Homologous Recombination Deficiency (HRD) as a predictive biomarker of response to neoadjuvant platinum-based therapy in patients with triple-negative breast cancer (TNBC): A pooled analysis

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Background and Rationale

- Genetic instability and a high frequency of BRCA1 and BRCA2 germline mutations are commonly associated with triple-negative breast cancer (TNBC).
- TNBC patients with homologous recombination (HR) deficient tumors have significantly higher pathologic complete response (pCR, ypT0) rates when treated with platinum-based chemotherapy regimens than TNBC patients whose HR are non-deficient.
- We performed a pooled analysis of 6 clinical trials that included patients with TNBC treated with neoadjuvant platinum-based chemotherapy to better estimate the pCR rates amongst HR deficient and HR non-deficient tumors.

Study Design

A total of 267 patients with TNBC and known HR deficiency status from the following neoadjuvant clinical trials were available for analysis:

- PrECOG 01052
- NCT001486945
- Trial of planned neoadjuvant therapy and trial.

Correlation of pCR and HR deficiency status was defined as no invasive disease in the breast/axilla with residual in situ disease allowed = ypT0/is.

Clinical Follow-Up:

- The HRD assay is a next generation sequencing assay performed using DNA extracted from a mutation in BRCA1 or BRCA2.

Results

- Overall, 67% of cases were HR deficient.
- HRD score was correlated with response:
  - Adjusted OR for pCR in HR deficient = 4.64; p<0.0001
  - Adjusted OR for pCR in HR deficient & no BRCA1/2 mutation = 4.50; p<0.0001

Conclusions

- In this pooled analysis of 6 phase II trials of platinum-based neoadjuvant chemotherapy, HR deficiency status was significantly associated with an improved odds of pCR among those with and without a BRCA1/2 mutation.
- Associated between response and stage, age and planned duration of therapy were not significant.
- The neoadjuvant chemotherapy regimens included heterogeneous (non-anticholinergic/non-taxane, taxane-based or anthracycline-and taxane-based) and the mechanisms of cytotoxic chemotherapies varied (1-3) as did the use of other investigational therapies (bevacizumab, iniparib, vorinostat).

References


Primary Analysis:

- Correlation of pCR and HR deficiency status

Secondary Analyses:

- Correlation of pCR and binary HRD score (<42 versus ≥42)

- Correlation of pCR and HR deficiency status

Cases with missing HR deficiency status were excluded. Logistic regression models were used to adjust for study effects. Analyses were adjusted for patient age at diagnosis, clinical stage, duration of planned neoadjuvant therapy and trial.

Determination of HRD Status

- The HRD assay is a next generation sequencing assay performed using DNA extracted from formalin-fixed paraffin-embedded or frozen tissue samples.
- The HRD score is the weighted sum of number of LOH regions (>15 Mb but less than the length of a whole chromosome) + TAIs (regions of allelic imbalance that extend to the subtelomere but do not cross the centromere) + LSTs (breakpoints between regions of imbalance <15Mb after filtering out regions <3 Mb).
- Variant and large rearrangement detection was performed on sequence from BRCA1 and BRCA2.
- HRD deficiency status, either HR deficient or HR non-deficient, combines the HRD score with BRCA1/2 mutation status.

Conclusion:

- In this analysis, HR deficiency status was associated with an improved odds of pCR.
- Adjusted OR = 4.64; p<0.0001

Figure 1. HR score by pCR status in BRCA1/2 mutation negative subset

- Patients lacking BRCA1 or BRCA2 mutations with higher HRD score are more likely to achieve pCR

OR = 0.0095

Table 1. Variables associated with pCR

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<th>Variable Category</th>
<th>Unadjusted</th>
<th>Adjusted</th>
<th>p Value</th>
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<td>Age (years)</td>
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<td>Clinical Stage</td>
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<tr>
<td>Trial</td>
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Table 2. Variables associated with pCR in BRCA1/2 mutation negative subset

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Table 3. Variables associated with pCR in BRCA1/2 mutation positive subset

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