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Prognostic value of immune gene-expression signatures (iGES) vs tumor-infiltrating lymphocytes (TILs) in early-stage HER2+ breast cancer: A combined analysis of CALGB 40601 (C40601) and PAMELA trials

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Background

TILs and iGES are associated with pathologic complete response (pCR) and relapse-free survival (RFS) in HER2+ breast cancer, however they have typically not been compared. Here we examine the prognostic value of iGES vs. TILs, alone and together, in two different HER2+ neoadjuvant trials: the chemotherapy plus HER2-targeting trial C40601, and the all-biologic trial PAMELA.

Methods

Gene expression profiling by mRNA sequencing (RNAseq) and TILs (per 2014 TILs working group) as a continuous variable were assessed on 230 C40601 and 139 PAMELA pre-treatment samples. iGES scores were calculated by extracting the median expression of all genes within a signature. Association with pCR and RFS was studied by logistic regression and Cox analyses. To compare the goodness of fit of different models, we used the Akaike Information Criterion (AIC). To compare the prognostic ability of two nested models, we used the Likelihood-Ratio test (LRT).

Results

Every 1% increase in TILs was associated with a significant 1% increase in the odds of pCR in C40601 (odds ratio [OR] 1.01, $p < 0.01$) and a 2% increase in PAMELA (OR 1.02, $p = 0.04$). TILs were not associated with RFS at 7 years in C40601 (Hazard ratio [HR] 0.99, $p = 0.21$). Of the 210 iGES tested, 130 (61.9%) were correlated with TILs across the 2 trials ($p < 0.05$), and 13 iGES were also significantly associated with higher pCR rates in both studies (ORs range 1.05-2.33, $p < 0.05$). 11 of 13 iGES outperformed TILs for pCR prediction, 7 of which were B-cell-related iGES. In a multivariate Cox model including clinical factors and PAM50 subtype, 8 of these iGES, but not TILS, were independently associated with RFS (iGES HRs range 0.56-0.72, p values < 0.05; TILs HR 0.99, $p = 0.38$).

Conclusions

In C40601 and PAMELA, multiple, mostly B-cell-related, iGES performed better than TILs for pCR prediction. In C40601, TILs did not provide additional RFS information to clinical parameters, subtype, and multiple GES. When both TILs and iGES are available, the prognostic value of RNA-based signatures is superior.

Clinical trial identification

CALGB-40601: NCT00770809; SOLTI 1114-PAMELA: NCT01973660. CALGB is part of the Alliance for Clinical Trials in Oncology.

Legal entity responsible for the study

The authors.

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Disclosure

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