BRCA1 and RAD51C Promoter Hypermethylation Confer Sensitivity to PARP Inhibitors in Patients with Platinum Sensitive Ovarian Carcinoma

Elizabeth Swisher, Maria Harrell, Kevin K. Lin, Clare Scott, Sandra Goble, Amit Oza, Robert L. Coleman, Gottfried Konecny, Anna V. Tinker, David M. O'Malley, Rebecca Kristeleit, Ling Ma, James Brenton, Katherine Bell-McGuinn, Ana Oaknin, Alexandra Leary, Elaina Mann, Heidi Giordano, Mitch Raponi, Iain McNeish and Scott H. Kaufmann

Abstract

Germline and somatic mutations in BRCA1 and BRCA2 (BRCA) confer PARP inhibitor sensitivity. Promoter hypermethylation is an alternate mechanism of gene down-regulation, and BRCA1 promoter methylation is relatively common in sporadic ovarian cancer. The clinical significance of BRCA1 methylation is less clear than for mutations, as the Cancer Genome Atlas (TCGA) and others have failed to show improved survival in ovarian carcinomas with BRCA1 methylation. No one has previously tested whether BRCA1 methylation confers in vivo sensitivity to PARP inhibitors in patients with ovarian cancer. ARIEL2 is a phase 2 study of the PARP inhibitor rucaparib in patients with recurrent platinum sensitive high-grade ovarian, peritoneal or fallopian tube carcinoma. At enrollment, ARIEL2 required pre-treatment tumor biopsies with the goal of developing tissue predictors of PARP inhibitor sensitivity other than BRCA mutations. The number of women with known germline mutations was capped at 15 patients in order to predominantly enroll BRCA wildtype cases. As presented at ASCO 2016, in cases with no BRCA mutations, a high fraction of genomic loss of heterozygosity (LOH) significantly predicted a better progression-free survival (the primary endpoint), longer duration of response, and a higher fraction of responders compared to cases with low LOH. We assessed BRCA1 and RAD51C promoter hypermethylation using methylation-sensitive polymerase chain reaction in paired archival and pre-treatment biopsies from patients on ARIEL2. Of 165 cases for which methylation analyses were completed, 21 (12.7%) were methylated at the BRCA1 promoter and four (2.4%) at the RAD51C promoter. Methylation of BRCA1 and RAD51C was mutually exclusive with mutation in BRCA or other homologous recombination genes. All four cases with RAD51C methylation and 15/19 (78.9%) with BRCA1 methylation were associated with high LOH. In 90 paired samples archival and pre-treatment tissues, RAD51C methylation was 100% concordant and BRCA1 methylation was highly concordant (p<0.001). For 13 cases with BRCA1 methylation in the archival specimen, 4 (30.8%) were unmethylated in the paired pretreatment tumor, but for 77 unmethylated archival specimens, gain of methylation in the pretreatment biopsy was observed just once. Confirmed RECIST responses were seen in 52.4% (11/21) BRCA1 methylated and 75.0% (3/4) RAD51C methylated cases. In conclusion, BRCA1 and RAD51C methylation in ovarian carcinomas correlates with a high response rate to PARP inhibitors. If methylation was to be used as a predictor of PARP inhibitor sensitivity, it would need to be assessed in a pre-treatment (not archival) specimen. The loss of BRCA1 methylation in recurrent ovarian carcinoma, which was common even in these platinum sensitive cases, could explain why BRCA1 methylation is
associated with similar survival to methylated cases, despite initial improved therapeutic sensitivity.