学 位 論 文 の 要 旨

氏名　澤田　希代加

学　位　論　文　名　Promising Therapeutic Impact of Immune Checkpoint Inhibitors in Type II Endometrial Cancer Patients With Deficient Mismatch Repair Status

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著　　者　　名　Kiyoka Sawada, Kentaro Nakayama, Sultana Razia, Hitomi Yamashita, Tomoka Ishibashi, Masako Ishikawa, Kosuke Kanno, Seiya Sato, Satoru Nakayama, Yoshiro Otsuki, Satoru Kyo

論 文 内 容 の 要 旨

INTRODUCTION

Endometrial carcinoma (EC) is classified into two types based on the histopathology of the tumors. Type I ECs are generally well to moderately differentiated low-grade endometrioid tumors and account for 80–85% of all ECs. Type I tumors develop in an estrogenic environment with a good prognosis having a 5-year survival rate of >80%. In contrast, type II ECs are high-grade by definition and represent approximately 15–20% of all ECs. They are generally poorly differentiated, without steroid receptors, and of a nonendometrioid histological subtype. Type II ECs have a poor prognosis as they are unresponsive to antiestrogen therapy and have a high recurrence rate. Therefore, the search for new treatments for type II EC is urgent.

Recently, molecular-targeted drugs have gained attention due to the development of genomic medicine, and immunotherapy has revamped cancer therapeutic paradigm. The PD-1 surface receptor is expressed on some tumor cells, and by attaching to PDL-1 on cytotoxic lymphocytes, it suppresses lymphocyte activation and maintains immune evasion. Immune checkpoint inhibitors (ICIs) remove the "brakes" from the immunological system, allowing an immune response to and elimination of cancer cells.

The mismatch repair (MMR) pathway plays a crucial role in correcting DNA replication errors. Four of MMR protein are clinically significant in terms of how human cancers develop: MLH1, MSH2, MSH6, and PMS2. Loss-of-function of MMR proteins (deficient MMR; dMMR) leads to impaired DNA repair capability and the loss-of-function of these gene products results in

dMMR that is connected to a condition known as microsatellite instability (MSI). This results in the accumulation of spontaneous genetic mutations across the genome leading to an increased risk of developing neoplasias. Therefore, dMMR is linked to an elevated risk of numerous forms of cancer. MSI-high tumors are thought to have a favorable response to ICIs.

EC is a gynecological tumor frequently showing MMR deficiency (25–30%) . The prevalence of dMMR tumors in type II EC remains unclear. Hence, the study aimed to evaluate the relationship between MMR status, lymphocyte infiltration into the tumor, and the expression of immune checkpoint molecules by histological staining in type II EC. We believe that our study is the first to provide an overview of the MMR status in type II EC.

MATERIALS AND METHODS

Samples were obtained from 60 patients with type II EC treated between January 2006 and January 2020 in the Department of Obstetrics and Gynecology at the Shimane University Hospital and Seirei Hamamatsu General Hospital. Among the 60 patients, 16, 5, 17, and 22 were endometrioid G3, serous, de-differentiated, and carcinosarcoma patients, respectively.

Expression of MMR proteins (MLH1, PMS2, MSH2, and MSH6), CD8+ lymphocyte infiltration into the tumor, and immune checkpoint molecule PD-L1 expression were evaluated by immunohistochemistry (IHC).

Statistical analyses were performed using the SPSS 24.0 software. The chi-square test was used to analyze the association between the status of MMR and expressions of CD8+ and PD-L1. The progression-free survival (PFS) and OS were compared using Kaplan-Meier curves and log-rank tests. A p value of <0.05 was considered statistically significant. The study protocol was approved by the Research Ethics Committee of Shimane University.

RESULTS AND DISCUSSION

In the 60 type II EC patients, stages I and II were identified in 25 patients, while stages III and IV were identified in 35 patients. The IHC results of MMR status was correlated to clinicopathologic variables. We found no significant association between dMMR and age ($p=0.093$), histological grade ($p=0.263$), FIGO stage ($p=0.593$), pelvic lymph metastasis ($p=0.093$), or depth of myometrial invasion ($p=0.733$).

In this study, 24/60 (40%) patients were dMMR (MSH2 loss, 11 cases; MLH1 loss, 11 cases; MSH6 loss, 5 cases; and PMS2 loss, 13 cases). The relationship between MMR status, CD8+, and PD-L1 expression was assessed using a chi-square test. In the dMMR group, the positivity rate of CD8+ ($p=0.0072$) and PD-L1 ($p=0.0061$) expression was higher than in the pMMR group.

Survival curves were created for the PFS and OS of patients within the dMMR and pMMR

groups. We found no significant difference in PFS or OS between the dMMR and pMMR groups evaluated by univariate analysis within all stages. When univariate analysis performed separately in stage I/II and stage III/IV cases for PFS or OS, in cases of stage III/IV, dMMR tumors were found to be significantly associated with longer PFS (p=0.0291) and OS (p=0.0096) than pMMR tumors. In contrast, there was no significant differences in PFS and OS between dMMR and pMMR cases in stage I/II patients. Similarly, there were no significant differences in PFS or OS between the CD8 (+) and CD8 (-) cases as well as PDL1 (+) and PDL1 (-) cases.

In this study, MMR deficiency was observed to be 40%, which is more frequent than type I EC (28.2%) . dMMR was significantly associated with immune checkpoint molecule PD-L1 expression (p=0.0061) and the presence of tumor-infiltrating lymphocytes (CD8+) (p=0.0072). The higher expression of CD8+ in the dMMR group confirmed the enhanced immune response. The increased level of PD-L1 in the dMMR group in this study indicates that PD-L1 promotes tumor immune escape. PD-L1 expression is closely related to dMMR /MSI-H status. Type II EC patients in the dMMR group may be good candidates for ICI treatment.

In this study, no statistical correlation was observed between the dMMR and pMMR groups in the survival curves in all stages. However, when the univariate analysis was performed separately according to the stage I/II and III/IV, longer PFS (p=0.0291) and OS (p=0.0096) were observed in the dMMR group than the pMMR group in the case of stage III/IV. dMMR tumors have proven to be more immunogenic, have better antitumor immune responses, and capable of inhibiting tumor cell growth. Cumulatively, the effect of MMR status on prognosis remains controversial.

Recently, pembrolizumab, an ICI, was approved as a second-line treatment of metastatic or recurrent EC with MSI-H or dMMR status. In attition, the combination of pembrolizumab and lenvatinib for use in patients with unresectable, advanced, or recurrent EC was approved. Although the combination of pembrolizumab and lenvatinib was proven efficacious in EC, further clinical studies are required to confirm their safety and efficacy in type II EC. Consequently, pembrolizumab and lenvatinib therapy need to be widely used in patients with type II EC to obtain more information about their response.

CONCLUSION

The high expressions of PD-L1 and CD8 positive T cells in the dMMR type II EC tumors in this study suggest that ICIs could be effective in the Japanese population; however, this should be directly tested, preferably in a large cohort, prospective study. The presence or absence of MMR proteins by immunostaining may be biomarkers for ICI response in the case of type II EC.