Gene expression of estrogen receptor, progesterone receptor and microtubule-associated protein Tau in high-risk early breast cancer: a quest for molecular predictors of treatment benefit in the context of a Hellenic Cooperative Oncology Group trial.

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Source

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Abstract

BACKGROUND:

Estrogen receptor (ER) and progesterone receptor (PgR) protein expression carry weak prognostic and moderate predictive utility for the outcome of early breast cancer patients on adjuvant chemohormonotherapy. We sought to study the predictive significance and correlations of transcriptional profiling of the ER, PgR and microtubule-associated protein Tau (MAP-Tau) genes in early breast cancer.

MATERIALS AND METHODS:

Messenger RNA (mRNA) was extracted from 279 formalin-fixed paraffin-embedded breast carcinomas (T1-3N0-1M0) of patients enrolled in the Hellenic Cooperative Oncology Group (HeCOG) trial HE 10/97, evaluating epirubicin-alkylator based adjuvant chemotherapy with or without paclitaxel (E-T-CMF versus E-CMF). Kinetic reverse transcription polymerase chain reaction (kRT-PCR) was applied for assessment of the expression of estrogen receptor, progesterone receptor and MAP-Tau genes in 274 evaluable patients. Cohort-based cut-offs were defined at the 25th percentile mRNA value for ER and PgR and the median for MAP-Tau.

RESULTS:

Two hundred and ten patients (77%) were ER and/or PgR-positive by immunohistochemistry (IHC). Positive ER and MAP-Tau mRNA status was significantly associated with administration of hormonal therapy and low grade, while MAP-Tau mRNA status correlated with premenopausal patient status. MAP-Tau strongly correlated with ER and PgR mRNA status (Spearmann r = 0.52 and 0.64, P < 0.001). The observed chance corrected agreement between determination of hormonal receptor status by kRT-PCR and IHC was moderate (Kappa = 0.41) for ER and fair (Kappa = 0.33) for PgR. At a median follow-up of 8 years, univariate analysis adjusted for treatment showed positive ER mRNA status to be of borderline significance for reduced risk of relapse (HR = 0.65, 95% CI 0.41-1.01, P = 0.055) and death (HR = 0.62, 95% CI 0.36-1.05, P = 0.077), while positive MAP-Tau mRNA status was significantly associated with reduced risk of relapse (HR = 0.50, 95% CI 0.32-0.78, P = 0.002) and death (HR = 0.49, 95% CI 0.29-0.83, P = 0.008). In multivariate analysis, only axillary nodal metastases (HR = 2.33, 95% CI 1.05-5.16, P = 0.04) and MAP-Tau mRNA status (HR = 0.46, 95% CI 0.25-0.85, P = 0.01) independently predicted patient outcome. However, MAP-Tau mRNA levels did not predict enhanced benefit from inclusion of paclitaxel in the adjuvant chemotherapy regimen (test for interaction P = 0.99). No correlation was evident between increasing ER and PgR mRNA transcription and increasing benefit from endocrine therapy

in 203 ER and/or PgR IHC-positive patients receiving adjuvant hormone therapy (Wald P = 0.54 for ER, 0.51 for PR).

CONCLUSIONS:

ER gene transcription carries weak predictive significance for benefit from endocrine therapy or for outcome, with no apparent dose-response association. The predictive significance is possibly exerted via MAP-Tau gene expression, an ER-inducible tubulin modulator with strong predictive significance for patient outcome. However, MAP-Tau mRNA did not predict benefit from the addition of a taxane to adjuvant chemotherapy. Further study of the biologic function and utility of MAP-Tau for individualising adjuvant therapy is warranted.

Comment in

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