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Expression of estrogens, progesterone and c-erbB-2 in patients with recurrent breast cancer in Mexico

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Background: Breast cancer is the most common form of malignancy occurring in women around the world. In Mexico, Breast cancer is the second cause of death in women. Some authors have reported a high concordance, ranging from 71% to 85% between estrogen receptor (ER) expression in primary breast carcinoma and its local, regional recurrence, or metastasis. No studies exist that estimate the frequency of breast cancer recurrence in Hispanic population from Mexico.
Objective: Compare the recurrence of breast cancer with the expression for estrogens, progesterone and c-erbB-2 in women of the northwest of Mexico.
Methods: Cross-sectional study in 397 cases of breast cancer. A correlation between clinical and pathological factors [estrogen receptor (ER), progesterone receptor (PGR) and c-erbB-2 in the primary tumor] including the recurrence of disease were evaluated. The immunohistochemical result for ER, PGR and c-erbB-2 was interpreted like (+) with a 10% or higher expression in the tumor cells. Those variables whose differences reached statistical significance were incorporated for logistic regression analysis to predict the biomarker's effect in disease recurrence. A p value <0.05 was considered statistically significant.
Results: Age average was 52±12 years old. Twenty-three percent presented recurrence of disease (95% CI 19−27) (p = 0.001), 152 cases (38%, 95% CI 33−43; OR = 0.35; p = 0.001) were in stage II, 201 cases (51%, 95% CI 46−56; OR = 0.64; p = 0.07) were positive to estrogens, 170 (43%, 95% CI 38−48; OR = 0.76; p = 0.27) to progesterone and 129 (32%, 95% CI 28−37; OR = 1.53; p = 0.08) to c-erbB-2. Death due to the disease was in 13 cases (3%, 95% CI 1−5; OR = 21.23; p = 0.001). Univariant analysis revealed that up to 9% of the recurrences are associated to the expression of receptors for estrogens (R = 0.09; p = 0.03).
Conclusions: Recurrence observed in our study is similar to the reported for other series, ER continuous being an excellent marker in the prognosis of breast cancer, the determination of PGR and c-erbB-2 receptors it does not add additional prognosis information to the recurrence risk in breast cancer.

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The PARP1 gene is over-expressed in triple negative breast cancer

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Background: Poly(ADP-ribose) polymerase (PARP1) is a critical enzyme of cell proliferation and DNA repair. Inhibition of PARP1 leads to apoptosis in BRCA1and BRCA2 deficient tumor cells and can facilitate the response to alkylating agents. Several PARP inhibitors are in clinical trials. We investigated PARP1 gene expression in major human primary cancers and corresponding morphologically normal tissues in order to direct clinical trial efforts toward cancers that over-express PARP1.
Methods: We used the Gene Logic BioExpress® System database to analyze PARP1 expression in human ovarian, breast, uterine, lung and prostate tumor samples in comparison to normal counterpart tissues. Gene expression was assessed on Affymetrix HU133AB microarrays and over-expression was defined by using upper confidence limits (UCL) calculated from the normal sample distribution for each tissue type. Samples from cancer subtypes were individually tested relative to the UCL and results tallied.
Results: The expression of PARP1 was above the 95% UCL of the corresponding normal tissue distribution in 25% of uterine cancers (n = 50; nl = 23), 75% of ovarian cancers (n = 64; nl = 88), 75% of lung cancers (n = 85;nl = 122) and 66% of infiltrating ductal breast cancers (n = 169; nl = 68). By contrast there was no difference in PARP1 expression in prostate cancer (n = 57) and normal prostate (n = 57). Mean PARP1 expression was 1.8-fold greater in breast cancers than in normals, $p = 2 \times 10^{-27}$, and was more pronounced in tumors that were negative when assayed for hormone and HER2 receptors by standard (non-microarray) diagnostic methods. PARP1 expression was above the 95% UCL in 88% (15/17) of patients whose tumors were ER−, 80% (15/19) that were PR− and 90% (8/9) that were HER2−. PARP1 expression was above the 99.9% UCL in 45% of all patients with infiltrating ductal breast cancer compared with 75% of ER−/PR− and 90% of HER2− patients. When all 169 infiltrating ductal breast cancer samples were categorized according to expression of the estrogen receptor1 transcript on the microarray, PARP1 gene expression was observed to be significantly higher in the ER− group (p = 0.009).
Conclusions: The PARP1 gene is over-expressed in some but not all types of cancer. If PARP1 gene over-expression defines increased responsiveness to PARP1 inhibition, then these results imply that a substantial fraction of patients with cancer of the breast, ovary, uterus and lung would be rational candidates for therapy with a PARP inhibitor. Increased PARP1 expression in the subset of patients with breast cancer of the triple negative phenotype strengthens the link of this subgroup to patients with basal derived or BRCA-related disease, and makes them particularly attractive candidates for studies of PARP inhibitor therapy. This information has been incorporated into the design of a trial of BSI-201, a novel PARP inhibitor, in patients with triple negative breast cancer.

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Antiangiogenic activity of combining gefitinib and rapamycin in a panel of pancreas cancer cell lines

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Background: Advances in molecular biology have greatly improved understanding of the pathogenesis and progression of pancreatic adenocarcinoma, generally considered resistant to common cytotoxic drugs. Our previous study showed that the combination of gefitinib plus rapamycin, acting at different levels of the EGFR cellular pathway, could induce a pronounced schedule-dependent antitumour effect in the pancreas cancer model; in fact, only the sequence gefitinib before rapamycin resulted in a synergistic cytotoxicity, through the strong inhibition of Akt and p70S6K phosphorylation. In this report, we investigated the antiangiogenic effects of the combination of gefitinib and rapamycin, acting on EGFR and mTor, respectively in the same panel of pancreas cancer cell lines (Panc-1, AsPC-1 and MiaPaCa-2).
Methods: The activity of the two drugs, both alone and in combination, were evaluated as modulation of HIFa by western blot analysis and as modulation of VEGF protein release by Elisa kit. According with rapamycin activity bound to a decrease in the transmission of proliferative signals, resulting in a cell cycle block in G0/G1 phase, we utilised, in the following characterization, 30 ng/ml rapamycin in Panc-1 cells and 100 ng/ml in the other cell lines for 3 days. Conversely, gefitinib was utilised at the IC50 values for 3 days. The 3 schedules utilised were the simultaneous and sequential ones.
Results: Preliminary results of the determination of VEGF release modulation showed that each drug reduced this growth factor release; this phenomenon was schedule dependent, with the max efficacy when gefitinib was given before rapamycin. In all cell lines, the Western Blot analysis of the modulation of HIFa in normoxia after exposure to gefitinib and rapamycin showed that gefitinib after 3 days exposure did not influence HIFa expression while 3-days-rapamycin slightly reduced its expression. The combination of the two drugs did not induce marked inhibition of HIFa expression, suggesting that this factor has not a relevant role in determining antiangiogenic effects of the two drugs.
Conclusions: Our results suggest that the combination of gefitinib plus rapamycin, acting at different levels of the EGFR cellular pathway, could induce a pronounced antitumour and antiangiogenic effect in the pancreas cancer model. Moreover, VEGF release is independent from HIFa inhibition in our pancreas cancer in vitro model.
Gefitinib is a trademark of the AstraZeneca group of companies.

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Identification of possible metastasis associated markers expressed on the surface of a breast cancer model

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Background: Despite advances in detection and treatment of cancer, mortality still remains high. Antibodies have in recent years become a growing field in cancer therapy, and the results obtained with monoclonal antibodies in the treatment of various cancers, show the great potential in this avenue. There is still, however, a growing need for new targets and a better understanding of the mechanisms involved in immunotherapy.
As metastasis is the main cause of cancer mortalities, we are focusing on identifying antibodies against possible metastasis associated markers. As a metastatic model system we are using two isogenic cell lines, NM-2C5 and M-4A4, derived from the MDA-MB-435 breast carcinoma cell line. Although equally tumorigenic, these two breast cancer cell lines have diametrically opposite metastatic capabilities. In 74% of inoculated athymic mice clone M-4A4 metastasised to the lungs, whereas clone NM-2C5 did not metastasise to any distant sites.
Methods: For the identification of differentially expressed surface proteins on NM-2C5 and M-4A4 we used subtractive immunisation of mice. Mice