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LETTER TO THE EDITOR

Potentially improved response of COVID-19 vaccinated nasopharyngeal cancer patients to combination therapy with anti-PD-1 blockade and chemotherapy

Anti-programmed cell death protein 1 (anti-PD-1) treatment was demonstrated to be effective in nasopharyngeal cancer (NPC) patients.[1] During the COVID-19 pandemic, concern was raised whether anti-PD-1 treatment can interfere with COVID-19 vaccination in NPC patients, although our previous study showed that the efficacy and safety of anti-PD-1 treatment was not reduced in general cancer patients vaccinated with SinoVac.[2] NPC affects the upper respiratory tract, where the COVID-19 infection takes place. Possible interferences between anti-PD-1 treatment and COVID-19 vaccination in NPC patients remain elusive. Our study aims to fill this gap.

A total of 2134 NPC patients were screened from 35 hospitals beginning on 28 January 2021. Eligible participants met these criteria: (i) confirmed NPC; (ii) received $\geq$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 25 June 2022.

A total of 1537 NPC patients met the criteria and were included from 23 hospitals (median age 45 years, 23.9% female; Table 1). All patients were in a recurrent metastatic (RM) stage and received first-line anti-PD-1 therapy at the time of relapse or diagnosis of metastasis, with most receiving concomitant anti-PD-1 therapy and chemotherapy. The most frequent immune-related adverse events (irAEs) include hepatitis (470; 30.6%) and reactive cutaneous capillary endothelial proliferation (424; 27.6%). The outcomes showed that 140 (9.1%) patients achieved complete remission, 503 (32.7%) partial remission, 526 (34.2%) stable disease, and 337 (21.9%) progressive disease (Table 1). In this cohort, 373 (24.3%) patients were vaccinated with SinoVac,[3] and were defined as the vaccinated subgroup. Median interval between vaccination and first dose of anti-PD-1 treatment was 105.0 days (range −24 to 154 days). The remaining 1164 (75.7%) were not vaccinated against COVID-19 and defined as the non-vaccinated subgroup.

Compared with the non-vaccinated subgroup, vaccinated patients showed a higher objective response rate (ORR 59.0% versus 38.8%, $P < 0.001$, Table 1) and disease control rate (DCR 80.2% versus 74.7%, $P = 0.031$) following anti-PD-1 treatment, were more likely to experience mild irAEs (73.6% versus 60.1%, $P < 0.001$) and mild vaccine-related adverse effects (21.7% versus 8.2%, $P < 0.001$). No significant difference in severe irAEs was observed between both subgroups. Through propensity score matching (ratio of 2 : 1) for age, gender, Karnofsky performance status (KPS) and body mass index (BMI) in this cohort, 1119 patients were selected for further analysis. Compared with the matched non-vaccinated subgroup, matched vaccinated patients still had a higher ORR (59.0% versus 35.7%, $P < 0.001$) and DCR (80.2% versus 72.5%, $P = 0.018$), and to more frequently experience mild irAEs (73.6% versus 61.1%, $P < 0.001$). No significant differences in severe irAEs were observed between both matched subgroups (4.9% versus 4.1%, $P = 0.482$).

NPC is characterized by peritumoral immune infiltration in the upper respiratory tract.[4] The tumor microenvironment (TME) in NPC may recruit myeloid-derived suppressor cells (MDSCs)[5] to escape immunotherapy, but this might also reduce the effect of COVID-19 vaccination. Our results showed that the safety of the combination of anti-PD-1 treatment and chemotherapy was not reduced for NPC patients during the vaccination period, and the efficacy of combination of anti-PD-1 treatment and chemotherapy was significantly improved for vaccinated NPC patients. Possible reasons include: (i) CD4+ T cells might be activated and enter into the TME during vaccination, preventing MDSCs or regulatory T cells (Tregs) recruitment[5]; (ii) exhausted CD8+ T cells might be reactivated in the TME during vaccination, facilitating immunotherapy.[6] Future studies are warranted to elucidate underlying mechanisms. The association of COVID-19 vaccination with increased efficacy of anti-PD-1 therapy with chemotherapy in RM NPC is interesting, but needs to be validated in a larger cohort study.

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Table 1. Clinical and demographic characteristics of the NPC patient cohort

Items	Vaccinated $n = 373$ n (%)	Non-vaccinated $n = 1164$ n (%)	P value
Age, years	47.1 ± 11.8	44.7 ± 11.7	0.100
BMI, kg/m^2	23.3 ± 3.19	22.6 ± 3.77	0.002
KPS	89.7 ± 3.99	89.5 ± 4.38	0.469
Gender			0.619
Male	288 (77.2)	882 (75.8)	
Female	85 (22.8)	282 (24.2)	
Comorbidity			0.906
Infection	37 (9.9)	132 (11.3)	
Hypertension	37 (9.9)	104 (8.9)	
Hepatitis	26 (7.0)	103 (8.8)	
Tuberculosis	6 (1.6)	17 (1.5)	
Others	21 (5.6)	58 (5.0)	
Side-effect of vaccination			
Muscle pain	30 (8.0)	—	
Allergy	28 (7.5)	—	
Fever	23 (6.2)	—	
Nausea	15 (4.0)	—	
Headache	10 (2.7)	—	
Others	17 (4.6)	—	
Treatment			<0.001
CR (complete remission)	21 (5.6)	118 (10.1)	
PR (partial remission)	169 (45.3)	334 (28.7)	
SD (stable disease)	109 (29.2)	417 (35.8)	
PD (progressive disease)	42 (11.3)	295 (25.3)	
ORR	190 (50.9)	452 (38.8)	<0.001
DCR	299 (80.2)	869 (74.7)	0.031
Duration	134.6 ± 154.4	221.9 ± 201.3	<0.001
Cycle	6.8 ± 7.4	11.0 ± 9.6	<0.001
Immune-related adverse effects	237 (73.6)	685 (60.1)	<0.001
RCCEP	112 (30.0)	312 (26.8)	
Hepatitis	136 (36.5)	334 (28.7)	
Hypothyroidism	83 (22.2)	233 (20.0)	
Others	59 (15.8)	109 (9.4)	
Anti-PD-1 agent			
Toripalimab	149 (39.9)	589 (50.6)	<0.001
Camrelizumab	164 (44.0)	507 (43.6)	0.905
Sintilimab	7 (1.9)	21 (1.8)	1.000
Tislelizumab	1 (0.3)	14 (1.2)	0.137
Pembrolizumab	1 (0.3)	4 (0.3)	1.000
Nivolumab	0 (0.0)	4 (0.3)	0.578
Combined chemotherapy	348 (93.3)	1115 (95.8)	0.070

BMI, body mass index; DCR, disease control rate; KPS, Karnofsky performance status; NPC, nasopharyngeal cancer; ORR, objective response rate; PD-1, programmed cell death protein 1; RCCEP, reactive cutaneous capillary endothelial proliferation.

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DISCLOSURE

The authors have declared no conflicts of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approached by the ethic committee of Sun Yat-sen University Cancer Center (B2022-146-01).

All participants agreed to take part in the present study.

CONSENT TO PUBLISH

All participants are consent for publication.

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