学 位 論 文 の 要 旨

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学 位 論 文 名　Prognostic Value of Peripheral Blood Lymphocyte Telomere Length in Gynecologic Malignant Tumors

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論 文 内 容 の 要 旨

INTRODUCTION

Telomeres, the terminal structures of chromosomes, are composed of long, repetitive 6-base pair nucleoproteins. Their vital role is to maintain chromosomal integrity and genomic stability by blocking the end-to-end fusion of chromosomes, nuclease degradation, and incomplete replication during cell division. In human somatic cells, the average length of telomeres is 10–15 kb, and telomeric DNA is shortened during each cell division by approximately 50–200 base pairs. When the telomere length reaches a critical point due to this progressive shortening, replicative senescence is triggered, resulting in cell-cycle arrest or apoptosis. Moreover abnormal shortening of telomeres causes genomic instability in the form of chromosomal rearrangement or abnormal chromosome numbers, which can trigger carcinogenesis. In recent years, it has been reported that there is a strong correlation between lymphocyte telomere length and patient prognosis in several malignant tumors. This is presumed to be a phenomenon related to tumor immunity. A few scattered studies have evaluated blood base intermediate biomarkers such as DNA repair capacity and telomere length for predicting the risk of developing various cancers, but up to date no studies have evaluated the prognostic signicance of lymphocyte telomere length in gynecological cancer patients. The purpose of this study is to clarify the prognostic significance of peripheral blood lymphocyte telomere length in gynecologic cancers.

MATERIALS AND METHODS

Clinical patient data and follow-up data were collected by retrospective review of medical archives and electronic medical records at Shimane University Hospital. Age, tumor stage, grade, residual tumor status, lymph node metastasis, histological categories, time of surgery, and time of recurrence or death were recorded. Tumor type and stage were assessed according to the World Health Organization and the International Federation of Gynecology and Obstetrics (FIGO), respectively. The telomere length of patient's lymphocyte in gynecological malignancies (Ovarian cancer: OC, 72, Cervical cancer: CC, 63 and Endometrial cancer: EC, 87) was examined by using Quantitive Reverse Transcription PCR. Only mononuclear cells were isolated from the 222 patient's peripheral blood using by Lymphoprep^{TM} according to the manufacture's instruction and DNA was extracted by QIAGEN DNase blood and tissue kit. Relative lymphocyte telomere length was measured by qRT-PCR using the thermal cycler dice real time system software TP800 which compare the signals from telomere repeat copy number (T) to a single gene copy number (S) and calculates the T/S ratio for each sample. Participants were categorized by quartile of telomere length (short and long). All patients were administered appropriate therapy at Shimane University Hospital between 2008 and 2018. Kaplan-Meier curves were used for survival analysis, and statistical significance was determined by the log–rank–test. All data were censored when the patients died or for lack of follow-up. Multivariate prognostic analysis was performed using a Cox proportional hazards regression model to calculate the hazard ratio and 95% confidence interval for the association of clinicopathological variables and RLT on OS and PFS. The χ^2 test was used to compare categorical data between subgroups. Student's *t*-tests (for comparison of two groups) or one-way analysis of variance was performed to compare RLTs of patients in different treatment conditions. $P < 0.05$ was considered statistically significant. The study protocol was approved by the Research Ethics Committee of Shimane University.

RESULTS AND DISCUSSION

Peripheral blood lymphocyte telomere length was quantified by qRT-PCR, and the optimal cutoff for the RLT to dichotomize patients into the long or short groups was determined by the median (OC: 0.75, CC: 1.94 and EC: 1.09). Spearman's correlation analysis showed that RLTs in all three cancer categories were negatively correlated with age. We also found that the correlation between FIGO stages (I, II, III, and IV) and lymphocyte telomere length was significantly higher in OC and CC patients with advanced stages than early stages .Shorter telomere length was significantly correlated with residual tumors (≥1 cm) in OC but no significant correlation was found in tumor grade (P = 0.69). Kaplan–Meier curve analysis

indicated that in both OC and CC, patients with short RLTs had significantly lower PFS than those with long RLTs (log-rank $P = 0.002$ for OC and $P = 0.001$ for CC). This analysis also revealed that patients of OC and CC with shorter relative lymphocyte telomeres length (RLT) had significantly poorer OS compare with longer RLT ($P = 0.003$, and $P = 0.001$ respectively). However, in EC, RLT was not significantly associated with either OS or PFS ($P = 0.567$ and $P = 0.304$). Univariate and multivariate Cox regression analyses revealed that age, WHO grade, histology, residual tumor were all independent prognostic factors for both PFS and OS of patients with OC and CC. Moreover univariate Cox regression analysis showed that both risks of death and progression increased in patients with short RLT in comparison with those with long RLT. Multivariate Cox regression analysis further confirmed RLT as an independent prognostic factor for both PFS and OS for OC ($P = 0.03$, $P = 0.04$, respectively) and CC ($P = 0.02$, $P = 0.03$, respectively).In this study. We assessed the prognostic value of lymphocyte telomere length in 222 gynecological malignant patients. We found that patients with short RLT showed significantly poorer PFS and OS than those with long RLT but no association found between RLT and EC patients.

CONCLUSION

In summary, our findings indicate that a short telomere length of blood lymphocyte significantly affects the OS and PFS of patients with ovarian and cervical cancers, but is not associated with endometrial cancer that may involve immune dependent activities. Our results also suggest that lymphocyte telomere length is an important prognostic biomarker in cancer. Further studies are warranted to evaluate the molecular mechanism of immunosuppressive phenotype associated with short telomere length in a large sample for precise results.