学 位 論 文 の 要 旨

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学　位　論　文　名　Loss of ARID1A Expression Is Related to Shorter Progression-Free Survival and Chemoresistance in Ovarian Clear Cell Carcinoma

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論 文 内 容 の 要 旨

INTRODUCTION

Ovarian cancer is the most lethal gynecological malignancy in the world and its incidence has increased in the last decade. Ovarian carcinoma is subdivided into four major histological types: serous, mucinous, endometrioid, and clear cell. Of these, ovarian clear cell carcinoma, which constitutes around 25% of cases in Japan, is genetically distinct from the other histological types. Ovarian clear cell carcinoma is diagnosed at an early stage in ~ 60% of patients; however, it carries a worse prognosis because resistance to conventional cytotoxic chemotherapeutic agents is common even with early disease. Identification of the molecular pathways, which confer chemoresistance in ovarian clear cell carcinoma, is essential for the development of novel targeted therapeutic agents. Recently, the *ARID1A* gene has been identified as a novel tumor suppressor in ovarian clear cell carcinoma. Although *ARID1A* mutation is proving to be a frequent alteration in ovarian clear cell carcinoma, its clinicopathological and prognostic role is unclear. The current study examined the prognostic significance of loss of ARID1A expression in ovarian clear cell carcinoma by investigating the relationship between ARID1A expression and various clinicopathological variables in ovarian clear cell carcinoma. Finally, we assessed the utility of ARID1A as a prognostic and chemoresistance marker in ovarian clear cell carcinoma.

MATERIALS AND METHODS

Tissue samples

Formalin-fixed, paraffin-embedded tissue samples of 77 ovarian cancers, including 60 clear cell carcinomas, and 17 high-grade serous adenocarcinomas were used in this study. All patients were primarily treated with cytoreductive surgery and adjuvant platinum and taxane or CPT-11 chemotherapy. Written informed consent for the analysis in this study was obtained for each individual case. Acquisition of tissue specimens and clinical information was approved by an institutional review board (Shimane University and Seirei Hamamatsu General Hospital).

Immunohistochemistry and statistical methods

Expression levels of ARID1A were assessed by immunohistochemistry. The antibodies used in this study were a mouse monoclonal antibody to ARID1A (BAF250a) (Santa Cruz Biotechnology Santa Cruz, CA) and the mouse monoclonal antibody to Ki-67, MIB1 (DAKO, Carpinteria, CA). Slides for all samples were evaluated with a light microscope by two researchers who were blind to the clinicopathologic factors. Survival data were plotted as Kaplan–Meier curves, and the statistical significance was determined by the Log rank test. A multivariate prognostic analysis was performed using a Cox proportional hazards model. Data were censored when patients were lost to follow-up. The chi-square test or Fisher's exact test was used for comparisons of categorical data.

RESULTS AND DISCUSSION

The correlations between the loss of ARID1A expression and clinicopathological characteristics, prognosis, and chemosensitivity were investigated. Loss of ARID1A expression was identified in 9 (15.0%) of 60 ovarian clear cell carcinoma samples. Loss of ARID1A staining intensity (0+) was more frequently found in cells of clear cell carcinomas than in high-grade serous carcinomas (P<0.01). Loss of ARID1A expression was significantly correlated with advanced FIGO stage, high CA125 levels, and CDDP+CPT-11 regimen (P=0.02, 0.01, 0.03). There were no significant correlations between loss of ARID1A expression and patient age, status of residual tumor, Ki-67 labeling index, or the status of endometriosis. Loss of ARID1A correlated with shorter progression-free survival of patients with clear cell carcinomas treated with platinum-based chemotherapy (P=0.01). Loss of ARID1A expression tended to correlate with shorter overall survival in patients with ovarian clear cell carcinomas treated with platinum-based chemotherapy. When data were stratified for the multivariate analysis, only the loss of ARID1A expression remained a significant (P=0.03) predictor of reduced progression free survival. Of the 60 patients with ovarian clear cell carcinomas, 14 patients had measurable residual tumor after primary cytoreductive surgery. Tumors with loss of ARID1A expression were more likely to be chemoresistant than tumors with positive ARID1A expression (100.0 vs 40.0%, P=0.04).

It has been reported that *ARID1A*, a recently identified tumor suppressor gene, is mutated in ~50% of ovarian clear cell and 30% of ovarian endometrioid carcinomas. The clinical significance

of *ARID1A* mutation is unknown. Recently, Maeda *et al* reported that *ARID1A* mutation was significantly correlated with the loss of ARID1A protein expression using immunohistochemistry. Therefore, we evaluated the clinicopathological and prognostic significance of ARID1A immunoreactivity in ovarian clear cell carcinoma. In the current study, the higher frequency of loss of ARID1A expression in ovarian clear cell carcinomas compared with ovarian high-grade serous adenocarcinomas is a finding of interest. It supports the hypothesis that ovarian clear cell carcinomas may be distinguished from their more common serous counterparts based on characteristic alterations in gene sequences and expression. Additionally, this observation further supports the theory that each histological type of ovarian carcinoma arises from a distinct molecular pathway. Our most notable finding is that loss of ARID1A in ovarian clear cell carcinomas predicted a shorter progression-free interval. To date, there are a few molecular markers that predict the risk of early tumor recurrence in ovarian clear cell carcinomas. Therefore, loss of ARID1A expression may have the potential to be used alone or in combination with other markers to identify ovarian clear cell carcinoma patients who are more susceptible to early recurrence. This is important because at least 60% of advanced-stage ovarian clear cell carcinoma patients with a complete response to primary therapy ultimately develop recurrent disease. Taken together, these observations may have an impact on clinical management. In the current study, patients with ARID1A negative tumors had a significantly inferior response to chemotherapy when compared with patients who had ARID1A tumors. The fact that loss of ARID1A expression assessed by immunohistochemistry is an independent predictor of the progression-free interval in ovarian clear cell carcinomas attests to its value as a marker for predicting platinum resistance.

In general, the prognosis of patients with clear cell adenocarcinoma is poor, which is largely due to a low response rate to conventional platinum- or taxane-based chemotherapy. Currently, little is known about the role ARID1A has in chemoresistance. Our results suggest a need to investigate the possible link between loss of ARID1A expression and chemoresistance in ovarian clear cell carcinoma. To our knowledge, this is the first report suggesting that loss of ARID1A protein expression is a marker of poor progression-free survival and platinum resistance in ovarian clear cell carcinomas. This study is limited by its small size given the relative rarity of ovarian clear cell carcinoma. Larger prospective trials are needed to confirm our findings and to more fully explore the role of ARID1A in ovarian clear cell carcinoma behavior.

CONCLUSION

This study demonstrates that loss of ARID1A in ovarian clear cell carcinoma is a negative prognostic factor in patients treated with platinum-based chemotherapy. Measurement of ARID1A expression may be a method to predict resistance to platinum-based chemotherapy in patients with ovarian clear cell carcinoma.