evolution to hepatocarcinomas) and increased ($p < 0.05$) number and % of remodeling PNL (rPNL; lesions that tend to disappear). Mechanisms associated to modulation of p53 subcellular compartimentalization could be involved with PNL aggressivity. Imunohistochemistry analysis showed that compared to CO group, TB group presented a smaller ($p < 0.05$) frequency of pPNL with aberrant p53 cytoplasmic localization. Furthermore, both pPNL and rPNL of TB group showed smaller ($p < 0.05$) and greater ($p < 0.05$) frequency of cytoplasmic and nuclear immunostaining of CRM1 (an exportin involved with p53 nuclear-cytoplasmic traffic), respectively. TB group also presented increased ($p < 0.05$) hepatic histone H3K9 acetylation specifically in PNL, as well as higher ($p < 0.05$) p21 expression, suggesting that TB acted as an HDACi. Also compared to CO group, TB group displayed increased ($p < 0.05$) hepatic expression of $p33^{ING1A}$, a tumor suppressor gene that plays an inhibitory role in p53 cytoplasmic degradation and that was shown to be downregulated ($p < 0.05$) in this phase of hepatocarcinogenesis. The present data suggest that TB presents suppressive chemopreventive activities of hepatocarcinogenesis by acting as an HDACi. In addition, $p33^{ING1A}$ and CRM1 seem to represent relevant targets for TB modulation of p53 compartimentalization. Financial assistance: FAPESP(2009/53407−5)/CNPq/CAPES.

653 POSTER

Evaluation of strychnine, a plant alkaloid for in vitro anti-angiogenesis, apoptosis and antioxidant potential in MCF-7 cancer cells

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Background: It is widely accepted that the growth of a solid tumor such as breast cancer is dependent on angiogenesis. Mechanism of action of strychnine on VEGF and other proangiogenic factors (TNF-α, IL 12) and about the possible role of VEGF regulation of breast cancer growth has not been elucidated yet. Thus, the study was designed to evaluate *in vitro* anticancer and anti-angiogenic effect of strychnine, an alkaloid isolated from *Strychnos nux-vomica* on human mammary tumor cell line (MCF-7).
Material and Methods: The effect of strychnine on cell death and intracellular targets that affect angiogenesis (VEGF), inflammation (IL-12, TNF-α), apoptosis (caspase-3, -8 & -9) and antioxidant (superoxide dismutase & catalase) were determined by MTT assay, ELISA and enzymatic activity assay. In addition, Anti-VEGF neutralization effect was evaluated alone and in combination with strychnine, to assess whether it could result in augmented anticancer efficacy than the single agent.
Result: Strychnine inhibited growth of cancer cells in a dose and time-dependent manner. Experiments aiming to investigate the anti-angiogenic activity of strychnine against MCF-7, revealed that following the treatment, a dose-dependent decrease ($p < 0.001$) in the levels of VEGF secreted by the cells was recorded. In another set of experiments, strychnine potentiated ($p < 0.001$) the cell death induced by anti-VEGF antibody. VEGF and its receptors are established as major mediators of tumor cell growth and invasiveness; taken together; the results of these experiments suggest that strychnine possesses antiangiogenic activity. Although strychnine appeared to decrease the levels of tumorigenesis factor, TNF-α ($p < 0.05$), it did not alter IL-12 level significantly. The pro-apoptotic effect of strychnine was confirmed by significant ($p < 0.001$) increase in caspases-3 and -9 but not 8 activity. Significant increase in antioxidant enzymes (SOD, catalase) activity was also recorded.
Conclusion: Strychnine acts via multiple albeit specific molecular targets to elicit anti-carcinogenic activity thus might be a candidate for developing multifunctional anti-cancer agent through its inhibitory activity on several aspects of tumor growth and angiogenesis.

Hormonal agents

654 POSTER

Predictive value of a dextromethorphan phenotyping test for endoxifen exposure

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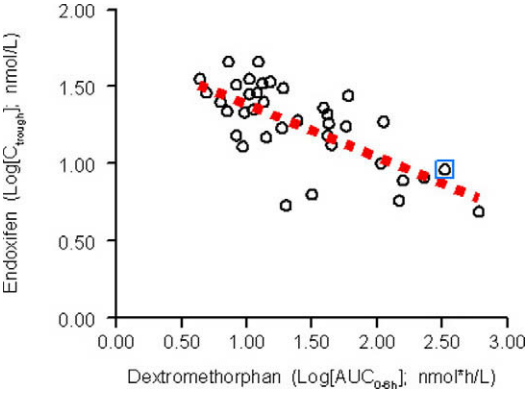
Background: Tamoxifen, a widely used selective estrogen receptor modulator for the prevention and treatment of breast cancer, is mainly metabolized by CYP2D6 and CYP3A4, to form the active metabolite endoxifen. Unfortunately, variability in toxicity and efficacy of this drug is substantial. Recently, genotyping for CYP2D6 polymorphisms was suggested to individualize tamoxifen therapy, which also translated into a shorter relapse free survival of CYP2D6 poor metabolizers (Schroth *et al*, JAMA 2009). However, other studies fail to confirm this observation. The inter-individual variability in the pharmacokinetics of tamoxifen is not only influenced by genetic profile, but is also affected by lifestyle factors and co-medication, interacting with cytochrome P450 activity. Therefore, we studied the usage of dextromethorphan, a known probe drug for both CYP2D6 and CYP3A4, as a potential phenotyping probe for tamoxifen metabolism by exploring correlations between the pharmacokinetics of dextromethorphan and tamoxifen.
Material and Methods: In this prospective study, 40 women with breast cancer using tamoxifen on steady state received a single dose of 30 mg dextromethorphan orally, 2 hours after oral tamoxifen intake (daily dose 20 mg in adjuvant setting or 40 mg for metastatic disease). Dextromethorphan and metabolites (dextrorphan, 3-methoxymorphinan, and 3-hydroxymorphinan) and tamoxifen and metabolites (4-hydroxy tamoxifen, N-desmethyl tamoxifen and endoxifen) were quantitated by LC-MS/MS. Next, C_{trough} levels, exposures and clearances of all compounds were estimated (WinNonLin), log transformed and subsequently correlated with a two-sided Pearson's correlation test (SPSS).
Results: A highly significant correlation ($r = -0.72$, $p = 0.0001$) was found between the clearances (CL/F) of dextromethorphan (0−6 h) and endoxifen (0−24 h). Also, between the AUC of dextromethorphan (0−6 h) and the daily trough endoxifen concentrations a highly significant correlation was observed ($r = -0.70$, $p = 0.0001$); see figure. In one patient (indicated in the figure by a box) using the strong CYP2D6 inhibitor paroxetine, the expected low endoxifen concentration caused by inhibition of CYP2D6 by paroxetine of this patient was accurately predicted by the dextromethorphan probe.
Conclusions: The dextromethorphan phenotyping probe showed to be an excellent tool to predict endoxifen exposure. This test could aid in future studies on the association of tamoxifen and CYP2D6 genotypes/inhibitors in relation to outcome, and in the further personalization of tamoxifen treatment by optimizing therapeutic benefit and reducing side-effects in individual patients.



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Preliminary report of efficacy of abiraterone acetate in patients with estrogen (ER) or androgen receptor (AR) positive, advanced breast carcinoma resistant to standard endocrine therapies

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Background: Approximately 50% of patients with estrogen receptor positive (ER+) breast cancer display intrinsic resistance to endocrine treatment with the remainder acquiring resistance. Epidemiological, preclinical and clinical data suggest that androgenic steroids upstream of aromatase drive steroid receptor signalling, that is critical to tumour growth. There is also preclinical evidence for the existence of an AR driven, ERα negative, subset of breast cancers transcriptionally similar to ER+ disease. We hypothesized that abiraterone acetate, a cytochrome (CYP) 17 inhibitor