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Effect by mRNA based COVID-19 vaccination on efficiency of therapy with anti-PD-1 blockade

Takuma Hayashi[1], Nobuo Yaegashi[2], Ikuo Konishi[2]

1 Kyoto Medical Center

2 Japan Agency for Medical Research and Development (AMED)

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Abstract

Immune checkpoint inhibitors are drugs that keep the immune system strong enough to attack cancer cells. To date, cancer immunotherapy using immune checkpoint inhibitors has been shown to be effective against various types of cancer. During the coronavirus infectious disease-2019 (COVID-19) pandemic, concern is raised whether clinical treatment with immune checkpoint inhibitors can interfere with COVID-19 vaccination in patients with several malignancies. Recent report shows significantly improved anti-tumor efficacy of the combination of anti-programmed cell death protein-1 (anti-PD-1) therapy and chemotherapy in patients with advanced nasopharyngeal cancer (NPC) who received COVID-19 vaccination, however, the incidence of severe immune-related adverse events was similar. However, our results revealed that there is no medical evidence stating that COVID-19 vaccination significantly improved the efficacy of the combination of anti-PD-1 therapy and chemotherapy in patients with advanced NPC. Clinical studies with large cohorts of large numbers of patients are required to clarify the impact of COVID-19 vaccines on the efficacy of cancer immunotherapy with immune checkpoint inhibitors.

Takuma Hayashi[1,2,*], **Nobuo Yaegashi**[2,3], **Ikuo Konishi**[1,2,4].

[1] *National Hospital Organization Kyoto Medical Centre, Kyoto, Japan.*

[2] *Medical R&D Promotion Project, The Japan Agency for Medical Research and Development (AMED), Tokyo, Japan.*

[3] *Department of Obstetrics and Gynecology, Tohoku University Graduate School of Medicine, Miyagi, Japan.*

[4] *Kyoto University Graduate School of Medicine, Kyoto, Japan.*

[*]**Corresponding Author:**

Takuma Hayashi

National Hospital Organization, Kyoto Medical Centre, Mukaihatake-cho, Fushimi-ku, Kyoto Kyoto, Japan.

e-mail: yoyoyo224@hotmail.com

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Research Letter

During the coronavirus infectious disease-2019 (COVID-19) pandemic, concern is raised whether clinical treatment with immune checkpoint inhibitors can interfere with COVID-19 vaccination in patients with several malignancies. Recent report shows significantly improved anti-tumor efficacy of the combination of anti-programmed cell death protein-1 (anti-PD-1) therapy and chemotherapy in patients with advanced nasopharyngeal cancer (NPC) who received COVID-19 vaccination, however, the incidence of severe immune-related adverse events was similar.[1]

Methods

A total of 54 NPC patients were screened from 18 hospitals beginning on 10 December 2019. Eligible participants met these criteria: (i) confirmed NPC; (ii) received 1 dose of anti-PD-1 treatment; (iii) available medical record and willingness for follow-up. Clinical and demographical data were collected at the enrollment. The last date of follow-up was 10 October 2022.

Result/Discussion

From December 2019 to November 2022, the treatment for 2651 patients (Ncc oncopanel test: 660 patients, FoundationOne CDx test: 1991 patients) of cancer genomic medicine was investigated at national universities in Japan. The treatment for 54 patients with advanced NPC was examined by cancer genomic medicine. The therapeutic efficacy of anti-PD-1 inhibitors in 52 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.[2],[3] In 18 patients with advanced NPC who received nivolumab alone and had not been vaccinated against COVID-19, the overall response rate (ORR) was 11.1% [CR in one patient (5.6%), PR in one patient (5.6%), SD in four patients (22.2%) and PD in four patients (66.7%)] (Table 1). In 27 patients with advanced NPC who received nivolumab alone and had not been vaccinated against COVID-19, ORR with nivolumab was 11.1% [CR in one patient (3.7%), PR in two patients (7.4%), SD in four patients (7.4%) and PD in 20 patients (74.1%)] (Table 1). Based on the results of the clinical studies, we found no medical evidence proving that COVID- 19 vaccination significantly improved the efficacy of the combination of anti-PD-1 therapy and chemotherapy in patients with advanced NPC. The median age of participants in our clinical study was 65.8-year-old (62-72). Therefore, Pfizer/BionTech's BNT162b2 mRNA vaccine was inoculated in 30 participants, excluding two participants. Additionally, nivolumab monotherapy for human papillomavirus (HPV)-infected participants with advanced NPC has been shown to provide a long survival of 9.1 months compared with the survival time (7.5 months) by administering nivolumab alone to HPV uninfected participants.[2],[3] The HPV infection

rate among participants in our clinical research was 44.2%. No significant differences in severe immune-related Adverse Events (irAEs) were observed between both matched subgroups (Supplementary Figure 1). These findings regarding second effects including irAE are in accordance with the safety profiles in the KEYNOTE-048 trial investigating anti-PD-1 hemotherapy versus chemotherapy alone in non-nasopharynx head and neck cancer.[4]

The COVID-19 vaccine inoculated in participants enrolled in the clinical study reported by other institution was Sinovac COVID-19, a virus-inactivated vaccine developed in China. Sinovac COVID- 19 has been approved for emergency use by the World Health Organization. However, it is not approved for use in the United States, Japan, etc. Furthermore, the age of the participants enrolling in the clinical study reported by other institution ranged from 33 to 59 years old, which is younger than the age of the participants enrolling in our clinical research. 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, type of anti- PD-1 agent or the age of the participants. In addition, information on HPV prevalence among participants enrolling in the clinical research reported by other institution is also needed. Rigorous

studies based on large cohort clinical research are needed to generalize and substantiate the results of the clinical study reported by other institution.

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Disclosure

The authors have declared no conflicts of interest.

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. After briefing regarding the clinical study and approval of the research contents, the participants signed an informed consent form.

All participants agreed to take part in the present study. We have obtained Informed Consent Statements from people participating in clinical studies.

Table 1. Clinical characteristics of the NPC patient cohort

Tumor Type	Administration group	Cases	Median [95% confidence interval] (months)	Hazard ratio [95% confidence interval]
recurrent/metastatic nasopharyngeal cancer in Japanese	methotrexate, docetaxel or	6	6.2 (5.2~6.8) months	0.71 [95% 0.42~1.19]
	Nivolumab	11	8.8 (7.3~9.5) months	
	In COVID-19 era, January 2021 ~ November 2022 (%)			
	Age, years	Total 52	65.8 (62~72)	
	Gender		Male 44 Female 8	
	HPV test-positive		Male 18 (34.6) Female 5 (9.6)	
	Treatment method		Result of treatment	
			DOR	ORR
	methotrexate, docetaxel or cetuximab	2	6.7 (6.4, 7.0) months	PD 2 (100)
	Nivolumab	18	8.6 (6.5~9.6) months	ORR: 11.1% [CR 1 (5.6), PR 1 (5.6), SD 4 (22.2), PD 12 (66.7)]
	BNT162b2 mRNA Vac +			
	methotrexate, docetaxel or	3	6.5 (5.2~7.6) months	SD 1 (33.3), PD 2 (66.7)
	cetuximab			
	mRNA-1273 Vac +			
	methotrexate, docetaxel or	2	NA	PD 2 (100)
	cetuximab			
	BNT162b2 mRNA Vac +	27	8.5 (6.8~9.4) months	ORR: 11.1% [CR 1 (3.7), PR 2 (7.4), SD 4 (7.4), PD 20 (74.1)]
	Nivolumab			
	mRNA-1273 Vac + Nivolumab	0	NA	NA.

DOR; Duration of Response, ORR; Overall Response Rate, CR; complete response, PR; partial response, SD; stable disease, PD; progressive disease.

Supplementary Figure 1

Items	Nivolvemab + Vaccinated $n = 27$ cases (%)	Nivolvemab $n = 18$ cases (%)	P value
Side-effect of vaccination			
Muscle pain	22 (81.5)	NA	
Allergy	2 (7.4)	NA	
Fever	3 (11.1)	NA	
Nausea	2 (7.4)	NA	
Headache	2 (7.4)	NA	
Others	3 (11.1)	NA	
Immune-related adverse effects	25 (92.6)	16 (88.9)	$P < 0.5$
ILD	3 (11.1)	2 (11.1)	
RCCEP	5 (25.9)	4 (22.2)	
Hepatitis	3 (11.1)	1 (5.6)	
Ulcerative colitis	4 (14.8)	3 (16.7)	
Hypothyroidism	4 (14.8)	2 (11.1)	
Others	6 (22.2)	4 (22.2)	

ILD; Interstitial lung disease, RCCEP; Reactive cutaneous capillary endothelial proliferation,

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