CÁNCER DE MAMA

Implication of miRNA in the diagnosis and treatment of breast cancer.

Castañeda CA, Agullo-Ortuño MT, Fresno Vara JA, Cortes-Funes H, Gomez HL, Ciruelos E.

Expert Rev Anticancer Ther. 2011 Aug; 11(8): 1265-75.

Abstract

Breast cancer (BC) comprises a group of different diseases characterized by changes in tissue structure and gene expression. Recent advances in molecular biology have shed new light on the participation of genes and their products in the biology of BC. MicroRNAs (miRNAs) are small noncoding endogenous RNA molecules that appear to modulate the expression of more than a third of human genes, and their implications in cancer have grasped the attention of the scientific community. Recently, several studies have described the association between miRNA expression profiles and pathological and clinical BC features. Moreover, these molecules represent a new type of molecular marker that can identify prognosis and guide the management of BC patients. With the increasing understanding of miRNA networks and their impact in the biology of BC, as well as the development of viable strategies to modulate specific miRNAs, we could improve the treatment of this disease.

A genomic predictor of response and survival following taxaneanthracycline chemotherapy for invasive breast cancer.

Hatzis C, Pusztai L, Valero V, Booser DJ, Esserman L, Lluch A, Vidaurre T, Holmes F, Souchon E, Wang H, Martin M, Cotrina J, Gomez H, Hubbard R, Chacón JI, FerrerLozano J, Dyer R, Buxton M, Gong Y, Wu Y, Ibrahim N, Andreopoulou E, Ueno NT, Hunt K, Yang W, Nazario A, DeMichele A, O'Shaughnessy J, Hortobagyi GN, Symmans WF.

JAMA 2011 May 11; 305(18): 1873-81.

Abstract

CONTEXT: Prediction of high probability of survival from standard cancer treatments is fundamental for individualized cancer treatment strategies. OBJECTIVE: To develop a predictor of response and survival from chemotherapy for newly diagnosed invasive breast cancer. DESIGN, SETTING, AND PATIENTS: Prospective multicenter study conducted from June 2000 to March 2010 at the M. D. Anderson Cancer Center to develop and test genomic predictors for neoadjuvant chemotherapy. Patients were those with newly diagnosed ERBB2 (HER2 or HER2/neu)-negative breast cancer treated with chemotherapy containing sequential taxane and anthracycline-based regimens (then endocrine therapy if estrogen receptor [ER]-positive). Different predictive signatures for resistance and response to preoperative (neoadjuvant) chemotherapy (stratified according to ER status) were developed from gene expression microarrays of newly diagnosed breast cancer (310 patients). Breast cancer treatment sensitivity was then predicted using the combination of signatures for (1) sensitivity to endocrine therapy, (2) chemoresistance, and (3) chemosensitivity, with independent validation (198 patients) and comparison with other reported genomic predictors of chemotherapy response. MAIN OUTCOME MEASURES: Distant relapse-free survival (DRFS) if predicted treatment sensitive and absolute risk reduction ([ARR], difference in DRFS between 2 predicted groups) at median follow-up (3 years). RESULTS: Patients in the independent validation cohort (99% clinical stage II-III) who were predicted to be treatment sensitive (28%) had 56% (95% CI, 31%-78%) probability of excellent pathologic response and DRFS of 92% (95% CI, 85%-100%), with an ARR of 18% (95% CI, 6%-28%). Survival was predicted in ER-positive (30% predicted sensitive; DRFS, 97% [95% CI, 91%-100%]; ARR, 11% [95% CI, 0.1%-21%]) and ER-negative (26% predicted sensitive; DRFS, 83% [95% CI, 68%-100%]; ARR, 26% [95% CI, 4%- 48%]) subsets and was significant in multivariate analysis. Other genomic predictors showed paradoxically worse survival for patients predicted to be responsive to chemotherapy. CONCLUSION: A genomic predictor combining ER status, predicted chemoresistance, predicted chemosensitivity, and predicted endocrine sensitivity identified patients with high probability of survival following taxane and anthracycline chemotherapy.

Topoisomerase II-α as a predictive factor of response to therapy with anthracyclines in locally advanced breast cancer.

Gómez HL, Pinto JA, Olivera M, Vidaurre T, Doimi FD, Vigil CE, Velarde RG, Abugattas JE, Alarcón E, Vallejos CS.

Breast. 2011 Feb; 20(1): 39-45.

Abstract

BACKGROUND: Topoisomerase II-α is a molecular target of anthracyclines; several studies have suggested that topoisomerase II-α expression is related to response to anthracycline treatment. The objective of this study was to evaluate if topoisomerase II-α overexpression predicts response to anthracycline treatment in locally advanced breast cancer patients. MATERIAL AND METHODS: Topoisomerase II-α, HER2, estrogen receptor (ER) and progesterone receptor (PR) expression were evaluated by immunohistochemistry in formalin-fixed, paraffin-embedded breast tumors from 111 patients presenting with locally advanced breast cancer between 1995 and 2002. The prognostic value of these markers was analyzed using a multivariate proportional hazards regression model and an interaction analysis between topoisomerase II-α status and dose intensity. RESULTS: Tumors from 40 patients (36%) showed topoisomerase II-α overexpression, 62 patients (56%) for ER, 39 (35%) for PR and 26 (23%) for HER2. There were no significant correlations between topoisomerase II-α expression and response to therapy, progressionfree survival (PFS) or overall survival (OS). Anthracycline dose intensity had a significant impact on PFS and OS in patients overexpressing topoisomerase II-α (P=0.010 and 0.027, respectively). Negative PR (P=0.041), positive HER2 (P=0.013) were identified as risk factors in the multivariate model. The multivariate analysis in patients topoisomerase II-α negative shown no significance (HR=0.92, IC 95% 0.39-2.15, P=0.839) while the multivariate analysis in topoisomerase II-α positive, dose intensity shown to be statistically significant (HR=2.725, IC 95% 1.07-6.95, P=0.036). CONCLUSIONS: Our data do not support a correlation between topoisomerase II-α expression in breast cancer patients and improved clinical benefit with anthracycline therapy. However, they do suggest that tumors overexpressing topoisomerase II-α may experience better clinical benefit with higher anthracycline dose intensity.

Phase I and pharmacokinetic study of lonafarnib, SCH 66336, using a 2-week on, 2-week off schedule in patients with advanced solid tumors.

Castaneda C, Meadows KL, Truax R, Morse MA, Kaufmann SH, Petros WP, Zhu Y, Statkevich P, Cutler DL, Hurwitz HI.

Cancer Chemother Pharmacol. 2011 Feb;67(2):455-63.

Abstract

This phase I study was performed to determine the safety profile, maximum tolerated dose (MTD) and biological activity of lonafarnib (SCH 66336). Single-dose and multi-dose pharmacokinetics were conducted. Twenty-one patients with advanced solid tumors were enrolled. Each patient received single-dose administration on day 1, cycle 1 then switched to a twice daily (BID) dosing regimen on days 2-14 of a 28- day cycle; subsequent cycles continued BID dosing on days 1-14. Dose-limiting toxicity (DLT) was assessed during the cycle one; toxicity evaluation was closely monitored throughout the treatment. Radiographic scans were completed to assess tumor response. Blood and urine pharmacokinetics were evaluated on days 1 and 14 in cycle 1. SCH 66336- induced farnesylation inhibition was assessed via conversion of prelamin A to lamin in buccal mucosa. DLT and most common adverse events were diarrhea, fatigue, nausea and anorexia. No grade 3 or 4 hematological toxicities were observed. Nineteen of 21 patients were evaluable for response; short-term stable disease was observed in 5 patients. SCH 66336 systemic exposure increased with dose; however, drug accumulation was higher than projected. Renal excretion of parent drug was negligible. Farnesyl transferase inhibition was detected at the 200 and 300 mg BID doses. The MTD and recommended phase II dose is 200 mg BID on days 1-14 of a 28-day dosing regimen. The plasma concentration profile suggests the pharmacokinetics of SCH 66336 is dose and time dependent. Farnesyl transferase target inhibition was observed at doses of lonafarnib recommended for further study.