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Letter to the Editor

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The Effect of mRNA-Based COVID-19 Vaccination on Anti-Programmed Cell Death Protein 1 Blockade for Nasopharyngeal Cancer May Differ From a Virus-Inactivated Vaccine

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To the Editor

During the coronavirus disease 2019 (COVID-19) pandemic, a concern arises on the effects of COVID-19 vaccination on the efficacy of immune checkpoint inhibitors (ICIs) in patients with malignancies. Our results revealed no medical evidence stating that COVID-19 vaccination significantly improved the efficacy of the combination of immune cancer therapy with anti-programmed cell death protein 1 (anti-PD-1) antibody and chemotherapy in patients with advanced nasopharyngeal cancer (NPC).

The cancer immunotherapy using anti-PD-1 antibody was effective in patients with NPC [1]. Its efficacy and safety were believed not to be affected by the timing of COVID-19 vaccination because of the long half-life of ICIs [1]. Therefore, COVID-19 vaccination is recommended for patients receiving cancer immunotherapy with ICIs. However, the details of the effect of COVID-19 vaccination on the therapeutic effect of ICIs in patients with cancer have not been reported for each cancer type [1]. Recent Chinese report reveals significantly improved antitumor efficacy of the combination of cancer immunotherapy with anti-PD-1 antibody and chemotherapy in patients with advanced NPC who received COVID-19 vaccination, but the incidence of severe immune-related adverse events was similar [2]. However, our study results differ from those of the clinical research conducted by the Chinese group.

This study investigated the treatment of 2,651 patients (OncoGuide™ NCC oncopanel* test: 660 patients, Foundation One CDx** test: 1,991 patients) with cancer genomic medicine at national universities in Japan from December 2019 to November 2022. The treatment of 108 patients with advanced NPC was examined by cancer genomic medicine. The therapeutic efficacy of anti-PD-1 inhibitors in 106 patients with advanced NPC who had documented COVID-19 vaccination status was investigated. On March 24, 2017, the Ministry of Health, Labor, and Welfare in Japan approved the insurance coverage of nivolumab for patients with recurrent or distant metastatic head and neck cancer who had previously received platinum-containing chemotherapy [3]. The overall response rate (ORR) was 11.1% in 36 patients with advanced NPC, who received nivolumab alone and had not been vaccinated against COVID-19 (complete response (CR) in one (5.6%) patient, partial response (PR) in one (5.6%), stable disease (SD) in four (22.2%), and progressive disease (PD) in four (66.7%)) (Table 1). ORR with nivolumab was 11.1% in 54 patients with advanced NPC who received nivolumab alone and had been vaccinated against COVID-19 (CR in one (3.7%), PR in two (7.4%), SD in four (14.8%), and PD in 20 (74.1%) patients) (Table 1). Clinical study results revealed no medical evidence proving that COVID-19 vaccination significantly improved the efficacy of the combination of cancer immunotherapy with anti-PD-1 antibody and chemotherapy in patients with advanced NPC. The median age of participants in our clinical study was 65.8 years (range: 62 - 72). Therefore, Pfizer/BionTech's BNT162b2 mRNA vaccine was inoculated in 60 participants, excluding six participants. Additionally, nivolumab monotherapy for human papillomavirus (HPV)-infected participants with advanced NPC has provided a long survival of 9.1 months compared with the survival time (7.5 months) by nivolumab administration alone to HPV-uninfected participants [3]. Our clinical research revealed a 40.6% HPV infection rate among participants (Tables 1-3). HPV tests for 15 (41.67%) participants were positive from the 36 patients with advanced NPC who received nivolumab alone and had not been vaccinated against COVID-19. Conversely, HPV tests were positive in 22 (40.74%) of 54 patients with advanced NPC who received nivolumab alone and had been vaccinated against COVID-19 (Tables 2, 3). No significant difference was found between the percentage of HPV-pos-

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Table 1. Clinical Characteristics of the NPC Patient Cohort

Tumor type	Study	Administration group	Cases	Median (95% CI) (months)	Hazard ratio (95% CI)
Recurrent/metastatic nasopharyngeal cancer in Japanese	ONO-4538-11/ CA209141 study[a]	Methotrexate, docetaxel or cetuximab	9 (Japanese)	6.2 (5.2 - 6.8)	0.71 (0.42 - 1.19)
		Nivolumab	18 (Japanese)	8.8 (7.3 - 9.5)	
	Our clinical research	In COVID-19 era, January 2021 - November 2022 (%)			
		Age, years	Total 106	65.8 (62 - 72)	
		Gender		Male 88/female 18	
		HPV test-positive		Male 37 (42.0)/female 6 (33.3)	
		Treatment method		Result of treatment	
				DOR (months)	ORR
		Methotrexate, docetaxel or cetuximab	4	6.7 (6.4 - 7.0)	PD 4 (100)
		Nivolumab	36	8.6 (6.5 - 9.6)	ORR: 11.1% (CR 2 (5.6), PR 2 (5.6), SD 8 (22.2), PD 24 (66.7))
		BNT162b2 mRNA Vac. + methotrexate, docetaxel or cetuximab	6	6.5 (5.2 - 7.6)	SD 2 (33.3), PD 4 (66.7)
		mRNA-1273 Vac. + methotrexate, docetaxel or cetuximab	6	NA	PD 6 (100)
		BNT162b2 mRNA Vac. + nivolumab	54	8.5 (6.8 - 9.4)	ORR: 11.1% (CR 2 (3.7), PR 4 (7.4), SD 8 (14.8), PD 40 (74.1))
		mRNA-1273 Vac + nivolumab	0	NA	NA

[a]The ONO-4538-11/CA209141 study was also reported as the CHECKMATE-141 study. COVID-19: coronavirus disease 2019; NPC: nasopharyngeal cancer; HPV: human papillomavirus; DOR: duration of response; ORR: overall response rate; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; Vac.: vaccine; CI: confidence interval; NA: not available.

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Table 2. HPV Test Positive Cases in Sub-Cohorts (ONO-4538-11/CA209141 Study)

HPV test	Treatment with nivolumab (n = 240)		Treatment without nivolumab (n = 121)	
	Total 240/Japanese 18 cases		Total 121/Japanese 9 cases	
Positive	63 (26.3%)	3 (16.7%)	29 (24.0%)	0
Negative	50 (20.8%)	0	36 (29.8%)	0
NA	127 (52.9%)	-	56 (46.3%)	-
No report	-	15 (83.3%)	-	9 (100.0%)

HPV: human papillomavirus; NA: not available.

itive patients (41.67%) in the nivolumab alone sub-cohort and that (40.74%) in the nivolumab plus COVID-19 vaccine sub-cohort (Tables 2, 3). Our clinical study revealed that HPV infection rates were not involved in the effects of COVID-19 vaccination on the antitumor efficacy of cancer immunotherapy with anti-PD-1 antibody. Severe immune-related adverse events (irAEs) were not significantly different between both matched subgroups (Table 4). These findings regarding second effects, including irAE, are following the safety profiles in the ONO-4538-11/CA209141 study, which investigated anti-PD-1 + chemotherapy versus chemotherapy alone in non-nasopharynx head and neck cancer [4].

The clinical study by other institutions reported that Sinovac COVID-19, which is a virus-inactivated vaccine developed in China, was inoculated in enrolled participants [5]. The World Health Organization approved Sinovac COVID-19 for emergency use. However, it is not approved for use in the United States, Japan, etc. Furthermore, the age of participants enrolled in the clinical study reported by other institutions ranged from 33 to 59 years old, which is younger than our participants. The difference in the therapeutic effect of anti-PD-1 therapies on patients with advanced NPC from the COVID-19 vaccination obtained in two clinical research studies might be due to the type of COVID-19 vaccine inoculated, the type of anti-PD-1 agent, or the age of participants. Additionally, information on HPV prevalence among participants enrolled in the clinical research reported by other institutions is also needed. Rigorous studies based on large cohort clinical research are needed to generalize and substantiate the clinical study results reported by other institutions.

Ethics approval and consent to participate

This study was reviewed and approved by the Central Ethics Review Board of the National Hospital Organization Headquarters in Japan (Tokyo, Japan) on November 08, 2019, and Kyoto University School of Medicine (Kyoto, Japan) on August 17, 2019, with approval codes NHO H31-02 and M192. The completion numbers for the authors are AP0000151756, AP0000151757, AP0000151769, and AP000351128. As this research was considered clinical research, consent to participate was required. The participants signed an informed consent form after briefing them regarding the clinical study and approval of the research contents.

Methods

A total of 108 patients with NPC were screened from 18 hospitals from December 10, 2019. Eligible participants should meet the following criteria: 1) confirmed NPC; 2) received one dose of anti-PD-1 treatment; 3) available medical record and willingness for follow-up. Clinical and demographic data were collected upon enrollment. The last date of follow-up was October 10, 2022.

OncoGuide™ NCC oncopanel*; Gene mutation analy-

Table 3. HPV Test Positive Cases in Sub-Cohorts (Our Clinical Research)

Tumor type	Treatment method	HPV test-positive cases, n (%)
		Male 37 (42.0)/female 6 (33.3)
Recurrent/metastatic nasopharyngeal cancer in Japanese	Methotrexate, docetaxel or cetuximab (n = 4)	2 (50)
	Nivolumab (n = 36)	15 (41.67)
	BNT162b2 mRNA Vac. + methotrexate, docetaxel or cetuximab (n = 6)	2 (33.33)
	mRNA-1273 Vac. + methotrexate, docetaxel or cetuximab (n = 6)	2 (33.33)
	BNT162b2 mRNA Vac. + nivolumab (n = 54)	22 (40.74)
	mRNA-1273 Vac + nivolumab (n = 0)	0

HPV: human papillomavirus; Vac.: vaccine.

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Table 4. Clinical Side-Effects of the NPC Patient Cohort (Our Clinical Research)

Items	Nivolumab + vaccinated (n = 54), n (%)	Nivolumab (n = 36), n (%)	P value
Side-effect of vaccination			
Common side effects			
Muscle pain	44 (81.5)	NA	
Allergy	4 (7.4)	NA	
Fever	6 (11.1)	NA	
Nausea	4 (7.4)	NA	
Headache	4 (7.4)	NA	
Others	6 (11.1)	NA	
irAE			
Immune-related adverse effects	50 (92.6)	32 (88.9)	< 0.5
ILD	6 (11.1)	4 (11.1)	
RCCEP	10 (25.9)	8 (22.2)	
Hepatitis	6 (11.1)	2 (5.6)	
Ulcerative colitis	8 (14.8)	6 (16.7)	
Hypothyroidism	8 (14.8)	4 (11.1)	
Others	6 (22.2)	4 (22.2)	

ILD: interstitial lung disease; irAE: immune-related adverse event; RCCEP: reactive cutaneous capillary endothelial proliferation.

sis set for cancer genome profiling test (Sysmex Corporation Kobe, Hyogo, Japan), Foundation One CDx**, and Foundation One CDx's cancer genome test (Foundation Medicine, Inc., Cambridge MA, USA) were used for the study.

Fever may be observed for 2 - 3 days after vaccination with mRNA-based COVID-19 vaccines according to the Japanese Ministry of Health, Labor and Welfare's guidelines on mRNA-based COVID-19 vaccines. Therefore, the clinical practice guidelines of the Japanese Society of Clinical Oncology stipulated that mRNA-based COVID-19 vaccination should preferably be administered at least 5 days before the scheduled date of administration of ICIs (i.e., nivolumab). In Japan, the standard treatment for advanced NPC with ICIs includes intravenous nivolumab at 3 mg/kg once daily, every 2 weeks. Therefore, all subjects in our clinical research received the mRNA-based COVID-19 vaccine 7 days after nivolumab administration.

Details of materials and methods are indicated here (Supplementary Material 1, www.wjon.org), which are available online.

Supplementary Material

Suppl 1. Materials and methods of the study.

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Conflict of Interest

The authors have declared no conflict of interest.

Informed Consent

Informed consent statements from people participating in clinical studies were obtained.

Author Contributions

All authors had full access to the data in the study and took responsibility for the integrity of the data and accuracy of the data analysis. Conceptualization: TH and IK. Writing-original draft: TH and IK. Writing-review and editing: IK. Visualization: TH and IK. Supervision: TH and IK. Funding acquisition: TH and IK.

Data Availability

The data supporting the study findings are available from the corresponding author upon reasonable request.

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