Investigation on the changes of leukocyte telomere length among urological cancer patients undergoing therapeutic intervention

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INTRODUCTION

Telomere is a repetitive region located at the end of a chromosome, plays a role in protecting genetic information. Telomere length reduction occurs along with aging and is affected by various factors such as gender, lifestyle, race, stress and illness. Shortening of telomere length is strongly associated with the risk of pathological conditions such as cancer, diabetes, and cognitive impairment. Although there are reports on the relationship between urological cancer and telomere length, there are many retrospective reports and few studies have explored changes in telomere length due to drug treatment.

In this study, we examined the changes of telomere length in urological cancer patients during therapeutic intervention with chemotherapy or immunotherapy and investigated whether leukocyte telomere length (LTL) was a useful therapeutic biomarker in clinical practice.

AIM

To investigate whether leukocyte telomere length is a useful therapeutic biomarker in clinical practice by prospectively tracking the changes of leukocyte telomere length in urological cancer patients with therapeutic intervention.

MATERIAL AND METHODS

◆Subjects

・56 patients with urological cancer undergoing chemotherapy or immunotherapy treatment at the Juntendo hospital were enrolled from April 2020 to March 2021.

・Blood samples were obtained before and after treatment (2-4 months).

・Objects were divided into response group and progression group. Evaluation of treatment efficacy was based on RECIST (ver. 1.1), tumor marker levels, diagnostic imaging findings, and progression of symptoms such as the appearance of pain.

・**LTL** was measured by using quantitative PCR, QuantStudio® 3(Thermo Fisher Scientific).
Genomic DNA was purified from peripheral leukocytes according to the kit instruction (Promega).
LTL expressed as the T/S ratio, calculated the copy number of the telomere (TTAGGG) repeat and the single-copy gene (HBG) from each sample.
Relative LTL was generated by dividing sample T/S value by the T/S value of the reference DNA extracted from pooled human female (Promega G152A).

◆ Statistical analysis

Data were expressed as mean ±SD. For statistical analysis, we used multivariate analysis of variance and regression analysis (SPSS). *P-value <0.05 was considered significant.

RESULTS

◆Among the patients underwent therapeutic intervention, 36 got good treatment results (including neoadjuvant chemotherapy). 20 patients showed negative treatment results and the disease progressed.

◆The changes of LTL before and after treatment between the response and progression groups were shown in Table.1. Most of the patients were men with urothelial carcinoma. There was no difference between the two groups in terms of age, smoking and BMI, which generally affected LTL (not shown).

◆**In chemotherapy, LTL increased significantly in the therapeutic response group and tended to shorten in the progression group.** While in immunotherapy, LTL tended to be longer in the therapeutic response group and shorter in the progression group. (Fig.1.)

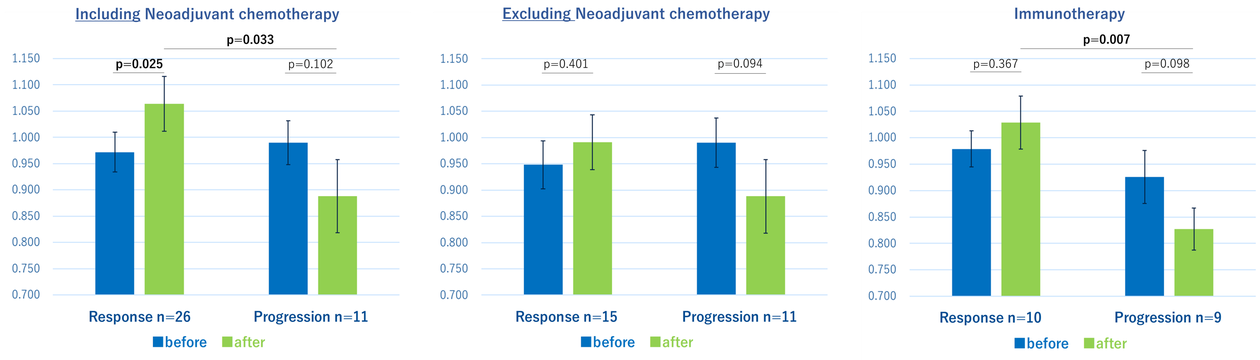
◆Quantitative PCR measurement accuracy: intra-assay CV of T/S ratio and inter-assay CV of the relative T/S ratio was less than 5%.

Table.1. The changes of Leukocyte telomere length associated with therapeutic intervention

				Response			Progression		
				n	LTL mean (min-Max)	variation	n	LTL mean (min-Max)	variation
Chemotherapy n=37 (**Including** Neoadjuvant chemotherapy)	Overall		Before	26	0.972 (0.678-1.583)	+0.092	11	0.990 (0.696-1.174)	-0.102
			After		1.064 (0.729-1.563)			0.888 (0.580-1.268)	
	Cancer types	Urothelial	Before	17	0.982 (0.719-1.583)	+0.137	5	1.027 (0.696-1.174)	-0.161
			After		1.119 (0.861-1.563)			0.866 (0.591-1.268)	
		Prostate	Before	5	0.992 (0.778-1.455)	-0.031	6	0.960 (0.774-1.133)	-0.054
			After		0.963 (0.741-1.090)			0.906 (0.580-1.130)	
		Testis	Before	4	0.904 (0.678-1.035)	+0.052	0	-	-
			After		0.956 (0.729-1.201)			-	
Chemotherapy n=26 (**Excluding** Neoadjuvant chemotherapy) ※			Before	15	0.948 (0.678-1.455)	+0.043	11	0.990 (0.696-1.174)	-0.102
			After		0.991 (0.729-1.332)			0.888 (0.580-1.268)	
Immunotherapy n=19	Overall		Before	10	0.979 (0.859-1.170)	+0.050	9	0.926 (0.661-1.216)	-0.099
			After		1.029 (0.806-1.413)			0.827 (0.603-1.068)	
	Cancer types	Renal	Before	5	1.017 (0.867-1.170)	+0.029	1	0.882	-0.082
			After		1.046 (0.806-1.413)			0.800	
		Urothelial	Before	5	0.941 (0.859-1.113)	+0.070	8	0.932 (0.661-1.216)	-0.101
			After		1.011 (0.957-1.112)			0.831 (0.603-1.068)	

※ 11 patients underwent neoadjuvant chemotherapy.

Fig.1. Comparison of LTL between Response group and Progression group by treatment



DISCUSSION

In patients with urological cancers (prostate, bladder, and renal), many studies have reported that patients with short LTL have a poor prognosis.[1) 2) 3)]

There are few reports of follow-up studies between chemotherapy and telomere length changes before and after treatment. Most of the chemotherapy reports were in hematological diseases and breast cancer among solid tumors.[4)] There are no reports of changes in LTL due to chemotherapy or immunotherapy in urological cancer.

In this study, we showed that LTL in urological cancer patients increased significantly in the therapeutic response group and decreased in the progression group.

The limitation of our study include the following
- sample size was small
- all patients were Japanese
- each patient has different factors that affect telomere length and with/without previous treatment

CONCLUSIONS

Our results indicate that LTL has the potential to be a promising biomarker for predicting treatment response and prognosis in urological cancer patients.

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