SARS-CoV-2 VACCINE-INDUCED T CELL RESPONSES IN CANCER PATIENTS UNDERGOING TREATMENT

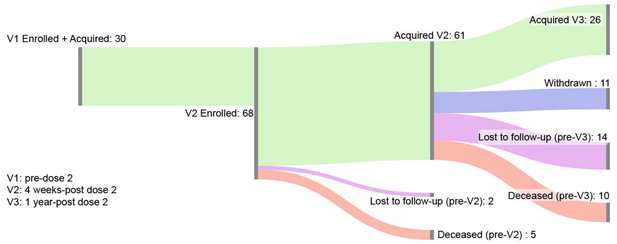
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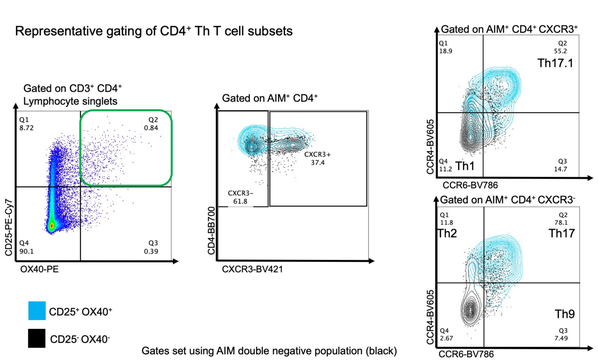
INTRODUCTION

SARS-CoV-2 mRNA vaccines have proven useful in protecting vulnerable populations against severe COVID-19. However, certain therapeutics, specifically those used in cancer treatment, reduce mRNA vaccine-induced humoral responses against SARS-CoV-2. The effects on T cell responses are not well characterized. Here, we evaluate SARS-CoV-2 spike-specific T cell responses over the course of one year following mRNA vaccination in solid tumor patients in British Columbia, Canada.

METHODS



81 solid-tumour patients from the BC Cancer Agency, Vancouver, Canada were enrolled in this prospective, cohort study, with 40 patients receiving cytotoxic chemotherapy and 31 patients receiving non-cytotoxic treatments. Whole blood was collected pre-dose 2 (V1) post mRNA vaccine series completion (V2) (2 doses given 1 month apart), and 1 year posts series completion (V3). Antigen-induced marker assays (AIM assays) were used to quantify T cell responses, where peripheral blood was stimulated with ancestral or omicron SARS-CoV-2 spike peptide pools for 48 hours at 37°C. SARS-CoV-2 spike-specific $CD4^+$ and $CD8^+$ T cells were analysed by flow cytometric detection of activation markers CD25 and OX40 (on $CD4^+$ T cells) or CD69 and CD137 (on $CD8^+$ T cells). Parallel phenotyping of spike-specific $CD4^+$ T cells enabled quantification of proportions of cTfh, Tregs, Th1, Th2, Th9, Th17, and Th17.1 cells.



RESULTS

	Chemotherapy (N=40)			Hormone (N=31)			Completed/No treatment (N=10)		
Average age	55.23 (+/- 13.74)			56.35 (+/- 13.20)			53.28 (+/- 9.76)		
Sex	Female: 37 (92.5%)	Male: 3 (7.5%)		Female: 30 (96.8%)	Male: 1 (3.2%)		Female: 9 (90%)	Male: 1 (10%)	
Deceased	13 (32.5%)			0 (0%)			2 (20%)		
Dose 3 (Received)	Yes: 22 (55%)	No: 5 (12.5%)	Unkown: 13 (32.5%)	Yes: 27.1 (87%)	No: 4 (12.9%)	Unkown: 0 (0%)	Yes: 8 (80%)	No: 0 (0%)	Unkown: 2 (20%)
Dose 4 (Received)	Yes: 17 (42.5%)	No: 10 (25.0%)	Unkown: 13 (32.5%)	Yes: 23 (74.2%)	No: 8 (25.8%)	Unkown: 0 (0%)	Yes: 6 (60%)	No: 2 (20%)	Unkown: 2 (20%)
Dose 5 (Received)	Yes: 11 (27.5%)	No: 16 (40%)	Unkown: 13 (32.5%)	Yes: 12 (38.7)	No: 19 (61.3%)	Unkown: 0 (0%)	Yes: 4 (40%)	No: 6 (60%)	Unkown: 2 (20%)
Ethnicity	Asian: 15 (37.5%)	Caucasian: 24 (60%)	Hispanic: 1 (2.5%)	Asian: 12 (38.7%)	Caucasian: 16 (51.6%)	Hispanic: 3 (9.7%)	Asian: 4 (40%)	Caucasian: 5 (50%)	Hispanic: 1 (10%)
Diagnosis	Endometriod Adenocarcinoma	2	5.0%	Endometriod Adenocarcinor	0	0%	Endometriod Adenocarcinom	0	0%
	Folicular Lymphoma	1	2.5%	Folicular Lymphoma	0	0%	Folicular Lymphoma	0	0%
	Invasive Ductal Carcinoma	19	47.5%	Invasive Ductal Carcinoma	22	70.90%	Invasive Ductal Carcinoma	7	70%
	Invasive Lobular Carcinoma	1	2.5%	Invasive Lobular Carcinoma	1	3.20%	Invasive Lobular Carcinoma	0	0%
	Mestastatic Uterine Sarcoma	1	2.5%	Mestastatic Uterine Sarcom	0	0%	Mestastatic Uterine Sarcoma	0	0%
	Metastatic Breast Carcinoma	1	2.5%	Metastatic Breast Carcinom	1	3.20%	Metastatic Breast Carcinoma	0	0%
	Metastatic Colon Carcinoma	1	2.5%	Metastatic Colon Carcinoma	0	0%	Metastatic Colon Carcinoma	0	0%
	Metastatic Ductal Carcinoma	9	22.5%	Metastatic Ductal Carcinom	2	6.50%	Metastatic Ductal Carcinoma	0	0%
	Metastatic Leiomyosarcoma	1	2.5%	Metastatic Leiomyosarcoma	1	3.20%	Metastatic Leiomyosarcoma	0	0%
	Metastatic Peritoneal Carcinomatosis	0	0.0%	Metastatic Peritoneal Carcinomatosis	0	0.00%	Metastatic Peritoneal Carcinomatosis	1	10%
	Ovarian Serous Carcinoma	1	2.5%	Ovarian Serous Carcinoma	1	3.20%	Ovarian Serous Carcinoma	0	0%
	Pelvic Osteosarcoma	0	0.0%	Pelvic Osteosarcoma	1	3.20%	Pelvic Osteosarcoma	0	0%
	Rectal Adenocarcomoama	1	2.5%	Rectal Adenocarcomoama	0	0%	Rectal Adenocarcomoama	0	0%
	Residual Invasive Colon Adenocarcinoma	1	2.5%	Residual Invasive Colon Adenocarcinoma	0	0%	Residual Invasive Colon Adenocarcinoma	1	10%
	Rhabdomyosarcoma	0	0.0%	Rhabdomyosarcoma	0	0%	Rhabdomyosarcoma	1	10%
	Serous Ovarian Carcinoma	1	2.5%	Serous Ovarian Carcinoma	0	0%	Serous Ovarian Carcinoma	0	0%
	Squamous Cell Carcinoma	0	0.0%	Squamous Cell Carcinoma	1	3.20%	Squamous Cell Carcinoma	0	0%
	Tubo-Ovarian Carcinoma	1	2.5%	Tubo-Ovarian Carcinoma	0	0%	Tubo-Ovarian Carcinoma	0	0%
	Uterine Serous Carcinoma	0	0.0%	Uterine Serous Carcinoma	1	3.20%	Uterine Serous Carcinoma	0	0%

Table 1. Study participant demographics

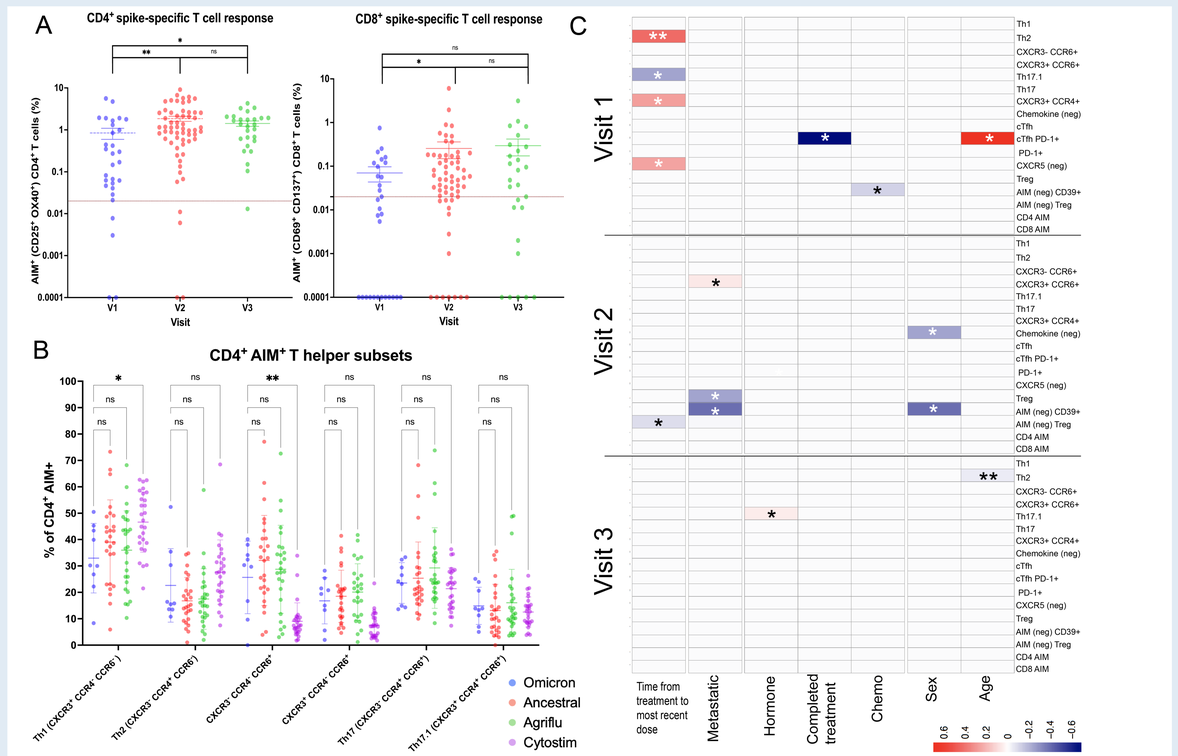


Figure 1. Characterization of antigen specific T cell responses
AIM assays were performed on fresh whole blood following venipuncture. Whole blood was stimulated with ancestral or omicron spike, Agriful ™, Cytostim, or unstimulated for 48 hours at 37°C. The percentages of spike-specific T cells were determined by flow cytometric detection of upregulated co-expression of AIM markers, CD25 and OX40 for $CD4^+$ T cells and CD69 and CD137 for $CD8^+$ T cells. Unstimulated wells were used to set AIM^+ gates and responses in these wells were subtracted as background. **(A)** Spike-specific $CD4^+$ and $CD8^+$ T cell responses across all visits (V1 N=30, V2 N=60, V3 N=26). **(B)** The frequencies of $CD4^+$ T cell subsets (percent of total $CD4^+$T cells) at V3. **(C)** Multilinear regressions between ancestral spike-specific T cell percentages (from A) and demographic information at each visit. *$P < 0.05$. **$P < 0.01$. *** $P < 0.001$. **** $P < 0.0001$.

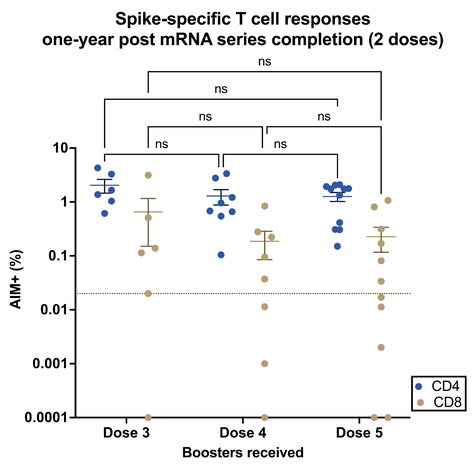


Figure 2. T cell responses at one-year post mRNA series completion (2 doses)
CD4+ and CD8+ T cell AIM responses from individuals who received a 3rd booster (N=6), 4th booster (N=8), or 5th dose (N=11). One-way ANOVA analyses were conducted for $CD4^+$ and $CD8^+$ T cells independently.

CONCLUSION

Here, we report that solid tumour patients, treated with either chemotherapy or biologic drugs, mount robust T cell immunity to SARS-CoV-2 ancestral and omicron spike antigen at one year following two doses of mRNA vaccination. We found modest associations between several spike-specific $CD4^+$ T cell subsets and age, sex, and treatment type. Most notably, we found negative associations between metastasis and spike-specific $CD4^+$ $CXCR3^+$ $CCR6^+$ and Treg populations. Further, 96% of cancer patients had detectable levels of spike-specific $CD4^+$ T cells following 2 mRNA doses, regardless of treatment type and additional boosters. Additional data is needed to determine if these responses correlate with antibody levels and clinical illness. However, our data suggests this cohort has some level of T cell immunity one-year post vaccine series completion.

We would like to thank all participants at the BC Cancer Agency for enrolling in this study. Additionally, we would like to thank the Canadian COVID-19 Immunity Task Force (CITF) for providing funding for this study.

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