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Prognostic significance of ESR1 gene amplification, mRNA/protein expression and functional profiles in high-risk early breast cancer: a translational study of the Hellenic Cooperative Oncology Group (HeCOG).

Pentheroudakis G, Kotoula V, Eleftheraki AG, Tsolaki E, Wirtz RM, Kalogeras KT, Batistatou A, Bobos M, Dimopoulos MA, Timotheadou E, Gogas H, Christodoulou C, Papadopoulou K, Efstratiou I, Scopa CD, Papaspyrou I, Vlachodimitropoulos D, Linardou H, Samantas E, Pectasides D, Pavlidis N, Fountzilas G.

Source

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Abstract

BACKGROUND:

Discrepant data have been published on the incidence and prognostic significance of ESR1 gene amplification in early breast cancer.

PATIENTS AND METHODS:

Formalin-fixed paraffin-embedded tumor blocks were collected from women with early breast cancer participating in two HeCOG adjuvant trials. Messenger RNA was studied by quantitative PCR, ER protein expression was centrally assessed using immunohistochemistry (IHC) and ESR1 gene copy number by dual fluorescent in situ hybridization probes.

RESULTS:

In a total of 1010 women with resected node-positive early breast adenocarcinoma, the tumoral ESR1/CEP6 gene ratio was suggestive of deletion in 159 (15.7%), gene gain in 551 (54.6%) and amplification in 42 cases (4.2%), with only 30 tumors (3%) harboring five or more ESR1 copies. Gene copy number ratio showed a significant, though weak correlation to mRNA and protein expression (Spearman's Rho <0.23, p=0.01). ESR1 clusters were observed in 9.5% (57 gain, 38 amplification) of cases. In contrast to mRNA and protein expression, which were favorable prognosticators, gene copy number changes did not obtain prognostic significance. When ESR1/CEP6 gene ratio was combined with function (as defined by ER protein and mRNA expression) in a molecular classifier, the Gene Functional profile, it was functional status that impacted on prognosis. In univariate analysis, patients with functional tumors (positive ER protein expression and gene ratio normal or gain/amplification) fared better than those with non-functional tumors with ESR1 gain (HR for relapse or death 0.49-0.64, p=0.003). Significant interactions were observed between gene gain/amplification and paclitaxel therapy (trend for DFS benefit from paclitaxel only in patients with ESR1 gain/amplification, p=0.066) and Gene Functional profile with HER2 amplification (Gene Functional profile prognostic only in HER2-normal cases, p= 0.029).

CONCLUSIONS:

ESR1 gene deletion and amplification do not constitute per se prognostic markers, instead they can be classified to distinct prognostic groups according to their protein-mediated functional status.