CÁNCER DE MAMA

Lactate dehydrogenase B: a metabolic marker of response to neoadjuvant chemotherapy in breast cancer.

Dennison JB, Molina JR, Mitra S, González-Angulo AM, Balko JM, Kuba MG, Sanders ME, Pinto JA, Gómez HL, Arteaga CL, Brown RE, Mills GB.

Clin Cancer Res. 2013 Jul 1;19(13):3703-13.

Abstract

Although breast cancers are known to be molecularly heterogeneous, their metabolic phenotype is less well-understood and may predict response to chemotherapy. This study aimed to evaluate metabolic genes as individual predictive biomarkers in breast cancer. mRNA microarray data from breast cancer cell lines were used to identify bimodal genes-those with highest potential for robust high/low classification in clinical assays. Metabolic function was evaluated in vitro for the highest scoring metabolic gene, lactate dehydrogenase B (LDHB). Its expression was associated with neoadjuvant chemotherapy response and relapse within clinical and PAM50-derived subtypes. LDHB was highly expressed in cell lines with glycolytic, basal-like phenotypes. Stable knockdown of LDHB in cell lines reduced glycolytic dependence, linking LDHB expression directly to metabolic function. Using patient datasets, LDHB was highly expressed in basal-like cancers and could predict basal-like subtype within clinical groups [OR = 21 for hormone receptor (HR)-positive/HER2-negative; OR = 10 for triple-negative]. Furthermore, high LDHB predicted pathologic complete response (pCR) to neoadjuvant chemotherapy for both HR-positive/HER2-negative (OR = 4.1, $P < 0.001$) and triple-negative (OR = 3.0, $P = 0.003$) cancers. For triple-negative tumors without pCR, high LDHB posttreatment also identified proliferative tumors with increased risk of recurrence (HR = 2.2, $P = 0.006$). Expression of LDHB predicted response to neoadjuvant chemotherapy within clinical subtypes independently of standard prognostic markers and PAM50 subtyping. These observations support prospective clinical evaluation of LDHB as a predictive marker of response for patients with breast cancer receiving neoadjuvant chemotherapy.

A randomized phase II study of lapatinib + pazopanib versus lapatinib in patients with HER2+ inflammatory breast cancer.

Cristofanilli M, Johnston SR, Manikhas A, Gomez HL, Gladkov O, Shao Z, Safina S, Blackwell KL, Alvarez RH, Rubin SD, Ranganathan S, Redhu S, Trudeau ME.

Breast Cancer Res Treat. 2013 Jan;137(2):471-82.

Abstract

This multi-center Phase II study evaluated lapatinib, pazopanib, and the combination in patients with relapsed HER2+ inflammatory breast cancer. In Cohort 1, 76 patients were randomized 1:1 to receive lapatinib 1,500 mg + placebo or lapatinib 1,500 mg + pazopanib 800 mg (double-blind) once daily until disease progression, unacceptable toxicity, or death. Due to high-grade diarrhea observed with this dose combination in another study (VEG20007), Cohort 1 was closed. The protocol was amended such that an additional 88 patients (Cohort 2) were randomized in a 5:5:2 ratio to receive daily monotherapy lapatinib 1,500 mg, lapatinib 1,000 mg + pazopanib 400 mg, or monotherapy pazopanib 800 mg, respectively. The primary endpoint was overall response rate (ORR). Secondary endpoints included duration of response, progression-free survival (PFS), overall survival, and safety. In Cohort 1, ORR for the lapatinib (n = 38) and combination (n = 38) arms was 29 and 45 %, respectively; median PFS was 16.1 and 14.3 weeks, respectively. Grade ≥3 adverse events (AEs) were more frequent in the combination arm (71 %) than in the lapatinib arm (24 %). Dose reductions and interruptions due to AEs were also more frequent in the combination arm (45 and 53 %, respectively) than in the lapatinib monotherapy arm (0 and 11 %, respectively). In Cohort 2, ORR for patients treated with lapatinib (n = 36), lapatinib + pazopanib (n = 38), and pazopanib (n = 13) was 47, 58, and 31 %, respectively; median PFS was 16.0, 16.0, and 11.4 weeks, respectively. In the lapatinib, combination, and pazopanib therapy arms, grade ≥3 AEs were reported for 17, 50, and 46 % of patients, respectively, and the incidence of discontinuations due to AEs was 0, 24, and 23 %, respectively. The lapatinib-pazopanib combination was associated with a numerically higher ORR but no increase in PFS compared to lapatinib alone. The combination also had increased toxicity resulting in more dose reductions, modifications, and treatment delays. Activity with single-agent lapatinib was confirmed in this population.

Cost-effectiveness analysis of breast cancer control interventions in Peru.

Zelle SG, Vidaurre T, Abugattas JE, Manrique JE, Sarria G, Jeronimo J, Seinfeld JN, Lauer JA, Sepulveda CR, Venegas D, Baltussen R.

PLoS One. 2013 Dec 10;8(12):e82575.

Abstract

OBJECTIVES: In Peru, a country with constrained health resources, breast cancer control is characterized by late stage treatment and poor survival. To support breast cancer control in Peru, this study aims to determine the cost-effectiveness of different breast cancer control interventions relevant for the Peruvian context. METHODS: We performed a cost-effectiveness analysis (CEA) according to WHO-CHOICE guidelines, from a healthcare perspective. Different screening, early detection, palliative, and treatment interventions were evaluated using mathematical modeling. Effectiveness estimates were based on observational studies, modeling, and on information from Instituto Nacional de Enfermedades Neoplásicas (INEN). Resource utilizations and unit costs were based on estimates from INEN and observational studies. Costeffectiveness estimates are in 2012 United States dollars (US$) per disability adjusted life year (DALY) averted. RESULTS: The current breast cancer program in Peru ($8,426 per DALY averted) could be improved through implementing triennial or biennial screening strategies. These strategies seem the most cost-effective in Peru, particularly when mobile mammography is applied (from $4,125 per DALY averted), or when both CBE screening and mammography screening are combined (from $4,239 per DALY averted). Triennially, these interventions costs between $63 million and $72 million per year. Late stage treatment, trastuzumab therapy and annual screening strategies are the least cost-effective. CONCLUSIONS: Our analysis suggests that breast cancer control in Peru should be oriented towards early detection through combining fixed and mobile mammography screening (age 45-69) triennially. However, a phased introduction of triennial CBE screening (age 40-69) with upfront FNA in non-urban settings, and both CBE (age 40-49) and fixed mammography screening (age 50-69) in urban settings, seems a more feasible option and is also cost-effective. The implementation of this intervention is only meaningful if awareness raising, diagnostic, referral, treatment and basic palliative services are simultaneously improved, and if financial and organizational barriers to these services are reduced.

Efficacy and safety of ixabepilone plus capecitabine in elderly patients with anthracycline- and taxane-pretreated metastatic breast cancer.

Vahdat LT, Vrdoljak E, Gómez H, Li RK, Bosserman L, Sparano JA, Baselga J, Mukhopadhyay P, Valero V.

J Geriatr Oncol. 2013 Oct;4(4):346-52.

Abstract

OBJECTIVES: Data on chemotherapy regimens in elderly patients with metastatic breast cancer (MBC) are limited. The aim of this retrospective pooled analysis was to determine efficacy and safety of ixabepilone plus capecitabine versus capecitabine alone in patients with MBC aged ≥ 65 years. MATERIALS AND METHODS: A total of 1973 patients with MBC previously treated with or resistant to anthracyclines and taxanes were randomized in two open-label, multinational, phase 3 studies (study 046 and study 048). Patients received ixabepilone (40 mg/m(2) as a 3-hour intravenous infusion every 3 weeks) plus oral capecitabine (1000 mg/m(2) administered twice each day), or capecitabine alone (1250 mg/m(2) twice each day). RESULTS: In total, 251 randomized patients were aged ≥ 65 years (ixabepilone plus capecitabine, n=116; capecitabine monotherapy, n=135). Efficacy results were consistent in patients aged < 65 years.

Triple negative breast cancer: a difficult disease to diagnose and treat.

Zaharia M, Gómez H.

Rev Peru Med Exp Salud Publica. 2013 Oct-Dec;30(4):649-56.

Abstract

Triple negative breast cancer (CMTN, Spanish acronym) is a malignant neoplasm characterized by the absence of expression of estrogen, progesterone and HER2 receptors. Recent studies have shown that CMTN is a heterogeneous group including different neoplasm with different prognosis. However, because genetic profiles are not a standard practice in conventional diagnosis of breast cancer, it is hard to properly identify this breast cancer subtype. CMTN is characterized by its high-incidence epidemiological patterns in African-American and Latin people, and lower incidence in Caucasian people, and constitutes a public health issue due to its high morbidity and mortality. Due to the absence of therapeutic targets, chemotherapy has a key role in treatment, and many efforts are being deployed to seek other combinations of chemotherapy and new drugs, while the current guides do not specify treatment for this type of cancer. This document reviews the epidemiological and clinical characteristics, the potential prognosis factors and some therapeutic strategies against CMTN.

Breast cancer in young women in Latin America: an unmet, growing burden.

Villarreal-Garza C, Aguila C, Magallanes-Hoyos MC, Mohar A, Bargalló E, Meneses A, Cazap E, Gomez H,López-Carrillo L, Chávarri-Guerra Y, Murillo R, Barrios C.

Oncologist. 2013;18 Suppl:26-34.

Abstract

BACKGROUND: Breast cancer (BC) is the leading cause of malignancy-related deaths among women aged ≤ 45 years. There are unexplored and uncertain issues for BC in this particular group in Latin America. The aim of this study is to evaluate BC incidence and mortality among young women and related clinicopathological and survivorship aspects in this region. MATERIALS AND METHODS: Data were obtained from Globocan 2008 and the International Agency for Research on Cancer's Cancer Incidence in Five Continents series plus databases. We requested collaboration from the 12 different national cancer institutes in Latin America through SLACOM, the Latin American and Caribbean Society of Medical Oncology, and conducted a systematic literature review to obtain local data regarding the prevalence of BC among young women and their characteristics, outcomes, and survivorship-related issues. RESULTS: BC incidence and mortality proportions for Latin American women aged <44 years were higher when compared with those of developed countries (20% vs. 12% and 14% vs. 7%, respectively). We found only a few Latin American series addressing this topic, and prevalence varied between 8% and 14%. Stage II and III disease, high histological grade, and triple-negative and HER2 BC were features frequently observed among young Latin American BC patients. CONCLUSION: The rising incidence and mortality of BC in young Latin American women is a call to action in the region. It is necessary to monitor the epidemiological and clinical data through reliable cancer registries and to consider the implementation of protocols for education of patients and health professionals. This unmet, growing burden must be considered as a top priority of the national programs in the fight against BC, and models of specialized units should be implemented for this particular group of patients to provide better care for this emergent challenge.

Activation of MAPK pathways due to DUSP4 loss promotes cancer stem cell-like phenotypes in basal-like breast cancer.

Balko JM1 , Schwarz LJ, Bhola NE, Kurupi R, Owens P, Miller TW, Gómez H, Cook RS, Arteaga CL.

Cancer Res. 2013 Oct 15;73(20):6346-58.

Abstract

Basal-like breast cancer (BLBC) is an aggressive disease that lacks a clinically approved targeted therapy. Traditional chemotherapy is effective in BLBC, but it spares the cancer stem cell (CSC)-like population, which is likely to contribute to cancer recurrence after the initial treatment. Dual specificity phosphatase-4 (DUSP4) is a negative regulator of the mitogen-activated protein kinase (MAPK) pathway that is deficient in highly aggressive BLBCs treated with chemotherapy, leading to aberrant MAPK activation and resistance to taxane-induced apoptosis. Herein, we investigated how DUSP4 regulates the MAP-ERK kinase (MEK) and c-jun-NH2-kinase (JNK) pathways in modifying CSC-like behavior. DUSP4 loss increased mammosphere formation and the expression of the CSC-promoting cytokines interleukin (IL)-6 and IL-8. These effects were caused in part by loss of control of the MEK and JNK pathways and involved downstream activation of the ETS-1 and c-JUN transcription factors. Enforced expression of DUSP4 reduced the CD44(+)/CD24(-) population in multiple BLBC cell lines in a MEKdependent manner, limiting tumor formation of claudin-low SUM159PT cells in mice. Our findings support the evaluation of MEK and JNK pathway inhibitors as therapeutic agents in BLBC to eliminate the CSC population.