CÁNCER DE MAMA

Adjuvant Exemestane with Ovarian Suppression in Premenopausal Breast Cancer.

Pagani O, Regan MM, Walley BA, Fleming GF, Colleoni M, Láng I, Gomez HL, Tondini C, Burstein HJ, Perez EA, Ciruelos E, Stearns V, Bonnefoi HR, Martino S,Geyer CE Jr, Pinotti G, Puglisi F, Crivellari D, Ruhstaller T, Winer EP, Rabaglio-Poretti M, Maibach R, Ruepp B, Giobbie-Hurder A, Price KN, Bernhard J, Luo W,Ribi K, Viale G, Coates AS, Gelber RD, Goldhirsch A, Francis PA; the TEXT and SOFT Investigators and the International Breast Cancer Study Group.

N Engl J Med. 2014 Jun 1.

Abstract

BACKGROUND Adjuvant therapy with an aromatase inhibitor improves outcomes, as compared with tamoxifen, in postmenopausal women with hormone-receptor-positive breast cancer. METHODS In two phase 3 trials, we randomly assigned premenopausal women with hormone-receptor-positive early breast cancer to the aromatase inhibitor exemestane plus ovarian suppression or tamoxifen plus ovarian suppression for a period of 5 years. Suppression of ovarian estrogen production was achieved with the use of the gonadotropin-releasing-hormone agonist triptorelin, oophorectomy, or ovarian irradiation. The primary analysis combined data from 4690 patients in the two trials. RESULTS After a median follow-up of 68 months, disease-free survival at 5 years was 91.1% in the exemestaneovarian suppression group and 87.3% in the tamoxifen-ovarian suppression group (hazard ratio for disease recurrence, second invasive cancer, or death, 0.72; 95% confidence interval [CI], 0.60 to 0.85; P<0.001). The rate of freedom from breast cancer at 5 years was 92.8% in the exemestane-ovarian suppression group, as compared with 88.8% in the tamoxifen-ovarian suppression group (hazard ratio for recurrence, 0.66; 95% CI, 0.55 to 0.80; P<0.001). With 194 deaths (4.1% of the patients), overall survival did not differ significantly between the two groups (hazard ratio for death in the exemestaneovarian suppression group, 1.14; 95% CI, 0.86 to 1.51; P=0.37). Selected adverse events of grade 3 or 4 were reported for 30.6% of the patients in the exemestane-ovarian suppression group and 29.4% of those in the tamoxifen-ovarian suppression group, with profiles similar to those for postmenopausal women. CONCLUSIONS In premenopausal women with hormone-receptor-positive early breast cancer, adjuvant treatment with exemestane plus ovarian suppression, as compared with tamoxifen plus ovarian suppression, significantly reduced recurrence. (Funded by Pfizer and others; TEXT and SOFT ClinicalTrials.gov numbers, NCT00066703 and NCT00066690 , respectively.).

Emergence of Constitutively Active Estrogen Receptor-α Mutations in Pretreated Advanced Estrogen ReceptorPositive Breast Cancer.

Jeselsohn R, Yelensky R, Buchwalter G, Frampton G, Meric-Bernstam F, GonzalezAngulo AM, Ferrer-Lozano J, Perez-Fidalgo JA, Cristofanilli M, Gómez H,Arteaga CL, Giltnane J, Balko JM, Cronin MT, Jarosz M, Sun J, Hawryluk M, Lipson D, Otto G, Ross JS, Dvir A, Soussan-Gutman L, Wolf I, Rubinek T, Gilmore L,Schnitt S, Come SE, Pusztai L, Stephens P, Brown M, Miller VA.

Clin Cancer Res. 2014 Apr 1;20(7):1757-67.

Abstract

PURPOSE: We undertook this study to determine the prevalence of estrogen receptor (ER) α (ESR1) mutations throughout the natural history of hormone-dependent breast cancer and to delineate the functional roles of the most commonly detected alterations. EXPERIMENTAL DESIGN: We studied a total of 249 tumor specimens from 208 patients. The specimens include 134 ER-positive (ER(+)/HER2(-)) and, as controls, 115 ER-negative (ER(-)) tumors. The ER(+) samples consist of 58 primary breast cancers and 76 metastatic samples. All tumors were sequenced to high unique coverage using next-generation sequencing targeting the coding sequence of the estrogen receptor and an additional 182cancer-related genes. RESULTS: Recurring somatic mutations in codons 537 and 538 within the ligand-binding domain of ER were detected in ER(+) metastatic disease. Overall, the frequency of these mutations was 12% [9/76; 95% confidence interval (CI), 6%-21%] in metastatic tumors and in a subgroup of patients who received an average of 7 lines of treatment the frequency was 20% (5/25; 95% CI, 7%-41%). These mutations were not detected in primary or treatment-naïve ER(+) cancer or in any stage of ER(-) disease. Functional studies in cell line models demonstrate that these mutations render estrogen receptor constitutive activity and confer partial resistance to currently available endocrine treatments. CONCLUSIONS: In this study, we show evidence for the temporal selection of functional ESR1 mutations as potential drivers of endocrine resistance during the progression of ER(+) breast cancer.

Molecular profiling of the residual disease of triplenegative breastcancers after neoadjuvant chemotherapy identifies actionable therapeutic targets.

Balko JM, Giltnane JM, Wang K, Schwarz LJ, Young CD, Cook RS, Owens P, Sanders ME, Kuba MG,Sánchez V, Kurupi R, Moore PD, Pinto JA, Doimi FD, Gómez H, Horiuchi D, Goga A, Lehmann BD, Bauer JA, Pietenpol JA, Ross JS, Palmer GA, Yelensky R, Cronin M, Miller VA, Stephens PJ, Arteaga CL.

Cancer Discov. 2014 Feb;4(2):232-45.

Abstract

Neoadjuvant chemotherapy (NAC) induces a pathologic complete response (pCR) in approximately 30% of patients with triple-negative breast cancers (TNBC). In patients lacking a pCR, NAC selects a subpopulation of chemotherapy-resistant tumor cells. To understand the molecular underpinnings driving treatment-resistant TNBCs, we performed comprehensive molecular analyses on the residual disease of 74 clinically defined TNBCs after NAC, including next-generation sequencing (NGS) on 20 matched pretreatment biopsies. Combined NGS and digital RNA expression analysis identified diverse molecular lesions and pathway activation in drug-resistant tumor cells. Ninety percent of the tumors contained a genetic alteration potentially treatable with a currently available targeted therapy. Thus, profiling residual TNBCs after NAC identifies targetable molecular lesions in the chemotherapy-resistant component of the tumor, which may mirror micrometastases destined to recur clinically. These data can guide biomarkerdriven adjuvant studies targeting these micrometastases to improve the outcome of patients with TNBC who do not respond completely to NAC. Significance: This study demonstrates the spectrum of genomic alterations present in residual TNBC after NAC. Because TNBCs that do not achieve a CR after NAC are likely to recur as metastatic disease at variable times after surgery, these alterations may guide the selection of targeted therapies immediately after mastectomy before these metastases become evident.

Attitudes of young patients with breast cancer toward fertility loss related to adjuvant systemic therapies. EORTC study 10002 BIG 3-98.

Senkus E , Gomez H, Dirix L, Jerusalem G, Murray E, Van Tienhoven G, Westenberg AH, Bottomley A,Rapion J, Bogaerts J, Di Leo A, Nešković-Konstantinović Z.

Psychooncology. 2014 Feb;23(2):173-82.

Abstract

OBJECTIVE: Infertility due to anticancer treatments is a major source of distress for young patients with cancer. A survey was performed among breast cancer patients younger than 35 years, to evaluate the acceptance of chemotherapy in the context of infertility risk. METHODS: After obtaining written informed consent, we asked 400 premenopausal, early stage breast cancer patients aged ≤35 years to complete a short, previously pilot-tested questionnaire. Three hundred and eighty-nine patients were evaluable. The association between the explanatory variables and the outcome variables was assessed using logistic regression. RESULTS: Two hundred and twenty-eight (59%) participants wanted to have (more) children in the future, whereas 158 (41%) did not. Fifty-seven (36%) of the latter did not want additional children because of fear of cancer recurrence. Thirty-two women (8%) stated they would not accept chemotherapy should it reduce their fertility. This was dependent upon already having children, the wish to have (further) children, geographical area, disease stage, and already planned chemotherapy. One hundred and seventy-one women who would agree to chemotherapy (48%) would accept a risk of infertility of 76-100%. This acceptance was dependent on already having children and the wish to have (more) children. Of the 355 participants (91%) accepting chemotherapy, 48 would accept it only for ≥20% gain in cure. CONCLUSION: For the majority of young patients with breast cancer, cure remains their first priority; for this, they are willing to accept a considerable decrease in future fertility, and only less than 10% will forego chances of cure to preserve fertility.

Prevalence of BRCA1 and BRCA2 mutations in unselected breast cancer patients from Peru.

Abugattas J, Llacuachaqui M, Allende YS, Velásquez AA, Velarde R, Cotrina J, Garcés M, León M, Calderón G, de la Cruz M, Mora P, Royer R, Herzog J, Weitzel JN, Narod SA.

Clin Genet. 2014 Sep 25.

Abstract

The prevalence of BRCA1 and BRCA2 mutations among breast cancer patients in Peru has not yet been explored. We enrolled 266 women with breast cancer from a National cancer hospital in Lima, Peru, unselected for age or family history. DNA was screened with a panel of 114 recurrent Hispanic BRCA mutations (HISPANEL). Among the 266 cases, 13 deleterious mutations were identified (11 in BRCA1 and 2 in BRCA2), representing 5% of the total. The average age of breast cancer in the mutation-positive cases was 44 years. BRCA1 185delAG represented 7 of 11 mutations in BRCA1. Other mutations detected in BRCA1 included: two 2080delA, one 943ins10, and one 3878delTA. The BRCA2 3036del4 mutation was seen in two patients. Given the relatively low cost of the HISPANEL test, one should consider offering this test to all Peruvian women with breast or ovarian cancer.

PIK3CA mutations in Peruvian patients with HER2-amplified and triple negative non-metastatic breast cancers.

Castaneda CA, Lopez-Ilasaca M, Pinto JA, Chirinos-Arias M, Doimi F, Neciosup SP, Rojas KI, Vidaurre T, Balko JM, Arteaga CL, Gomez HL.

Hematol Oncol Stem Cell Ther. 2014 Dec;7(4):142-8.

Abstract

PURPOSE: To determine the frequency of PIK3CA mutations in a Peruvian cohort with HER2-amplified and triple negative breast cancers (TNBC). METHODS: We analyzed two cohorts of 134 primary non-metastatic breast cancer patients from Peru. Cohorts consisted of 51 hormone receptors (+)/HER2-amplified breast tumor patients surgically resected as first treatment included in the ALTTO trial (ALTTO cohort) and 81 TNBC patients with residual disease after neoadjuvant treatment (neoadjuvant cohort). Genomic DNA was extracted from paraffin-embedded tumor samples. Samples from the ALTTO and neoadjuvant cohorts were taken at biopsies and from residual tumors, respectively. PIK3CA mutations were detected by sequencing DNA fragments obtained by PCR amplification of exons and their flanking introns. All of the detected PIK3CA mutations were confirmed in a second independent run of sample testing. RESULTS: PIK3CA mutations were present in 21/134 cases (15.7%). Mutations in exon 9 and 20 were present in 10/134 (7.5%) and 11/134 (8.2%), respectively. No cases had mutations in both exons. Mutations in exon 9 consisted of E545A (seven cases), E545K (two cases) and E545Q (one case); while in exon 20, mutations consisted of H1047R (10 cases) and H1047L (one case). Compared to TNBC patients, HER2-amplified patients were more likely to have PIK3CA mutated (23% vs 9.6%; P=0.034). There were no associations between mutational status of PIK3CA with estrogen receptor status (P=0.731), progesterone receptor status (P=0.921), age (P=0.646), nodal status (P=0.240) or histological grade (P=1.00). No significant associations were found between PIK3CA mutational status and clinicopathological features. CONCLUSIONS: We found a similar frequency of PIK3CA mutations to that reported in other series. Although we did not include HR+/HER2 patients, those with HER2-amplified tumors were more likely to present PIK3CA mutations compared to patients with triple negative tumors.

Association between mammographic features and response to neoadjuvant chemotherapy in locally advanced breast carcinoma.

Castaneda CA, Flores R, Rojas K, Flores C, Castillo M, Milla E.

Hematol Oncol Stem Cell Ther. 2014 Dec;7(4):149-56.

Abstract

PURPOSE: Mammography is the cornerstone of breast cancer (BC) evaluation. This report investigates whether breast density (BD) and mammographic features of the tumor can provide information on both BC susceptibility to chemotherapy and other clinicopathologic features of locally advanced BC (LA BC). MATERIALS AND METHODS: We evaluated mammography films and clinicopathological information of patients with LA BC who received neoadjuvant chemotherapy (NAC) followed by tumor resection at the Instituto Nacional de Enfermedades Neoplásicas (INEN) from 2000 to 2011. RESULTS: We selected 494 LA BC cases. Most cases were at clinical tumor stage 4 (48.5%), node stage 1 (58.8%) and had high histologic grade (53.3%). BI-RADS 1, 2, 3, and 4 BD were found in 16.9%, 22%, 35.7% and 25.1% of patients, respectively. High BD has been associated with younger age ($p<0.001$), obesity ($p=0.017$) and no skin infiltration (T3 vs T4) ($p=0.018$). An association between dusty microcalcifications and HER2 group, as well as between casting microcalcifications and TN BC group ($p=0.05$) was found. NAC included anthracyclines and taxanes in 422 (85.5%) cases. Miller-Payne pathologic responses 4 and 5 (pCR) in the primary lesion and absence of axillary lymph nodes involvement were found in 15.3% of cases and were associated with younger age ($p<0.001$) and HG-3 lesions ($p<0.001$), but not with mammographic images. CONCLUSION: Mammographic features are associated with specific clinicopathological features of pre-NAC BC lesions but do not predict pCR. The implications and biological reasons for these findings require further study.