Abstracts

Conclusion Pelvic and para-aortic lymphadenectomy in surgical staging of eOC improves DFS for the price of increasing post-operative complications and time to chemotherapy but does not affect OS.

IGCS20_1319

Prevalence and Prognosis of Lynch Syndrome and Sporadic Mismatch Repair Deficiency in the Combined PORTEC-1,2 and -3 Endometrial Cancer Trials

Introduction Here we aimed to evaluate the prevalence and prognosis of Lynch Syndrome (LS)-associated endometrial cancer (EC) in relation to sporadic mismatch repair deficient EC (MMRd-EC) in the combined PORTEC-1,2 and 3 trials comprising 1336 ECs.

Methods MMR-status was determined by MMR-immunohistochemistry (MLH1/PMS2/MSH6/MSH2). MMRd-ECs with detected promoter hypermethylation of MLH1 were classified as sporadic (methylated MMRd-EC). For unmethylated MMRd-EC cases tumor and normal tissue next-generation sequencing was performed. ECs with MMR germline mutations were classified as LS-associated (LS MMRd-EC). Unmethylated MMRd-ECs with MMR germline mutations were classified as MMRd-EC due to other causes (other MMRd-EC). Overall and recurrence-free survival were estimated and compared using Kaplan-Meier method and pairwise log-rank test.

Results Among the 1336 ECs, 926 were MMR proficient. Of the 410 MMRd-EC, 376 could be fully triaged; 281 (75%) were methylated MMRd-ECs; 37 (10%) LS MMRd-ECs, and 58 (15%) other MMRd-ECs. The overall LS prevalence was 2.8%. Overall 5-year survival for LS MMRd-EC was 89% (95%CI 79–100%; p = 0.055), other MMRd-EC 96% (92–100%; p = 0.001), both compared to methylated MMRd-EC 79% (74–84%); 5-year recurrence-free survival was 92% (84–100%; p = 0.123), 95% (89–100%; p = 0.002), compared to 79% (74–84%), respectively.

Conclusion The prevalence of LS in the PORTEC EC trial population was 3% and within the MMRd group 10%. LS MMRd-EC seems to have a better overall and recurrence-free survival than sporadic MMRd-EC caused by hypermethylation. Further research into the underlying causes of non-hypermethylated somatic MMRd-EC is ongoing.

IGCS20_1217

Comprehensive Molecular Assessment of Mismatch Repair Deficiency in Lynch-Associated Ovarian Cancers Using Next-Generation Sequencing (NGS) Panel

Objectives Abnormalities in mismatch repair (MMR) gene may be the result of pathogenic germline (Lynch syndrome) and somatic mutations as well as epigenetic events. We aimed to examine the cause of MMR defects (MMRd) in non-serous/non-mucinous ovarian cancer (OC) through targeted mutational sequencing.

Methods Women with non-serous/mucinous OC (N = 215) were prospectively recruited from three cancer centers in Ontario, Canada. Tumors were assessed for MMR protein expression by immunohistochemistry. Matched MMRd tumor-normal samples were run on a custom NGS panel to identify germline and somatic mutations, copy number variants, rearrangements and promoter methylation in MMR and associated genes.

Results Of 215 women enrolled in our study, 185 (86%) had OC and 30 (14%) had synchronous OC and endometrial cancer. Twenty-eight (13%) cases were MMRd, 11 of which were synchronous. Using the NGS panel, Lynch syndrome (LS) was detected in 39% of MMRd cases (11/28; 7 OC and 4 synchronous): 7 MSH6, 2 MLH1, 1 PMS2, and 1 MSH2. An explanation for the observed MMR phenotype was available for 18/20 deficient cases, including 9/10 MLH1/PMS2- (7 somatic methylation, 1 bi-allelic somatic deletion, 1 germline mutation), 0/1 PMS2-, 6/7 MSH6- (6 germline mutations) and 2/2 MSH2-/MSH6- (1 germline mutation, 1 bi-allelic somatic mutation). Concordance between clinical and research panel sequencing results was 90%.

Conclusions Use of our custom NGS panel allows for the streamlined assessment of hereditary and somatic causes of MMR deficiency in OC and may be an attractive screening strategy for LS in this population.