



島根大学学術情報リポジトリ

SWAN

Shimane University Web Archives of kNnowledge

Title

Multi-Drug Therapy Including Immune Checkpoint Inhibitors in Ovarian Cancer

Author(s)

Hitomi Yamashita, Kentaro Nakayama and Satoru Kyo

Journal

Diagnostic Pathology

Published

January 11, 2020

URL

<https://www.omicsonline.org/open-access/multidrug-therapy-including-immune-checkpoint-inhibitors-in-ovarian-cancer-111211.html>

この論文は出版社版ではありません。

引用の際には出版社版をご確認のうえご利用ください。

Multi-drug therapy including immune checkpoint inhibitors in ovarian cancer

Hitomi Yamashita, Kentaro Nakayama* and Satoru Kyo

Department of Obstetrics and Gynecology, Shimane University School of
Medicine, 6938501, Izumo, Japan

***Correspondence to:**

Kentaro Nakayama, MD, PhD
Shimane University School of Medicine
Enyacho 89-1, Izumo, Shimane, Japan 6938501
81-853-20-2268 (phone); 81-853-20-2264 (fax); kn88@med.shimane-u.ac.jp

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.

Main text:

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.

Keywords: microsatellite instability, ovarian cancer, immune checkpoint inhibitor,

immunohistochemistry, mismatch repair protein

Running title: Multi-drug therapy including immune checkpoint inhibitors in ovarian cancer

Abbreviations

PD-1: programmed cell death-1, PD-L1: programmed cell death-ligand 1, MSI: microsatellite instability, MMR: mismatch repair, PFS: progression-free survival,

Conflict of Interest: The authors declare no potential conflicts of interest.

References

1. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Niksic M, Bonaventure A, et al. Global surveillance of trends in cancer survival 2000-14(CONCORD-3): analysis of individual records for 37,513,025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet* **2018**, 391(10125): 1023-1075
2. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Powderly JD, Carvajal RD, Sosman JA, Atkins MB, Leming PD, Spigel

DR, Antonia SJ, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* **2012**, 366: 2443-2454.

3. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, Bignell GR, Bolli N, Borg A, Børresen-Dale AL, Boyault S, Burkhardt B, Butler AP, et al. Signatures of mutational processes in human cancer. *Nature* **2013**, 500: 415-421.
4. Aysal A, Karnezis A, Medhi I, Grenert JP, Zaloudek CJ, Rabban JT. Ovarian endometrioid adenocarcinoma: incidence and clinical significance of the morphologic and immunohistochemical markers of mismatch repair protein defects and tumor microsatellite instability. *Am J Surg Pathol* **2012**,36:163-72.
5. Howitt BE, Strickland KC, Sholl LM, Rodig S, Ritterhouse LL, Chowdhury D, D'Andrea AD, Matulonis UA, Konstantinopoulos PA. Clear cell ovarian cancers with microsatellite instability: A unique subset of ovarian cancers with increased tumor-infiltrating lymphocytes and PD-1/PD-L1 expression. *Oncoimmunology* **2017**, 6:e1277308.
6. Yamashita H, Nakayama K, Ishikawa M, Ishibashi T, Nakamura K, Sawada K, Yoshimura Y, Tatsumi N, Kurose S, Minamoto T, Iida K, Sultana R,

- Ishikawa N, Kyo S. Relationship between microsatellite instability, immune cells infiltration, and expression immune checkpoint molecules in ovarian carcinoma: Immunotherapeutic Strategies for the future . *Int J Mol Sci* **2019**, 20(20).
7. Voron T, Colussi O, Marcheteau E, Pernot S, Nizard M, et al. VEGF-A modulates expression of inhibitory checkpoints on CD8+ T cells in tumors. *J Exp Med* **2015**, 212:139-148,.
 8. Apostolos C Ziogas, Nikos G Gavalas, Marinos Tsiatas, Ourania Tsitsilonis, et al. VEGF directly suppresses activation of T cells from ovarian cancer patients and healthy individuals via VEGF receptor type2. *Int J Cancer* **2012**, 130(4),857-64.
 9. Magali Terme, Simon Pernot, Elie Marcheteau, Federico Sandoval, Nadine Benhamouda, et al. VEGFA-VEGFR pathway blockade inhibits tumor-induced regulatory T-cell proliferation in colorectal cancer. *Cancer Res* **2013**, 73(2), 539-49.
 10. Rajeev K Shrimali, Zhiya Yu, Marc R Theoret, Dhanalakshmi Chinnasamy, et al. Antiangiogenic agents can increase lymphocyte infiltration into tumor and enhance the effectiveness of adoptive immunotherapy of cancer.

Cancer Res **2010**, 70(15),6171-80.

11. Norman Chan, Robert G. Bristow. "Contextual" synthetic lethality and/or loss of heterozygosity: tumor hypoxia and modification of DNA repair. *Clin Cancer Res* **2010**, 16(18), 4553-60.
12. Ranjit S. Bindra, Shannon L. Gibson, Alice Meng, Ulrica Westermark, Maria Jasin, et al. Hypoxia-induced down-regulation of *BRCA1* expression by E2Fs. *Cancer Res* **2005**, 65(24), 11597-604
13. R.L. Coleman, G.F. Fleming, M.F. Brady, E.M. Swisher, K.D. Steffensen, et al. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. *N Engl J Med* **2019**, PMID:31562800.
14. Gelmon KA et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicenter, open-label, non-randomised study. *Lancet Oncol* **2011**, 12:852-61.
15. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomized phase 2 trial. *Lancet Oncol* **2014**, 15:852-61.

16. Mouw KW, Konstantinopoulos PA. From checkpoint to checkpoint: DNA damage ATR/ Chk1 checkpoint signaling elicits PD-L1 immune checkpoint activation. *Br J Cancer* **2018**, 118:933-935.
17. Jin Peng, Junzo Hamanishi, Noriomi Matsumura, Kaoru Abiko, et al. Chemotherapy induces programmed cell death-ligand 1 overexpression via the nuclear factor- κ B to foster an immunosuppressive tumor microenvironment in ovarian cancer. *Cancer Res* **2015**, 75:5034-45.
18. Shiping Jiao, Weiya Xia, Hirohito Yamaguchi, Youngkun Wei, Mei-Kuang Chen, et al. PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression. *Clin Cancer Res* **2017**, 23:3711-3720.
19. Kimberly Levinson, Oliver Dorigo, Krista Rubin, APRN-BC, Kathleen Moore. Immunotherapy in Gynecologic Cancers: What We Know Now and Where We Are Headed. *Am Soc Clin Oncol Educ Book* **2019**. 39:e126-e140.