学 位 論 文 の 要 旨

氏名　福島　瑠璃子

学 位 論 文 名　Dedifferentiated Endometrial Carcinoma Could Be A Target for Immune Checkpoint Inhibitors (Anti PD-1/PD-L1 Antibodies)

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著 者 名　Ruriko Ono, Kentaro Nakayama, Kohei Nakamura, Hitomi Yamashita, Tomoka Ishibashi, Masako Ishikawa, Toshiko Minamoto, Sultana Razia, Noriyoshi Ishikawa, Yoshiro Otsuki, Satoru Nakayama, Hideyuki Onuma, Hiroko Kurioka, Satoru Kyo

論 文 内 容 の 要 旨

INTRODUCTION

Dedifferentiated endometrial carcinoma is defined as the undifferentiated carcinoma admixed with differentiated endometrioid carcinoma (Grade 1 or 2). It has poor prognosis compared with Grade 3 endometrioid adenocarcinoma and is often associated with the loss of mismatch repair (MMR) proteins, which is seen in microsatellite instability (MSI)-type endometrial cancer. MMR-deficient tumors are burdened with somatic mutations due to a defective DNA MMR system. It has been reported that tumors with higher numbers of somatic mutations are more immunogenic and have immune escape mechanisms, such as the programmed cell death-1 (PD-1) and PD-1 ligand 1 (PD-L1) pathways. In addition, it has been suggested that immune checkpoint inhibitors may be effective when there is a high infiltration of CD8+ T cells into the tumor. However, the relationship between MMR deficiency and the expression of PD-L1 and CD8+ T cell tumor-infiltration remains poorly understood in dedifferentiated endometrial carcinoma. In the present study, we investigated the relationship between the expression of PD-L1 protein and CD8+ T cell tumor-infiltration and MMR deficiency in dedifferentiated endometrial carcinoma.

MATERIALS AND METHODS

The study protocol was approved by the Research Ethics Committee of Shimane University.

Samples were collected from 17 patients who were diagnosed with low-grade endometrioid carcinoma (Grade 1–2) that contained an undifferentiated component. The expression of MMR proteins (MLH1, PMS2, MSH2, and MSH6), CD8, PD-L1, were examined by immunostaining. Tumors were considered to be MMR deficient if at least one of the four MMR proteins (MLH1, PMS2, MSH2, or MSH6) was deficient. The level of tumor infiltrating lymphocytes was classified into four categories by CD8 expression: 0, undetectable; 1+, weakly positive (percentage of CD8 positive cells per tumor cells 0–30%); 2+, moderately positive (30−60%); and 3+, strongly positive (≥60%). Cases that were 2+ or 3+ were counted as positive in our analysis. Immunostaining of PD-L1 was evaluated as positive if more than 5% of the tumor cells were stained.

We performed MSI analysis for three cases that were indicated as MMR deficient according to IHC. DNA was extracted from formalin-fixed paraffin-embedded (FFPE) tissues affording to protocols for the isolation of total DNA. Well-differentiated and undifferentiated components were separately collected macroscopically with reference to Hematoxylin-Eosin (HE) staining and interstitial tissue was collected to use as a control in the analysis.

RESULTS AND DISCUSSION

Out of 17 cases, 11 (64.7%) were MMR-deficient; loss of MMR proteins was observed in the well-differentiated component for 8 cases (MLH1, 8 cases; PMS2, 4 cases; MSH2, 2 cases; and MSH6, none), in the undifferentiated component for 9 cases (MLH1, 6 cases; PMS2, 5 cases; MSH2, 2 cases; and MSH6, 1 case). Overall, 6 cases out of 17 cases had MMR deficiency in both the well-differentiated component and undifferentiated components. Furthermore, 11 cases (64.7%) had PD-L1 expression. PD-L1 expression was observed only in the undifferentiated component. Our results showed that MMR deficiency was significantly associated with PD-L1 expression ($p = 0.026$) and the presence of tumor-infiltrating lymphocytes (CD8+) ($p = 0.026$).

We analyzed genomic MSI in 3 cases that were indicated as having MMR deficiency by IHC. All cases were considered as MSI-high based on the MSI analysis.

Interestingly, even within the same tumor, staining results were different in the undifferentiated and well-differentiated components, and PD-L1 was expressed only in the undifferentiated component in our results.

Dedifferentiated endometrial carcinoma has a poorer prognosis as compared with

Grade 3 endometrial carcinoma. Therefore, individual treatment strategies for dedifferentiated endometrial carcinoma need to be devised. Although the reason for dedifferentiated endometrial carcinoma aggressiveness is not clear, it is most likely due to the undifferentiated component. Our results show that dedifferentiated endometrial carcinoma could be a target for immune checkpoint inhibitors (anti PD-L1/PD-1 antibodies), especially in the undifferentiated component.

Based on intra-tumor heterogeneity, conventional paclitaxel plus carboplatin and cisplatin plus doxorubicin therapies for endometrial carcinoma are effective for the well-differentiated component, although it is suggested that combination therapy with different targeting of well-differentiated component and undifferentiated component may improve the prognosis of dedifferentiated endometrial carcinoma.

CONCLUSION

This is the first report to suggest that dedifferentiated endometrial carcinoma with MMR deficiency could be a target for immune checkpoint inhibitors (anti PD-1/PD-L1 antibodies). The staining results were different for undifferentiated and well-differentiated components, and this finding suggest that dedifferentiated endometrial carcinoma has intra-tumor heterogeneity. As a treatment strategy for dedifferentiated endometrial carcinoma, by using immune checkpoint inhibitors in combination with conventional treatments, it may be possible to control the undifferentiated component and improve prognosis.