WOMEN'S HEALTH

Openventio PUBLISHERS

ISSN 2380-3940 Open Journal http://dx.doi.org/10.17140/WHOJ-3-e013

Editorial

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Volume 3 : Issue 3
Article Ref. #: 1000WHOJ3e013

Article History
Received: November 1st, 2017
Accepted: November 1st, 2017
Published: November 1st, 2017

Citation
Koshiyama M. Potential efficacy of anti-PD-1 or PD-L1 antibody treatments for gynecologic cancers. *Women Health Open J*. 2017; 3(3): e21-e23. doi: 10.17140/WHOJ-3-e013

Potential Efficacy of Anti-PD-1 or PD-L1 Antibody Treatments for Gynecologic Cancers

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Programmed cell death-1 (PD-1; CD279) is an immunosuppressive co-inhibitory molecule that belongs to the CD28 family of receptors on T-cells. It was discovered by Ishida et al in 1992.[1] The most important peripheral regulatory pathway is the interaction between the PD-1 receptor, expressed on T-cells, and programmed cell death ligands-1 and 2 (PD-L1 and PD-L2) on the cancer cell surface.[2] This immune checkpoint exists in a normal physiological state to protect against autoimmunity and inflammation. In a neoplastic state, dysfunction of these immune checkpoint proteins can lead to tumor tolerance and eventually allow tumors to 'escape' from the immune system. PD-1 blockage enhances the proliferation of transferred T-cells at the tumor site. In addition, the combination of adoptive T-cell transfer and anti-PD-1 antibody results in significant inhibition of tumor progression.[3] These therapeutic effects of PD-1 blockage require the INF-γ signal. Targeting the molecules that regulate the immune response using the new drug nivolumab, an anti-PD-1 antibody has been the subject of much research and has yielded some promising and exciting results.[4-6]

The effects of anti-PD-1 treatment have been reported in a study of 296 patients, including patients with melanoma, renal cancer and lung cancer,[7] with cumulative response rates in these patients of 28%, 27% and 18%, respectively.

However, there have been few reports of anti-PD-1 or anti-PD-L1 treatments for gynecologic cancers. Hamanishi et al treated 20 patients with platinum-resistant ovarian cancer with an intravenous infusion of an anti-PD-1 antibody (nivolumab) every 2 weeks at 1 or 3 mg/kg.[8] The best overall response was 15%, which included 2 patients who had a durable complete response (2CR; 1 partial response (PR)). The disease control rate in all 20 patients was 45%. Varga et al reported on 26 ovarian cancer patients treated with an anti-PD-1 antibody (pembrolizumab) every 2 weeks at 10 mg/kg for up 2 years.[9] The best overall response was 11.5% (3/26; 1 CR, 2 PR), and 23.1% (6/26) of the patients had evidence of tumor reduction. Brahmer et al reported on 17 ovarian cancer patients treated with an anti-PD-L1 antibody (MS-936559).[10] An objective response (CR or PR) was observed in 1 of 17 (5.9%; 1 PR) with ovarian cancer. Gulley et al reported on 184 ovarian cancer patients treated with an anti-PD-L1 antibody (avelumab),[11] and objective responses were observed in 22 (12%;1 CR, 21 PR).

There are few reports concerning the efficacy of anti-PD-L1/PD-1 immunotherapies for endometrial cancer. Immunohistochemically, 61.3% of human endometrial cancers are positive for PD-1, which is almost exclusively found in the tumor-infiltrating immune cells.[12] By contrast, PD-1 is not expressed in the tumor cells or normal endometrial tissues. PD-1 expression in the tumor-infiltrating immune cells is more frequently found in moderately and poorly-differentiated endometrial cancers and non-endometrioid (type II) cancers than in well-differentiated endometrial cancers and endometrioid (type I) cancers. These findings suggest a better outcome for future treatment with anti-PD-1 antibody-based therapies against the subgroups of endometrial cancers with a high expression of PD-1. However, anti-PD-1 antibodies have yet to be applied to the treatment of patients with endometrial cancer.

Recently, a trial to identify predictive markers for the assessment of PD-1 expression

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was performed. The genomic assessment of an exceptional response to anti-PD-1 antibodies can provide important insight into a patient's potential response.[13] An analysis of The Cancer Genome Atlas (TCGA) revealed that the presence of DNA polymerase epsilon (POLE) mutations was associated with a high mutational burden and the elevated expression of several immune checkpoint genes.[14] Approximately 10% of endometrial cancers analyzed by the TCGA analyses harbored POLE mutations. These data suggest that endometrial cancers with POLE mutations are good candidates for immune checkpoint inhibitor therapy.[13]

Regarding uterine cervical cancer, the PD-L1 expression was immunohistochemically detected in 12 (44.4%) of 27 patients with stage IB1-IIA cervical cancer.[15] However, anti-PD-1 antibody has not been used to treat patients with cervical cancer. In a single case of cervical small cell carcinoma, which is a rare subtype of cervical cancer characterized by an aggressive behavior, a patient with advanced chemo-refractory disease was treated with a tumor vaccine combined with 1 mg/kg of anti-PD-1 antibody (pembrolizumab). She showed a sharp decrease in the size of the liver-metastasized lesion to less than its maximum diameter.[16]

Several points remain to be addressed with this therapy, such as the identification of reliable predictors of responsiveness to anti-PD-1 or PD-L1 antibody treatments and the determination of the optimum clinical setting of gynecologic cancer. We also need to clarify whether these drugs are most effective as monotherapy or in combination with other agents.

GRANT SUPPORT

This work was supported by a Grant-in-Aid for Scientific Research (KAKENHI) from the Japan Society for the Promotion of Science (JSPS).

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