Combined Homologous Recombination Deficiency (HRD) Scores and Response to Neoadjuvant Platinum-Based Chemotherapy and/or BRCA1/2 Mutation-Associated Breast Cancer

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**ABSTRACT**

Genealogical and a high frequency of BRCA1 and BRCA2 germline mutations are commonly associated with serious ovarian cancer and triple negative breast cancer (TNBC). Breast cancer associated with germline mutations is characterized by homologous recombination deficiency (HRD).

Recently, three independent DNA-based measures of genomic instability have been developed based on loss of heterozygosity (LOH), isochromatic allelic imbalance (IAI), and large-scale state transitions (LST). These measures have been shown to be associated with an increased likelihood of response to platinum-containing regimens in TNBC or ovarian cancer.

The HRD-LOH score is significantly associated with favorable response to neoadjuvant platinum-based therapy in PEO1901 [4].

We set out here to assess the combined HRD score, an unweighted sum of LOH, IAI, and LST.

**METHODS**

**RESULTS**

**CONCLUSIONS**

In this study, HRD status provides significant improvement over clinical variables, or BRCA1/2 mutation status in identifying women with increased likelihood of response to platinum-based neoadjuvant therapy among patients with TNBC.

Clinical use of the HRD test has the potential to identify TNBC patients likely to respond to DNA damaging therapy beyond those currently identified by germline BRCA1/2 mutation screening. Prospective evaluation is warranted.

**REFERENCES**


**ACKNOWLEDGEMENTS**

This study was supported by a grant from the Department of Defense (W81XWH-09-2-0234). The study was also funded by Myriad Genetics, Inc., Salt Lake City, UT.

HRD scoring was performed by Myriad Genetics, Inc., Salt Lake City, UT.

Presented at ASCO - May 30, 2015

BACKGROUND

- Genealogically and a high frequency of BRCA1 and BRCA2 germline mutations are commonly associated with serious ovarian cancer and triple negative breast cancer (TNBC).
- Breast cancer associated with germline mutations is characterized by homologous recombination deficiency (HRD).
- Recently, three independent DNA-based measures of genomic instability have been developed based on loss of heterozygosity (LOH), isochromatic allelic imbalance (IAI), and large-scale state transitions (LST).
- These measures have been shown to be associated with an increased likelihood of response to platinum-containing regimens in TNBC or ovarian cancer.

METHODS

- The HRD score is a new generation sequencing assay performed using DNA extracted from formalin-fixed paraffin-embedded or frozen tumor tissue.
- The HRD score is an unweighted sum of LOH (number of LOH regions >15 Mb) but less than the length of a whole chromosome) + IAI (regions of allelic imbalance that extend to the scaffold but do not cross the centromere) + LST (breakpoints between regions of imbalance >10Mb after filtering out regions <3 Mb).
- Variant and large rearrangement detection was performed on sequence from BRCA1 and BRCA2.

RESULTS

- Homologous Recombination (HR) deficiency status, either HR deficient or HR non-deficient, combines the HRD score with BRCA1/2 mutation status. HR deficiency corresponds to a HRD score equal to or above a predefined cutpoint and/or a mutation in BRCA1/2.
- A training set was established to determine the cutpoint.
- A training set was established using four publicly available or previously published cohorts: a 497 breast and 851 ovarian cancer cases, 497 breast and 851 ovarian tumors lacking a functional copy of either BRCA1 or BRCA2 (i.e., BRCA1/2 deficient) upon mutation analysis.
- These tumors had either (a) a deleterious mutation in BRCA1 or BRCA2 or promoter methylation of BRCA1 with >50% of the affected gene or (b) two deleterious mutations in the same gene.
- This cohort was used to define a threshold for the HRD score intended to reflect HR deficiency versus HR intact status. The threshold selected was the 5th percentile of HRD scores in BRCA1/2 deficient tumors.
- Patient Samples and Clinical Data
  - The PEO1901 trial enrolled 85 patients with either triple negative or a BRCA1/2 germline mutation-associated breast cancer. These patients were treated neoadjuvantly with either 4 or 6 cycles of a combination of carboplatin, gemcitabine, and iniparib.
  - Pathologic response was assessed using the residual cancer burden (RCB) index and two dichotomous measures of tumor response were used. Favorable pathologic response was defined as RCB 0. Pathologic complete response (pCR) was defined as RCB score of 0.

CONCLUSIONS

- In this study, HRD status provides significant improvement over clinical variables, or BRCA1/2 mutation status in identifying women with increased likelihood of response to platinum-based neoadjuvant therapy among patients with TNBC.
- Clinical use of the HRD test has the potential to identify TNBC patients likely to respond to DNA damaging therapy beyond those currently identified by germline BRCA1/2 mutation screening. Prospective evaluation is warranted.