INTRODUCTION

The majority of women with advanced stage ovarian cancer are diagnosed with high grade serous carcinomas and they are usually treated with combination platinum-taxane- based chemotherapy. Unfortunately, most patients recur and receive additional platinum-based chemotherapy, that is followed by other cytotoxic agents and subsequent recurrence. Survival statistics are dismal with only 27% of the patients alive ten years after diagnosis.

Included in the small group of patients with more favorable prognoses are those with germline BRCA1 or BRCA2 mutations (1-3). Improved outcomes have been attributed to biological differences in these tumors as well as greater sensitivity to platinum-based therapy (2,3). Moreover, recent work suggests that patients with BRCA2 mutated cancers may do better than BRCA1 mutants and have greater genomic instability (4). BRCA2 carriers comprise 8-18% of the serous ovarian cancer population and an additional 5-10% of patients are reported to have somatic mutations of these genes. The increased responsiveness to platinum agents has been linked to defects in DNA repair associated with loss of BRCA1 and BRCA2 function since they are components of the homologous recombination pathway for repair of double strand breaks in DNA.

HYPOTHESIS and APPROACH

We hypothesized that other factors may contribute to the more favorable prognoses of patients with BRCA-related cancers, including aberrations in cell cycle and survival pathways.

As a first step to address this hypothesis, we used data produced by The Cancer Genome Atlas (TCGA) project team, who recently performed large-scale genomic analyses of 489 high-grade, advanced-stage serous ovarian cancers. Their published study revealed the presence of aberrations in genes comprising key proliferation and survival pathways (RAS, PI3K, RB-E2F) in the majority of tumors (5).

MATERIALS and METHODS

Genomic data. Mutation and copy number data (BTBR) for 316 TCGA- profiled serous ovarian tumors were downloaded (Nov 2011) from The dbGaP Cancer Genomics Portal (http://www.ncbi.nlm.nih.gov). Mutation (MUT), amplification (AMP, i.e., >2) or deletion (HOMDEL), -1 calls were made by the TCGA. Tumors with BRCA2 AMP (>2) and 3 BRCA2 double MUT (<2) were excluded from the analyses.

Pathway gene selection and tumor scores. Genes comprising each pathway were selected by their (a) TCGA-reported association with serous ovarian cancer (5) and (b) known role as components of that pathway. Given the high frequency of CNV, only genes with demonstrated significant mRNA-DNA copy number correlation were included. Each tumor was scored as aberrant for a pathway if any gene in that pathway was MUT, AMP, or HOMDEL.

Clinical data and survival analyses. Clinical characteristics and survival data for 316 patients were obtained from TCGA supplementary data (5). Patients were predominantly stage IIIC and most were initially treated with platinum-taxane doublets.

Statistical analyses. The Fishers exact test was used to compare categorical variables for scored pathway alteration status with BRCA1/2 mutation status. Median survival was estimated using the survfit function of the survival library in the R statistical software. Cox proportional hazards models were used to report p-values for survival analysis. P-values < 0.05 were considered significant.

REFERENCES


Proliferation pathway aberration frequencies differ in BRCA1- and BRCA2-mutated ovarian cancers

Deborah A. Zajchowski, PhD1, Hugh Salamon, PhD2 and Ken D. Yamaguchi, PhD2

1The Cleary Foundation, San Diego, CA; 2Knowledge Synthesis, Berkeley, CA