Safety dose and prediction of immune-related adverse event of nivolumab combined with IFN- β in patients with advanced melanoma

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Background

Nivolumab for advanced melanoma

Nivolumab significantly prolongs survival in patients with metastatic melanoma, but only 31–43% of patients who receive nivolumab monotherapy experience objective tumor regression [1, 2]. Therefore, reagents that enhance the antitumor immune response induced by nivolumab are necessary to further optimize its use for the treatment of advanced melanoma. Although recent studies suggest that such nivolumab-based combined therapy might prove effective for treatment of advanced melanoma [1], the associated risk of immune-related adverse events (irAE), such as severe hepatitis, interstitial pneumonia, colitis, type 1 diabetes mellitus, hypophysitis, or myasthenia gravis, is an important consideration.

Interferon beta (IFN- β)

IFN- β inhibits the growth of melanoma cells and induces cross-priming of CD8⁺ T cells by dendritic cells *in vitro* and *in vivo*, and has been clinically used for the treatment of malignant melanoma [3].

In melanoma patients, peritumoral injection of IFN- β recruits effector cells including CD8⁺ and TIA1-positive cytotoxic T cells (CTLs) into the tumor microenvironment [4], which might explain one of the possible mechanisms for the therapeutic effects of IFN- β in the treatment of melanoma.

Therapeutic effects of IFN- β in combination with anti-PD-1 Abs for B16F10 melanomas.

IFN- β enhances the anti-tumor immune response of anti-PD-1 antibodies against B16F10 melanoma by the reduction of CCL22 from Tumor-associated macrophages, leading to suppress the recruitment of Tregs *in vivo* [4].

Kakizaki et al. Oncoimmunology 2015.

Hypothesis

Since IFN- β increases the tumor-infiltrating lymphocytes (TILs) in melanoma, and the number of TILs correlates with the efficacy of nivolumab in various cancers, we hypothesized that IFN- β could enhance the therapeutic effects of nivolumab in patients with advanced melanoma.

Purpose

To explore the potential of this property of IFN- β as part of a combination therapy for the treatment of metastatic melanoma patients, first we explored the safety dose of IFN- β in combination with nivolumab by a phase 1 trial, using a traditional rule-based 3 + 3 design, on patients with advanced melanoma.

Material and Methods

Patients and methods

Patients were eligible if they had unresectable stage III melanoma, if their tumor was resectable but they had declined resection, or if they had stage IV melanoma with accessible cutaneous, subcutaneous, and/or nodal lesions (patients were staged according to the AJCC Staging Manual, 7th Edition, 2011). Other inclusion criteria were: age of at least 20 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; and adequate bone marrow and liver function. Exclusion criteria were: active autoimmune disease; history of hypersensitivity to nivolumab or IFN- β ; interstitial pneumonia; cancer originating in other organs; psychological disorders; and concurrent therapy with any other anti-melanoma chemotherapeutic drugs.

Study design and treatment

This phase 1 trial (UMIN000020222) was an open label, non-randomized, traditional rule-based 3 + 3 design. The intravenous administration of nivolumab was fixed at 2 mg/kg every 3 weeks (Fig. 1). IFN- β was intra-dermally administered at 1 million units, 2 million units, and 3 million units to the three patients in each group at the site of the primary tumor. We set the maximum tolerated dose at the conventional IFN- β therapeutic dose approved in Japan (3 million units).

Assessment

All study patients were evaluated for DLT during the first 6 weeks of treatment. Adverse events were graded using NCI CTCAE version 4.03. DLT were defined as grade 3–5 adverse events at least possibly related to nivolumab and IFN- β that occurred between day 0 and day 42. The first three patients received nivolumab (2 mg/kg) and IFN- β (1 million units) at day 1 (dose level 1+) as per protocol design. With 0 of 3 patients exceeding a DLT of grade 3, three more patients were evaluated at dose level 2+ of nivolumab (2 mg/kg) and IFN- β (2 million units) at day 1. With no DLT reported in any of the three patients in level 2+, three more patients were evaluated at dose level 3+ of nivolumab (2 mg/kg) and IFN- β (3 million units) at day 1. With no DLT reported at level 3+, we finalized the study. After the treatment period, patients were assessed every 3 weeks with physical examination, conventional blood examination, and chest radiography, and assessed every 3 months with follow-up computed tomography (CT) scans. The tumor response was clinically evaluated by measuring the longest diameter of the target lesions over time. A partial response (irPR) was defined as a decrease of >30%, while progressive disease (irPD) was defined as an increase of >20%, as compared to the baseline measurement. Complete response (irCR) corresponded to the disappearance of all target lesions. We measured tumors 3 months and 6 months after the treatment period.

Study oversight

The study protocol and all amendments were approved by the institutional review board at Tohoku University Graduate School of Medicine (2016-2-023). The study was conducted in accordance with the Declaration of Helsinki and with Good Clinical Practice guidelines as defined by the International Conference on Harmonisation. All patients provided written informed consent before enrollment. A data and safety monitoring committee was established to provide oversight of safety and efficacy considerations. The study was registered with UMIN (UMIN000020222).

An open label, non-randomized, traditional rule-based 3 + 3 design

irAE: Immune-related adverse event

Conclusion

Of the nine patients who received this combined therapy, none experienced dose-limiting toxicities, and all completed the treatment phase of the study, suggesting that the safe dose of IFN- β , when combined with nivolumab, is 3 million units.

To determine the efficacy of this combination therapy, further phase II trials are required.

Immune-related adverse events (irAE) might be predicted by serum levels of sCD163 and CXCL5 at day 42.

Treatment periods

Results

Table 1

	Age	Sex	Stage	Pretreatment	PS	primary sites
IFN- β 1MU	Case 1	87	M	pT3bNM1b stage IV	monthly IFN- β	EOOG 0 sole
	Case 2	88	M	pT4eNM1b stage IV	monthly IFN- β	EOOG 0 sole
	Case 3	83	F	pT3bNM1a stage IV	nivolumab	EOOG 1 sole
IFN- β 2MU	Case 4	93	M	pT4bNM1a stage IV	contact immunotherapy	EOOG 1 sole
	Case 5	74	M	pT2bNM1b stage IV	monthly IFN- β	EOOG 0 upper arm
	Case 6	84	F	pT4eNM1a stage IV	nivolumab	EOOG 1 back
IFN- β 3 MU	Case 7	74	M	pT4eNM1b stage IV	chemotherapy	EOOG 0 lower leg
	Case 8	58	F	pT4eNM1b stage IV	chemotherapy	EOOG 0 lower lip
	Case 9	34	M	pT4eNM1b stage IV	weekly IFN- α	EOOG 0 back

Table 2

	Case 1	monthly IFN β	lung	AGTH deficiencies	2	IrPR
IFN- β 1MU	Case 2	monthly IFN β	lung, pelvic LN			IrOR
	Case 3	nivolumab	pelvic LN, Ir-transit			IrPD
	Case 4	contact immunotherapy	pelvic LN, Ir-transit			IrPD
IFN- β 2MU	Case 5	monthly IFN β	lung			IrOR
	Case 6	nivolumab	multiple Ir-transit			IrPD
	Case 7	chemotherapy	lung, Ir-transit			IrPD
IFN- β 3 MU	Case 8	chemotherapy	lung, liver	fever	1	IrPD
	Case 9	weekly IFN- α	bile duct	abdominal pain,	2	SD

Fig. 1: Change levels of serum sCD163 and CXCL5 at day 42.

The serum levels of sCD163 (A) and CXCL5 (B) from each patient at day 0 and day 42 were examined by ELISA. These data represent changes of serum sCD163 and CXCL5 at day 42 compared to day 0.

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