Circulating tumor DNA for monitoring treatment response to anti-PD-1 immunotherapy in melanoma patients

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Introduction

Nivolumab has high therapeutic efficacy in metastatic melanoma. Evaluation of clinical response largely relies on radiological imaging criteria, such as response evaluation criteria in solid tumors (RECIST). However, radiological evaluation usually requires substantial time. In addition, immunotherapeutic agents occasionally induce paradoxical reactions, such as decreased lesion size despite the appearance of new metastases. Therefore, reliable markers to evaluate tumor responses and predict therapeutic effects are required. Serum lactate dehydrogenase (LDH) is widely used as a surrogate marker for tumor progression in melanoma. However, as LDH levels occasionally remain within a normal range despite tumor progression. In addition, increases in LDH levels can occur in response to several conditions, such as infections, liver dysfunction and myocardial disorders. Therefore, the utility of LDH levels as a biomarker is limited. Circulating tumor DNA (ctDNA) is a novel marker to evaluate treatment response and monitor disease progression in patients with advanced cancer. In this study, we assessed the efficacy of ctDNA levels compared with that of LDH levels in determining the response to nivolumab in patients with metastatic melanoma. We also assessed computed tomography (CT) findings. Our findings demonstrated that *BRAF*- and *NRAS*-mutated ctDNAs were potentially useful biomarkers of tumor burden in patients with melanoma.

Methods

Five patients with metastatic melanoma at Shinshu University between July 2014 and June 2016 were enrolled in the study. *BRAF* and *NRAS* mutations in tumor specimens were assessed by Sanger sequencing. *BRAF*- and *NRAS* mutated ctDNA levels in 45 serial plasma samples from these patients were analyzed using droplet digital PCR.

Results

- The ctDNA levels changed within 2–4 weeks after nivolumab initiation and closely correlated with the radiological changes in four patients (Patients 1, 3, 4, and 5). The ctDNA levels began decreasing 2–3 weeks after the first administration of nivolumab in responders (Patients 1, 2, and 3). In contrast, the ctDNA levels began increasing 2-4 weeks after the first administration of nivolumab in non-responders (Patients 4 and 5).
- Alterations in ctDNA levels preceded radiological changes after nivolumab initiation in all patients.
- The ctDNA levels increased at the time of tumor recurrence.
- The LDH levels did not correspond with clinical findings in three patients (Patients 1, 3, and 4).

Conclusions

Thus, our findings suggest that ctDNA is useful in determining the efficacy of nivolumab even before initial assessment using CT. Furthermore, ctDNA might be a useful biomarker of clinical response and tumor recurrence while monitoring patients with metastatic melanoma treated with nivolumab..

References

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Characteristics of Patients

Patient	Age	Gender	Primary site	Mutation	Metastatic organs at baseline	Previous therapy before nivolumab	Following therapy after nivolumab
1	63	F	Upper eyelid	<i>BRAF</i> ^{V600E}	Brain, liver, skin, soft tissue, peritoneal cavity, LN	DTIC	vemurafenib
2	47	F	Head	<i>BRAF</i> ^{V600E}	Bone, skin, soft tissue, LN	<i>BRAF</i> inhibitor	ipilimumab
3	74	F	Head	<i>BRAF</i> ^{V600K}	Lung	(-)	on going
4	51	M	Neck	<i>BRAF</i> ^{V600E}	Pleural and peritoneal cavity, LN	DAC	(-)
5	83	M	Foot	<i>NRAS</i> ^{Q61K}	Lung, liver, skin, LN	(-)	(-)

LN, lymph node; DTIC, dacarbazine; DAC, dacarbazine, nimustine and cisplatin

Monitoring of ctDNA and LDH & Clinical information

BRAF^{V600E} ctDNA level was undetectable on Day 21. The metastatic tumor responded well, and CT scan showed partial response (PR) on Days 58, 105, and 185. On Day 240, new bladder metastasis appeared. Subsequently, *BRAF*^{V600E} ctDNA level rebounded on Day 268. Furthermore, new brain metastases appeared, and almost all existing metastases were progressive. At the time of tumor recurrence, *BRAF*^{V600E} ctDNA levels increased, whereas LDH levels remained below the normal range. Treatment was switched to vemurafenib on Day 352. .

BRAF^{V600E} ctDNA levels decreased on Day 19. Although they remained low until Day 82, CT scan revealed new brain metastases and multiple skin metastases on Day 96. Further, *BRAF*^{V600E} ctDNA levels gradually increased from Day 103. Treatment was switched to ipilimumab on Day 147. Subsequently, both *BRAF*^{V600E} ctDNA and LDH levels increased.

BRAF^{V600K} ctDNA levels began decreasing on Day 12. Tumor responded well, and CT scans on Days 54 and 117 indicated stable disease (SD). Although lung metastases were stable, a new spleen metastasis appeared on Day 222, indicating progressive disease (PD). The patient underwent surgery to remove the spleen metastasis on Day 281, and nivolumab therapy was re-started on Day 327. The LDH levels remained above the upper limit of normal range during the monitoring.

BRAF^{V600E} ctDNA levels increased on Day 9. The patient had significantly increased pleural effusion and ascites despite nivolumab administration, and his condition deteriorated rapidly. Although *BRAF*^{V600E} ctDNA levels increased with tumor progression, LDH levels remained below normal range until the terminal stage.

NRAS^{Q61K} ctDNA level was not detected at the time of nivolumab initiation but was detected at high level on Day 27. The patient's condition deteriorated rapidly despite nivolumab administration. Both *NRAS*^{Q61K} ctDNA and LDH levels simultaneously increased with tumor progression.

COI: I have no financial relationships to disclose.