Yamashita et al., Diagn Pathol Open 2019, 4:3

Diagnostic Pathology: Open Access

Short Communication Open Access

Multi-Drug Therapy Including Immune Checkpoint Inhibitors in Ovarian Cancer

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Received: December 20, 2019; **Accepted**: January 06, 2020; **Published**: January 11, 2020

Abstract

Ovarian cancer has the worst prognosis among gynecological cancers. Since only a few cases of ovarian cancer could be treated effectively with immune checkpoint inhibitor monotherapy, to improve the prognosis of ovarian cancer, multi-drug therapy including immune checkpoint inhibitors is necessary. In this short commentary, we highlight the need for studies on novel treatment strategies.

Keywords: Microsatellite instability; Ovarian cancer; Immune checkpoint inhibitor; Immunohistochemistry; Mismatch repair protein

Abbreviations: PD-1: Programmed Cell Death-1; PD-L1: Programmed Cell Death-Ligand 1; MSI: Microsatellite Instability; MMR: Mismatch Repair; PFS: Progression-Free Survival

Content

Ovarian cancer has the poorest prognosis of all gynecological cancers, and therefore new therapies are needed to improve the prognosis [1]. Currently, new drugs such as immune checkpoint inhibitors and poly (ADP-ribose) polymerase inhibitors (PARP inhibitors) are in the spotlight. Anti-programmed cell death-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) antibody, one of immune checkpoint inhibitors, have been gradually applied in the treatment of various carcinomas, but are not effective in all patients [2].

More tumor neoantigens are produced from tumors with many genetic mutations such as microsatellite instability (MSI)-H. Then more lymphocytes infiltrate around these tumors. Therefore, it is considered that anti PD-1/PD-L1 antibody is particularly effective for tumors having many genetic mutations [3]. Among epithelial ovarian cancers, endometrioid carcinoma and clear cell carcinoma are reported to have many MSI-H cases [4,5]. We investigated the correlation between MSI status, immune checkpoint molecules (PD-1 and PD-L1) and tumor-infiltrating lymphocytes (CD8) by immunostaining to investigate the efficiency of anti PD-1/PD-L1 antibody for each histologic type of epithelial ovarian cancer [6]. Six of 136 cases (4.4%) were determined to be MSI status. No significant differences were found between MSI status and expression of PD-1, PD-L1 and CD8. These results may be attributed to the low proportion of MSI in epithelial ovarian cancer. We thought that epithelial ovarian cancer with very few cases could be treated effectively by immune checkpoint inhibitor monotherapy. Therefore, we believe that the use of immune checkpoint inhibitors in combination with other anticancer drugs and molecular targeted drugs is essential for improving the prognosis of ovarian cancer.

Recently, Attention has been focused on the relationship between Vascular Endothelial Growth Factor (VEGF) and immune function in worldwide. It has been reported that VEGF contributes to upregulate PD-1 expression of CD8 lymphocytes in tumor [7]. Moreover VEGF inhibitors are reported to increase lymphocyte infiltration into tumor and inhibit regulatory T-cell proliferation [8-10].The previous reports suggested that hypoxia caused by VEGF inhibitors suppresses the expression of mismatch repair genes and homologous recombination genes such as BRCA1 and RAD51 [11,12]. Therefore, the combined therapy of immune checkpoint inhibitor, VEGF inhibitor and PARP inhibitor might be more efficacious than immune checkpoint inhibitor monotherapy.

Ovarian cancer treated with PARP inhibitors have recently been found useful therapy. PARP inhibitors are currently applied for initial maintenance therapy of platinum-sensitive ovarian cancer with BRCA mutation or recurrent ovarian cancer of platinum-sensitive. Many large-scale clinical trials have been conducted to expand the application of PARP inhibitors. Phase 3, placebo-controlled trial was conducted in untreated patients with high-grade serous advanced ovarian cancer to evaluate the efficacy and safety of PARP inhibitor (Veliparib) when added to first-line chemotherapy with paclitaxel and carboplatin and followed by maintenance monotherapy [13]. In analysis of all trial populations, veliparib introduced to chemotherapy and kept continuously as maintenance had significantly effect on longer progression free survival (PFS) than using carboplatin plus paclitaxel therapy alone. However, in the non-homologous recombination deficiency (non-HRD) cohort, there was no significant difference in PFS between a regimen of paclitaxel, carboplatin, and veliparib induction therapy subsequently using veliparib maintenance therapy and a regimen of carboplatin plus paclitaxel induction therapy alone. Platinum drugs and PARP inhibitors are effective in ovarian cancer with HRD [14,15]. However, ovarian cancer with non-HRD is thought to be less effective to platinum drugs and PARP inhibitors. Therefore, new treatment strategies for ovarian cancer with non-HRD are needed. When ovarian cancer with non-HRD is treated with platinum drugs or PARP inhibitors, both the pathway of activating immune functions (Interferon (IFN) response and neoantigen production due to repair errors) and suppressing immune functions (PD-L1 upregulation *via* Ataxia Telangiectasia Mutated/Ataxia Telangiectasia and Rad3 Related Protein/Checkpoint kinase1 (ATM/ATR/Chk1) pathway activation) acts during the normal homologous recombination repair mechanism [16]. Therefore, using the combined therapy of immune checkpoint inhibitors with PARP inhibitors will be more effective than each agent alone in ovarian cancer non-HRD patients. Nowadays, chemotherapy and PARP

inhibitors have been reported to upregulate PD-L1 expression [17,18]. From these results, combined treatment of immune checkpoint inhibitors with chemotherapy or PARP inhibitors is expected to be useful. Long-term treatment with PARP inhibitors, even in ovarian cancer patients with HRD, can sometimes weaken the anti-tumor effects of PARP inhibitors. Even with PARP inhibitor monotherapy resistance, the combination of immune checkpoints and PARP inhibitors may contribute to tumor shrinkage in ovarian cancer with HRD.

Currently, many clinical trials have been performed to evaluate the efficiency of multi-drug therapies together with immune checkpoint inhibitors and various anti-cancer drugs and molecular targeted therapies in ovarian cancer patients [19]. Recently, we are examining the effects of multi-drug therapies along with immune checkpoint inhibitors in ovarian cancer using immunocompetent mice. We believe that new treatments for platinum-resistant ovarian cancer might be discovered by administering platinum-resistant cell lines to mice and verifying the potency of combination therapy. In addition, in order to discover new treatments for PARP inhibitors resistant ovarian cancer with HRD, we would like to create PARP inhibitors resistant cell lines using BRCA mutant cell lines and evaluate the effectiveness of immune checkpoint inhibitors.

In summary, ovarian cancer has only a few cases of MSI. Therefore, there are few ovarian cancer patients who can be expected to benefit from immune checkpoint inhibitor monotherapy. For better prognosis of ovarian cancer, multi-drug therapy together with immune checkpoint inhibitors is necessary. New therapeutic strategies for ovarian cancer may be found.

Conflict of Interest

The authors declare no potential conflicts of interest.

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