Prognostic and predictive immune gene signatures and correlation with homologous recombination deficiency in high grade serous ovarian cancer.

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Abstract

The majority of patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer presents with advanced malignancy (stage III or IV disease). Standard treatment consists of primary debulking surgery (PDS) followed by chemotherapy, whereas neoadjuvant chemotherapy (NACT) can be given to patients who have unresectable disease or represent poor surgical candidates. Multiple studies have indicated that survival after NACT approximates that of suboptimal PDS. Approximately 50% of high grade serous ovarian cancers (HGSOCs) display genetic and epigenetic alterations in genes of the homologous recombination (HR) DNA repair pathway, mostly in BRCA1 and BRCA2 genes. A recent study demonstrated that tumors with higher neoantigen load show increased expression of immune genes related to tumor cytotoxicity. Moreover, immune checkpoint inhibitors (such as PD-1 and PD-L1) have shown remarkable efficacy against various hypermutated cancers. This might be due to the increased amount of tumor-specific neoantigens in hypermutated lesions which stimulates the recruitment of an elevated number of tumor-infiltrating lymphocytes (TILs) and is counterbalanced by the increased expression of immune checkpoints. Additionally, BRCA1/2-mutated tumors have been found to show a significantly increased amount of CD3+ and CD8+ TILs, and enhanced expression of PD-1 and PD-L1 in HR deficient tumor-associated immune cells compared to HR proficient tumors. Taken together, there might be a link between BRCA1/2-mutation status and immunogenicity, and BRCA1/2-mutated HGSOCs might be more sensitive to immune checkpoint inhibitors compared to HR-proficient HGSOCs. Accordingly, this project is focused on the study of prognostic and predictive immune gene signatures and correlation with homologous recombination deficiency in HGSOC, using a combination of Immunohistochemistry, Nanostring Immuno-Oncology Assay and targeted Sequencing using Foundation one technologies. For this study, we intend to use a patient population consisting of 90 matched samples HGSOC (n=45 pts), treated with neoadjuvant induction chemotherapy (carboplatin and paclitaxel standard dose). The matched samples will be baseline biopsy and samples from Interval Debulking Surgery (IDS). We hypothesize that homologous recombination deficiency in high grade serous ovarian cancer results in a higher tumor-specific neoantigen load, and, therefore, increased tumor-infiltrating lymphocytes as well as increased expression of the immune checkpoint genes.

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