Objective: Despite widespread adoption of chemoradiation for women with locally advanced cervical cancer, 30%–40% will recur. Interactions of BRCA1 and ERCC1 with other molecules in the homologous recombination/nucleotide excision repair pathways are well characterized, but their roles in the transcriptional response to DNA damage is poorly understood. BRCA1 mutations confer a favorable prognosis in some subsets (high-grade serous ovarian cancer) but have also been associated with poor survival (breast). We studied BRCA1 and ERCC1 expression in pooled cervical cancer specimens from 2 NCI-sponsored studies of cisplatin-based chemoradiation.

Method: GOG 191 and 219 were phase III randomized trials that studied maintaining hemoglobin levels >12.0 g/dL) or incorporation of the hypoxic cell sensitizer tirapazamine, respectively. Pretreatment excisional biopsies were prospectively collected and assessed for BRCA1 and ERCC1 by immunohistochemistry (IHC). Nuclear staining was scored by blinded GOG pathologists as absent (0), weak (1), moderate (2), or strong (3). BRCA1 was also given a composite score (nuclear + cytosolic). Associations of DNA repair proteins with clinical endpoints were evaluated in an exploratory analysis without adjustment for multiplicity.

Results: Of 516 evaluable patients, 375 submitted tissue. Adequate tumor was found in 358 cases for BRCA1 and 329 for ERCC1. BRCA1 scores were 0 (n = 82), 1 (n = 128), 2 (n = 109), 3 (n = 39) and were not associated with age, ethnicity, stage, or cell type. Nuclear staining (0 vs 1–3) for BRCA1 tracked only with PFS (HR = 0.61, 95% CI 0.43–0.88; Figure 1) and OS (HR =0.61, 95% CI 0.42–0.90). Patients with BRCA1 1–3 had twice the odds of maintaining local control versus those with no staining (OR = 2.0, 95% CI 1.1–3.7).

Conclusion: Intact genetic machinery may render cervical cancer more vulnerable to chemoradiation, while genetic chaos measured by absent BRCA1 nuclear localization may be a poor prognostic factor. Prospective validation and exploration of BRCA1’s putative role as a tumor suppressor gene in this disease may be warranted. The therapeutic potential to exploit synthetic lethality using PARP inhibitors in molecularly categorized subsets of women with cervical cancer is
Product-Limit Survival Estimates

Authors

Teresa Codini Longoria
University of California Irvine Medical Center

Jai Hyun Kim
University of California Irvine Medical Center

Mike Sill
Gynecologic Oncology Group Statistical and Data Center

Robert Scott Mannel
The University of Oklahoma Health Sciences Center

Bradley J. Monk
University of Arizona Cancer Center

Yi-Chun Lee
SUNY Downstate

John Fruehauf
University of California, Irvine

Cara A. Mathews
Women & Infants Hospital, Brown University

Shu-Yuan Liao
St. Joseph's Hospital and Medical Center

Leslie M. Randall
University of California at Irvine Medical Center

Robert Emerson
Indiana University School of Medicine
Kathleen M. Darcy  
Gynecologic Cancer Center of Excellence, John P. Murtha Cancer Center, Walter Reed National Military Medical Center, Uniformed Services University of the Health Sciences

Michael J. Birrer  
Massachusetts General Hospital/Harvard University

Krishnansu S. Tewari  
University of California Irvine Medical Center

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