hypoxic conditions. The molecular analysis show a few quantity of cells in apoptosis and an increase of ROS and pimonidazol-monoclonal antibody in cells incubated at hypoxic conditions when compared with normoxic ones. In vivo studies evidence a propensity for proportionality in 99mTc-HL-91 tumor/muscle and tumor/blood ratios and tumor size. The biodistribution studies show higher values of 99mTc-HL-91 tumoral uptake till 90 min after injection (%ID/g=4.4) and renal and hepatobilliary excretion. The molecular evaluation in the xenograft cells reveals also slight quantity of cells in apoptosis, increasing of ROS that correlates with tumor size, and increasing of pimonidazol-monoclonal antibody binding in the biggest tumors.

Conclusion: With our results we can conclude that the 99mTc-HL-91 is a good hypoxic imaging tracer what is confirmed by molecular studies, which can be translated to clinical use.

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Relationship between tumor and plasma levels of telomerase reverse transcriptase mRNA in patients with colorectal cancer: implications for non-invasive monitoring of neoplastic disease

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Purpose. Colorectal cancer (CRC) is one of the most common cancers in western countries. Identification of circulating markers for CRC would optimize early stage diagnosis and the monitoring for disease recurrence. Expression of hTERT, the catalytic component of the telomerase complex, that extends telomeres at the end of eukaryotic chromosomes thus preventing cell senescence and death, is essential to the oncogenic process.Recent data suggest that hTERT mRNA in plasma may be a marker of neoplastic disease; however, no data are available comparing tumor and plasma hTERT levels.

Experimental procedures. 85 CRC tumors (25 stage I, 15 stage II, 15 stage III, and 30 stage IV), and the corresponding available adjacent non-cancerous mucosa (n=42(and plasma collected at the time of surgery (n=49) were analyzed. Control plasma samples were obtained from 43 age-matched healthy subjects. All hTERT transcripts (hTERT-AT) and transcripts encoding the functional protein (hTERT-FL) were quantified by real-time PCR. Results. hTERT-AT was found to correlate with hTERT-FL mRNA levels in tumors ($r=0.849$, $p<0.0001$) and both mRNAs increased along with tumor progression ($p<0.0001$). Conversely to controls, all but two samples from CRC patients were positive for hTERT mRNAs. Using a cut-off of 180 copies hTERT-AT/mL, the sensitivity and specificity of the assay for CRC were 92% and 100%, respectively. Furthermore, hTERT-AT mRNA levels in plasma significantly correlated with hTERT-AT mRNA levels in tumors ($r=0.702$, $p<0.0001$).

Conclusions. Overall, these findings indicate that quantification of circulating hTERT mRNA levels may be used as marker for the non-invasive monitoring of neoplastic disease.

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Potencial prognostic and predictive factors in diffuse large B-cell lymphoma – the role of NFkappaB

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Introduction: Diffuse Large B-cell Lymfoma constitutes app.30-40% of non-Hodgkin lymphomas, Anon (1993), Armitage et al. (1998).The potencial prognostic and predictive factors in diffuse large B-cell lymfoma (DLBCL)