CÁNCER DE MAMA

The phosphatidyl inositol 3-kinase/AKT signaling pathway in breast cancer.

Castaneda CA, Cortes-Funes H, Gomez HL, Ciruelos EM.

Cancer Metastasis Rev. 2010 Dec; 29(4): 751-9.

Abstract

The phosphatidyl inositol 3-kinase (PI3K)/Akt pathway mediates the effects of a variety of extracellular signals in a number of cellular processes including cell growth, proliferation, and survival. The alteration of integrants of this pathway through mutation of its coding genes increases the activation status of the signaling and can thus lead to cellular transformation. The frequent dysregulation of the PI3K/Akt pathway in breast cancer (BC) and the mediation of this pathway in different processes characteristically implicated in tumorigenesis have attracted the interest of this pathway in BC; however, a more comprehensive understanding of the signaling intricacies is necessary to develop clinical applications of the modulation of this pathway in this pathology. We review a series of experiments examining the contribution of alteration of integrants of this signaling network to human BC and we make an update of the information about the effect of the modulation of this pathway in this cancer.

Prognostic effect of hormone receptor status in early HER2 positive breast cancer patients.

Gómez HL, Castañeda CA, Vigil CE, Vidaurre T, Velarde RG, Cruz WR, Pinto JA, Suazo JF, Garcés MR, Neciosup SP, Vallejos CS.

Hematol Oncol Stem Cell Ther. 2010; 3(3): 109-15.

Abstract

BACKGROUND: This study was conducted to determine the prognostic effect hormone receptor (HR) status in early HER2 positive (HER2+) breast cancer patients, since it has not yet been established whether HR status can be used in the prognosis of patients with (HER2+) breast cancer. PATIENTS AND METHODS: We obtained data from 299 patients with early HER2+ breast cancer who underwent surgery and received standard adjuvant chemotherapy, hormonal therapy and/or radiation between 2000 and 2002 at the Instituto Nacional de Enfermedades Neoplasicas, Perú. Clinical and pathological features were compared. Endpoints analyzed were disease free survival (DFS) and overall survival (OS). RESULTS: Overall, 155 patients were HR-positive (HR+) and 144 were negative (HR-). The two groups had similar characteristics except for histologic grade and extracapsular extension. With a median follow-up of 93 months, 5-year DFS was statistically different between the two groups: 65.0% for (HER2+/ HR-) and 74.6% for the (HER2+/ HR+) patients (p=.045). OS at 5 years was not statistically different between the two groups with 75.5% for (HER2+/ HR-) patients and 82.4% for the (HER2+/ HR+)(p=.140). CONCLUSIONS: Patients with (HER2+/ HR-) breast cancers treated with surgery and standard adjuvant chemotherapy exhibited a statistically worse DFS compared to those with (HER2+/ HR+) tumors. However, OS was similar in both groups.

Evaluation of a 30-gene paclitaxel, fluorouracil, doxorubicin, and cyclophosphamide chemotherapy response predictor in a multicenter randomized trial in breast cancer.

Tabchy A, Valero V, Vidaurre T, Lluch A, Gomez H, Martin M, Qi Y, BarajasFigueroa LJ, Souchon E, Coutant C, Doimi FD, Ibrahim NK, Gong Y, Hortobagyi GN, Hess KR, Symmans WF, Pusztai L.

Clin Cancer Res. 2010 Nov 1; 16(21): 5351-61.

Abstract

PURPOSE: We examined in a prospective, randomized, international clinical trial the performance of a previously defined 30-gene predictor (DLDA-30) of pathologic complete response (pCR) to preoperative weekly paclitaxel and fluorouracil, doxorubicin, and cyclophosphamide (T/FAC) chemotherapy, and assessed if DLDA-30 also predicts increased sensitivity to FAC-only chemotherapy. We compared the pCR rates after T/FAC versus FACx6 preoperative chemotherapy. We also did an exploratory analysis to identify novel candidate genes that differentially predict response in the two treatment arms. EXPERIMENTAL DESIGN: Two hundred and seventy-three patients were randomly assigned to receive either weekly paclitaxel × 12 followed by FAC × 4 (T/FAC, n = 138), or FAC × 6 (n = 135) neoadjuvant chemotherapy. All patients underwent a pretreatment fine-needle aspiration biopsy of the tumor for gene expression profiling and treatment response prediction. RESULTS: The pCR rates were 19% and 9% in the T/FAC and FAC arms, respectively ($P < 0.05$). In the T/FAC arm, the positive predictive value (PPV) of the genomic predictor was 38% [95% confidence interval (95% CI), 21-56%], the negative predictive value was 88% (95% CI, 77-95%), and the area under the receiver operating characteristic curve (AUC) was 0.711. In the FAC arm, the PPV was 9% (95% CI, 1-29%) and the AUC was 0.584. This suggests that the genomic predictor may have regimen specificity. Its performance was similar to a clinical variable-based predictor nomogram. CONCLUSIONS: Gene expression profiling for prospective response prediction was feasible in this international trial. The 30-gene predictor can identify patients with greater than average sensitivity to T/FAC chemotherapy. However, it captured molecular equivalents of clinical phenotype. Next-generation predictive markers will need to be developed separately for different molecular subsets of breast cancers.

Breast cancer classification according to immunohistochemistry markers: subtypes and association with clinicopathologic variables in a peruvian hospital database.

Vallejos CS, Gómez HL, Cruz WR, Pinto JA, Dyer RR, Velarde R, Suazo JF, Neciosup SP, León M, de la Cruz MA, Vigil CE.

Clin Breast Cancer. 2010 Aug 1; 10(4): 294-300.

Abstract

BACKGROUND: Molecular classification is an excellent prognostic and predictive method in breast cancer (BC). In this study. we evaluated differences in clinicopathologic features and overall survival (OS) in four BC molecular subtypes: luminal A, luminal B, basal cell-like, and HER2/neu. PATIENTS AND METHODS: Immunohistochemical evaluation of estrogen receptor (ER), progesterone receptor (PgR), and HER2 was performed using a Peruvian hospital database of 1198 BC patients who were diagnosed between 2000 and 2002. Overall survival was calculated. RESULTS: Out of 1198 patients with invasive BC, 49.3% were luminal A; 13.2%, luminal B; 21.3%, basal-like; and 16.2%, HER2. The mean of age at diagnosis was 51.5 years for luminal A; 49.6 for luminal B; 49.5 for basal-like; and 49.4 for HER2. The HER2 subtype showed 63.7% positive lymph nodes, 42.3% stage III and 9.7% stage IV cases. Basal subtypes showed the highest prevalence of a poorly differentiated phenotype (70.3%). Average follow-up was 60 months. Five-year OS was significantly different between all 4 groups ($P < .0001$); luminal A had the highest OS, followed by luminal B, basal-like; and HER2. Results are compared with other population studies. CONCLUSION: This study shows significant differences between the distribution of molecular subtypes and clinicopathologic features. Immunohistochemistry is useful in the clinical management of BC patients.

Analysis of overall survival from a phase III study of ixabepilone plus capecitabine versus capecitabine in patients with MBC resistant to anthracyclines and taxanes.

Hortobagyi GN, Gomez HL, Li RK, Chung HC, Fein LE, Chan VF, Jassem J, Lerzo GL, Pivot XB, Hurtado de Mendoza F, Xu B, Vahdat LT, Peck RA, Mukhopadhyay P, Roché H.

Breast Cancer Res Treat. 2010 Jul; 122(2): 409-18.

Abstract

Limited proven treatment options exist for patients with metastatic breast cancer (MBC) resistant to anthracycline and taxane treatment. Ixabepilone, a novel semisynthetic analog of epothilone B, has demonstrated single-agent activity in MBC resistant to anthracyclines and taxanes. In combination with capecitabine in a phase III trial (CA163-046) in this setting, ixabepilone prolonged progression-free survival and increased objective response rate relative to capecitabine (Thomas et al. J Clin Oncol 25:5210-5217, 2007). Here, we report the results of overall survival (OS), a secondary efficacy endpoint from the CA163- 046 trial. Seven hundred fifty-two patients with MBC resistant to anthracyclines and taxanes were randomized to ixabepilone (40 mg/m(2) intravenously on day 1 of a 21-day cycle) plus capecitabine (2,000 mg/m(2) orally on days 1 through 14 of a 21-day cycle) or capecitabine alone (2,500 mg/m(2) on the same schedule). Patients receiving ixabepilone plus capecitabine treatment had a median survival of 12.9 months compared to 11.1 months for patients receiving capecitabine alone (HR = 0.9; 95%CI: 077-1.05; P = 0.19). This observed increase in median OS favored the combination; however, the difference was not statistically significant. Predefined subset analyses showed a clinically meaningful increase in OS in KPS 70-80 patients receiving ixabepilone plus capecitabine (HR = 0.75; 95% CI: 0.58-0.98). Ixabepilone plus capecitabine did not show a significant improvement in survival compared to capecitabine alone in patients with MBC resistant to anthracyclines and taxanes. The observed differences in survival favored the combination arm. A clinical benefit was also seen in patients in the KPS 70-80 subgroup.

Clinical benefit of lapatinib-based therapy in patients with human epidermal growth factor receptor 2-positive breast tumors coexpressing the truncated p95HER2 receptor.

Scaltriti M, Chandarlapaty S, Prudkin L, Aura C, Jimenez J, Angelini PD, Sánchez G, Guzman M, Parra JL, Ellis C, Gagnon R, Koehler M, Gomez H, Geyer C, Cameron D, Arribas J, Rosen N, Baselga J.

Clin Cancer Res. 2010 May 1; 16(9): 2688-95.

Abstract

PURPOSE: A subgroup of human epidermal growth factor receptor 2 (HER2)- overexpressing breast tumors coexpresses p95HER2, a truncated HER2 receptor that retains a highly functional HER2 kinase domain but lacks the extracellular domain and results in intrinsic trastuzumab resistance. We hypothesized that lapatinib, a HER2 tyrosine kinase inhibitor, would be active in these tumors. We have studied the correlation between p95HER2 expression and response to lapatinib, both in preclinical models and in the clinical setting. EXPERIMENTAL DESIGN: Two different p95HER2 animal models were used for preclinical studies. Expression of p95HER2 was analyzed in HER2-overexpressing breast primary tumors from a first-line lapatinib monotherapy study (EGF20009) and a secondline lapatinib in combination with capecitabine study (EGF100151). p95HER2 expression was correlated with overall response rate (complete + partial response), clinical benefit rate (complete response + partial response + stable disease > or =24 wk), and progression-free survival using logistic regression and Cox proportional hazard models. RESULTS: Lapatinib inhibited tumor growth and the HER2 downstream signaling of p95HER2-expressing tumors. A total of 68 and 156 tumors from studies EGF20009 and EGF100151 were evaluable, respectively, for p95HER2 detection. The percentage of p95HER2-positive patients was 20.5% in the EGF20009 study and 28.5% in the EGF100151 study. In both studies, there was no statistically significant difference in progression-free survival, clinical benefit rate, and overall response rate between p95HER2-positive and p95HER2-negative tumors. CONCLUSIONS: Lapatinib as a monotherapy or in combination with capecitabine seems to be equally effective in patients with p95HER2-positive and p95HER2-negative HER2- positive breast tumors.

Quality-of-life and quality-adjusted survival (Q-TWiST) in patients receiving lapatinib in combination with paclitaxel as first-line treatment for metastatic breast cancer.

Sherrill B, Di Leo A, Amonkar MM, Wu Y, Zvirbule Z, Aziz Z, Bines J, Gomez HL.

Curr Med Res Opin. 2010 Apr; 26(4): 767-75.

Abstract

BACKGROUND: In a phase 3 randomized, multicenter, double-blind, placebo-controlled study, first-line therapy with lapatinib plus paclitaxel significantly improved clinical outcomes based on a pre-planned analysis of ErbB2+ metastatic breast cancer patients (GSK Study #EGF30001; ClinicalTrials.gov identifier: NCT00075270). Patients with ErbB2- or untested did not significantly benefit. This article focuses on the quality of life (QOL) and quality-adjusted survival outcomes (Q-TWiST) in the study. METHODS: QOL was assessed using the Functional Assessment of Cancer TherapyBreast (FACT-B). Changes from baseline were analyzed using ANCOVAs, repeated measures and pattern mixture modeling. The Q-TWiST method was used to examine the trade-off between toxicities and delayed progression. RESULTS: The study included 579 subjects, of whom 86 were ErbB2+. In the ITT population, no significant differences in QOL or Q-TWiST scores were observed. In the ErbB2+ subgroup, the lapatinib plus paclitaxel (L + P) arm demonstrated stable FACT-B scores over the first year, while average scores for patients on P + placebo (P + pla) monotherapy decreased (change from baseline: L + P, $p = 0.99$; P + pla, $p = 0.01$). Clinically meaningful differences were observed between treatment arms on the FACT-B, Trial Outcome Index and breast cancer subscale scores. Pattern mixture models suggested more QOL differentiation between treatments among patients who progressed or withdrew early. Q-TWiST differences between the arms in the ErbB2+ subgroup ranged from 2 to 15 weeks with an L + P advantage across all utility weight combinations. CONCLUSIONS: In the ITT population, results provide no evidence of QOL differences between treatment groups. In a small, prospectively-defined subgroup of ErbB2+ patients, L + P resulted in more stable QOL and more quality-adjusted survival than paclitaxel monotherapy, representing clinically important differences between treatments.