Title: Association of Estrogen Receptor (ER) levels and prediction of antiproliferative effect of hormone therapy (HT) in lower ER-expressing tumors

Intro

Accurate measurement of ER in early stage invasive breast cancer (EBC) is important to identify patients (pts) likely to benefit from HT. While immunohistochemistry (IHC) is the most common method to quantify ER, other methods also accurately measure ER, such as RT-PCR. ER is one of the genes included in the RT-PCR based 21-gene Recurrence Score assay (Onco*type* DX®, Genomic Health, Inc) and is also reported separately as a single gene expression. Additionally, only ER expression by RT-PCR (ER-PCR) has shown an association with tamoxifen benefit (Kim, et al 2011). A recent study reported that pts with ER levels <10% by IHC were largely negative by RT-PCR (Singh, et al 2014). This has potential implications for which pts may be expected to benefit from HT. Robust measures of ER and the proliferative response may be useful in identifying patients likely to respond to HT. We undertook a study to: (1) Correlate ER expression as assessed by IHC-based Allred Score (AS) versus RT-PCR in the 21-gene assay; (2) Describe changes in ER, Recurrence Score, and measures of proliferation after 2wks of an aromatase inhibitor (AI); (3) Perform exploratory analyses of factors associated with changes in proliferation.

Methods

55 postmenopausal EBC pts with low ER (AS 2-7) were treated with 2 wks of an AI followed by wide excision. All pts had a 21-gene assay on a pre-and post-treatment (Tx) sample. Proliferation was measured by both Ki67 by IHC (in 45 pts) and by the proliferation gene group score (PGS) in the RT-PCR based 21-gene assay (in all pts). Proliferation response was defined by a 20% relative decrease in Ki67 or a decrease in PGS. Changes in proliferation were correlated with AS, ER-PCR and Recurrence Score result.

Results

Overall there was moderate correlation of AS (2-7) with ER-PCR measured in the pre-Tx ($r=0.83$) samples. However, 92% of AS (2-4) pts were ER(-) by RT-PCR There was a significant change (pre to post) in the average Ki67 level (18% to 11%; $p<0.001$) but not PGS or Recurrence Score result. 37/45 pts showed a $\geq$20% decrease in Ki67 while only 32/55 had a decrease in PGS. Changes in Ki67 levels were greatest in AS 5-7 pts with a 73% relative decrease vs 28% in AS 2-4 pts. The range of PGS change was 1% increase in AS 2-4, and 11% decrease in AS 5-7 pts. Univariate predictors of decrease in Ki67 were AS of 5-7 (vs 2-4), Recurrence Score result, ER-PCR (continuous or binary), and PR-PCR. The same variables were predictors of PGS change.

Conclusions

- Results confirm earlier reports showing substantial disagreement in ER measured by IHC vs RT-PCR in pts with lower ER-expressing tumors
- The clinical implications are that a substantial number of pts with low ER by IHC may have little to no benefit from HT
- The 21-gene assay may be useful in selecting patients likely to benefit from HT

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