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Genome-wide copy number alteration as a prognostic biomarker in esophageal squamous cell carcinoma

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Background/Aims: Although neoadjuvant chemoradiation (CRT) plus surgery or definitive CRT are the standard treatment for locally advanced esophageal squamous cell carcinoma (ESCC), the prognosis in those patients remains unsatisfactory. In addition, there are no reliable clinical assessment tools for predicting prognosis or monitoring treatment response for CRT in ESCC. We aimed to identify a biomarker for predicting outcomes using cell-free DNA (cfDNA) in ESCC patients receiving CRT. **Methods:** This prospective biomarker study analyzed plasma cfDNA from patients with neoadjuvant CRT followed by surgery (n=24) and patients with definitive CRT for locally advanced ESCC (n=21) at Asan Medical Center in South Korea from Feb. 2017 to Feb. 2018. Plasma cfDNA was collected before and after CRT. Low depth whole-genome sequencing of cfDNA was used to identify copy number alteration (CNA) and I-score was developed to express genomic instability. I-score was defined as the sum of absolute Z-scores of sequenced reads on each chromosome. **Results:** The pathologic complete response (pCR) was achieved in 7 patients (29%) in neoadjuvant CRT followed by surgery group, and the clinical complete response (cCR) was achieved in 5 (24%) in definitive CRT group. The baseline cfDNA concentrations were no significant association with the clinical T (cT 1-2 vs. cT 3-4; 0.42 vs. 0.36 ng/μL; p=0.18), pathologic response (pCR vs. non-pCR; 0.34 vs. 0.40; p=0.80), ypT (ypT 0-2 vs. ypT 3-4; 0.34 vs. 0.42; p=0.54) and ypTNM (ypTNM 1 vs. ypTNM 2-4; 0.31 vs. 0.42; p=0.31). When analyzing cfDNA concentration before and after CRT, cfDNA concentration was significantly increased after CRT (0.38 vs. 0.67; p<0.01). However, the I-score tended to increase at higher clinical T (cT 1 vs. cT 2-4; 2.49 vs. 648.7; p=0.07), was also significantly higher at higher ypT (ypT 0-2 vs. ypT 3-4; 47.04 vs. 839.10; p=0.05) and ypTNM (ypTNM 1 vs. ypTNM 2-4; 1.26 vs. 615.8; p=0.04). **Conclusions:** The cfDNA concentration is not a good biomarker for prognostication and monitoring the course of treatment in esophageal cancer patients treated with CRT. But the I-score, an indicator of genomic instability in ctDNA, was a significant predictor of poor prognosis.

Table 1. Association between cancer stage and Cell-free DNA concentration / I-score

Cell-free DNA concentration				I-score			
Variable	n	Mean (ng/μL)	p-value	Variable	n	Mean	p-value
cT 1-2	10	0.42	0.18	cT 1	8	2.49	0.07
cT 3-4	17	0.36		cT 2-4	19	648.70	
ypT 0-2	11	0.34	0.54	ypT 0-2	11	47.04	0.05
ypT 3-4	6	0.42		ypT 3-4	6	839.10	
ypTNM 1	7	0.31	0.31	ypTNM 1	7	1.26	0.04
ypTNM 2-4	10	0.42		ypTNM 2-4	10	615.80	
pCR	5	0.34	0.80	pCR	5	2.01	0.27
non-pCR	12	0.40		non-pCR	12	461.83	

* cT, ypT, and ypTNM stage were according to AJCC 8th edition.

* pCR: pathologic complete response

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Immune checkpoint inhibitor induced immune thrombocytopenia: A case series

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Immune checkpoint inhibitors (ICIs) induced have recently been used as standard therapies in a variety of cancers, and various immune-related adverse events (irAEs) have been reported. Hematologic toxicity of immune checkpoint inhibitor may occur as a relatively rare adverse event, ranging from mild cytopenia to immune thrombocytic purpura, autoimmune hemolytic anemia, and disseminated intravascular coagulopathy. Here we describe two cases of patients with immune thrombocytopenia following ICI use. A 61 year old male patient diagnosed with metastatic renal cell carcinoma underwent Lt. nephrectomy and lung metastasectomy followed chemotherapy with high dose IL-2, sunitinib. After progression, he started third-line therapy with nivolumab 100 mg fixed dose q 3 weeks. After the first dose, thrombocytopenia was observed, which continued to deteriorate gradually and the severe thrombocytopenia of platelet 21,000/ul was confirmed. Tumor response was stable disease with 10% increase. Another 68 year old male patient who had metastatic melanoma had treated with dacarbazine plus interferon-alpha and wide excision subsequently. After that, pembrolizumab was used for treatment, but thrombocytopenia (29,000/ul) was observed after 2 cycles. The bone marrow examination was compatible with idiopathic thrombocytopenic purpura, and platelet counts were recovered after steroid use and discontinuation of pembrolizumab. Tumor response was stable disease. As the use of ICI becomes popular, a better understanding of the pattern and mechanism of hematologic irAEs is needed.

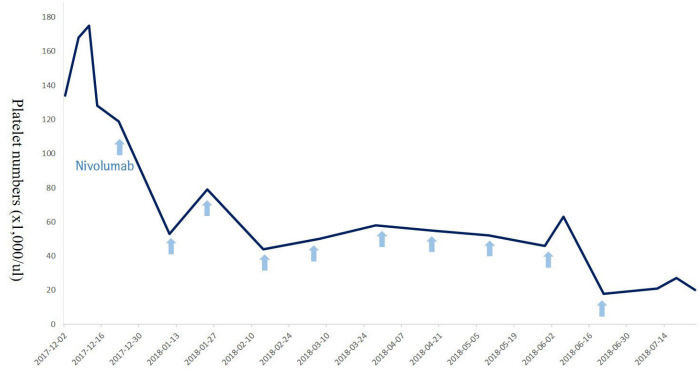

Figure 1. Course of thrombocytopenia of patient 1