Durable tracking anti-SARS-CoV-2 antibodies of cancer patients recovered from COVID-19

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Abstract

Cancer patients are more susceptible to SARS-CoV-2 infection and generally have higher mortality rate. Anti-SARS-CoV-2 IgG is an important consideration for the patients in this COVID-19 pandemic. Recent researches suggested the rapid decay of anti-SARS-CoV-2 antibodies in the general population, but the decline rate of the antibodies in cancer patients was unknown. In this observational study, we reported the clinical features of the 53 cancer patients infected by SARS-CoV-2 from two hospitals in Wuhan, China and tracked the presence of anti-SARS-CoV-2 antibodies in the patients for more than 12 months. We found the duration (days) of anti-SARS-CoV-2 IgG in the patients was significant longer in chemotherapy (mean: 175; range: 75 to 315) and radiotherapy groups (mean: 168; range: 85 to 265) than in non-chemo- or radio-therapy group (mean: 58; range:21 to 123) after their recovery from COVID-19. We also used single-cell RNA sequencing to track the immunologic changes in a representative patient infected by COVID-19 for more than one year, and found that CD8 + effective T cells, memory B cells and plasma cells were persistently activated in the patient undergoing chemotherapy. Together, our findings show that chemotherapy and radiotherapy might be beneficial to extend the duration of anti-SARS-CoV-2 IgG.

Introduction

The emergence of COVID-19, caused by SARS-CoV-2, has led to an unprecedented and ongoing global health crisis [1]. Patients with cancer were reported to be more susceptible to SARS-CoV-2 infection and have higher mortality rate compared with regular COVID-19 patients [2,3]. Therefore, cancer patients should be monitored more carefully during the treatment, and the anti-SARS-CoV-2 IgG level is important as they provide the immunity against second infection [4]. Previous studies suggested the rapid decay of anti-SARS-CoV-2 antibodies after three months in the general population after the recovery from COVID-19 [5–7]. The duration of the antibodies in cancer patients has not been established. In this study, we tracked the anti-SARS-CoV-2 antibodies in 53 cancer patients after their recovery from COVID-19 for more than 12 months, aiming to better comprehend the effects of different treatments on the durability of anti-SARS-CoV-2 antibodies and their impact on the immune system of COVID-19 cancer patients.

Results

Anti-SAS-Cov-2 IgG antibody has longer duration in the patients with chemotherapy and radiotherapy.

A total of 53 cancer patients (24 women and 19 men) who were infected by SARS-CoV-2 had serial measurements of IgG (Table 1). Infection was confirmed by polymerase chain-reaction assay in all participants. The mean age of patients was 56 years (range: 33 to 78). The mean duration of IgM is 28 days (range: 15 to 65), and the mean duration of IgG is 137 days (range: 21 to 315). There were 17 non-small-cell lung cancer (NSCLC), 6 breast cancer, 5 colon cancer, 5 cervical squamous cell carcinoma (CSCC) and 20 other types of cancer patients in this study (Supplementary Table 1). When we divided the participants into different groups by treatment, we found the duration of IgG was significant longer in chemotherapy (mean: 175; range: 75 to 315) and radiotherapy groups (mean: 168; range: 85 to 265) than in non-chemo- or radio- therapy group (mean: 58; range: 21 to 123) (Fig. 1) (Table 1). The correlation between chemotherapy (Regression coefficient: 95.655; 95% confidence interval (CI): 35.702 ~ 155.608; $p = 0.003$) or radiotherapy (Regression

coefficient:102.329; 95%CI: 38.107 ~ 166.551; $p = 0.003$) on antibody duration was further proved by linear regression model (Table 2). However, we found that the duration of IgG was not significantly correlated with initial IgG levels, gender, cancer type, stage or underlying disease (Table 2).

Table 1
Basic clinical characteristics of the cancer patients recovered from COVID-19 under different treatments

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Variables	**All**	**None**	**Chemotherapy**	**Radiotherapy**	**radio-therapy**	**Targeted therapy**
Patient number	53	13	19	9	7	5
Male/Female	29/24	6/7	10/9	5/4	5/2	3/2
Age (years)	56 (33 ~ 78)	58 (41 ~ 78)	53 (37 ~ 69)	61 (33 ~ 72)	57 (44 ~ 66)	55(47 ~ 66)
Duration of IgM (days)	28 (15 ~ 65)	22 (16 ~ 28)	31 (21 ~ 51)	25 (15 ~ 30)	36 (23 ~ 65)	26 (15 ~ 33)
Duration of IgG (days)	137 (21 ~ 315)	58 (21 ~ 123)	175 (75 ~ 315)	168 (85 ~ 265)	168 (84 ~ 206)	101 (69 ~ 190)
≥ 90	34 (64.2%)	1 (7.6%)	17 (89.5%)	8 (88.9%)	6 (85.7%)	2 (40.0%)
≥ 180	8 (15.1%)	0 (0%)	9 (47.4%)	3 (33.3%)	3(42.9%)	1 (25.0%)
≥ 240	6 (11.3%)	0 (0%)	4 (21.1%)	1 (11.1%)	1 (14.3%)	0 (0%)
Initial blood features:						
IgG (ng/ml)	22.0(1.8 ~ 80.4)	9.6(5.9 ~ 17.2)	23.7(6.9 ~ 56.4)	17.0(6.4 ~ 52.6)	46.7(12.4 ~ 80.4)	9.2(1.8 ~ 15.4)
WBC (* 10^9/L)	6.07(1.56 ~ 19.30)	6.18(2.77 ~ 13.12)	5.97(1.56 ~ 10.58)	4.25(3.67 ~ 7.61)	9.69(4.04 ~ 19.30)	4.36(3.02 ~ 4.90)
HB (g/dl)	115(53 ~ 155)	115(75 ~ 150)	118(69 ~ 155)	107(53 ~ 143)	101(84 ~ 127)	132(118 ~ 146)
PLT (*10^9/L)	172(56 ~ 347)	222(144 ~ 347)	160(56 ~ 125)	146(71 ~ 222)	156(85 ~ 285)	136(87 ~ 207)
LY (*10^9/L)	0.96(0.21 ~ 2.19)	1.03(0.29 ~ 1.41)	1.04(0.35 ~ 2.01)	1.10(0.34 ~ 2.19)	0.79(0.27 ~ 1.97)	0.46(0.21 ~ 0.66)
CRP (mg/L)	24.97(0.16 ~ 196.3)	10.24(2.30 ~ 80.44)	25.15(0.16 ~ 196.3)	5.05(0.79 ~ 13.72)	52.77(1.11 ~ 126.9)	54.65(1.63 ~ 175.7)

Data are numbers, mean (range) or n (%) unless otherwise indicated Abbreviations: WBC, white blood cell; HB, Haemoglobin; PLT, Platelet;LY, Lymphocyte; CRP, C-reactive protein. None: non-chemo or radio-therapy.

Table 2
Factors that affect the duration of anti-SARS-CoV-2 in cancer patients recovered from COVID-19 as analyzed with linear regression model

Variables	Regression coefficient	95% CI	p value
Initial IgG levels	0.015	-1.303 ~ 1.417	0.933
Cancer Stage			
Stage I	Ref.	-	-
Stage II	14.860	-86.123 ~ 115.843	0.767
Stage III	13.489	-90.434 ~ 117.412	0.794
Stage IV	10.083	-92.691 ~ 112.856	0.843
Age	-1.816	-3.798 ~ 0.166	0.071
Gender			
Female	Ref.	-	-
Male	11.625	-24.186 ~ 47.436	0.514
Treatment			
None	Ref.	-	-
Chemotherapy	95.655	35.702 ~ 155.608	0.003*
Radiotherapy	102.329	38.107 ~ 166.551	0.003*
Chemotherapy + Radiotherapy	95.186	10.611 ~ 179.760	0.028*
Target Therapy	24.750	-46.835 ~ 96.334	0.488
Underlying Disease			
No	Ref.	-	-
Yes	8.770	-29.838 ~ 47.378	0.648
* p value less than 0.05 means statistically significant. Abbreviation: CI, confidence interval.			

The immune system is continuously activated in the chemotherapy patient after the recovery of COVID-19. Interestingly, six participants (11.3%) in our cohorts showed durable presence of the anti-SARS-CoV IgGs, which has already lasted for more 240 days (Table 1). Of these patients, four received chemotherapy, one received radiotherapy and one received both chemotherapy and radiotherapy after COVID-19 recovery. We collected peripheral blood mononuclear cells (PBMC) from one representative chemotherapy patient infected by COVID-19 for more than one year and performed single-cell RNA sequencing. The uniform manifold approximation and projection (UMAP) (Fig. 2A-C) and trajectory analysis(Figure 2D)showed the CD8 + effective T cells, memory B cells and plasma cells were persistently activated in this patient after chemotherapy.

Discussion

It has been reported that SARS-CoV-2 could undergo evolution during the treatment of chronic infection [8]. Anti-SARS-CoV-2 IgG antibodies in the cancer patient is important for them to prevent the long-term existence of the virus and avoid second infection. In this study, we found that the anti-SARS-CoV-2 IgG antibodies decayed fast in the patients without chemotherapy and radiotherapy, which is consistent with the previous finding in the general population [5–7]. However, our findings raise concern that human immunity against SARS-CoV-2 may be long lasting in patients with radiotherapy and chemotherapy. As we know, chemotherapy or radiotherapy can damage the immune system by destroying the hematopoietic stem cells in bone marrow, which may cause immunosuppression [4]. However, cell death caused by the chemotherapy or radiotherapy might also activate the adaptive immune system [9], resulting in immunogenic cell death effect. Lee et al.[3] found there was no significant effect on mortality for patients with chemotherapy and radiotherapy use within the 4 weeks after testing positive for COVID-19. Hess et al.[10] reported low-dose, whole-lung radiation for patients with COVID-19-related pneumonia appeared safe and might be an effective immunomodulatory treatment. Besides, our group[11] and one group in Italy[12] showed that very few patients required treatment interruptions in radiotherapy services, and few patients undergoing radiotherapy were diagnosed with COVID-19 during their treatment course (0.48%, 1 of 209 patients)[11]. Thus, chemotherapy and radiotherapy should be safe treatments for the cancer patient recovered from COVID-19. Interestingly, there is also a report that anti-SARS-CoV-2 antibody triggered the anti-tumor immune response in a Hodgkin's lymphoma patient [13]. Therefore, the protective role of IgG antibodies against SARS-CoV-2 in the cancer patient is not only important for them to prevent virus infection, but maybe also beneficial for the cancer treatment. Our study has several limitations. Firstly, this is a cross-section study from two hospitals in Wuhan, and we could not acquire all the information such as IgG expression levels of patients at each time point. Thus, we mainly focused on the duration but not the expression level of IgG antibody. Secondly, some cancer patients were discharged, died or in unstable physical condition in the process, which resulted in a relatively small sample size. Further large-scale investigations on IgG antibodies against SARS-CoV-2 in different type of cancer patients over longer time periods should be done to assess the kinetics of immunity.

In sum, to the best of our knowledge, this study first report that chemotherapy and radiotherapy might provide benefits to prolong the duration of anti-SARS-CoV-2 IgG in human body. This should be important to devise new strategies for cancer treatment and improve antibody therapy in the future.

Methods

Patient data. We reviewed the medical records, including clinical and treatment data of 5,146 patients with cancer who were admitted to the Zhongnan Hospital of Wuhan University and Wuhan Tongji Hospital from December 31, 2019, to March 31, 2021. COVID-19 infection was confirmed by polymerase-chain-reaction (PCR) assay. The chat flow of the cancer patients in the study was shown in Supplementary Fig. 1, and the detailed information and clinical features of patients were shown in Supplementary Table 1. During the treatment of patients, venous blood samples were serially collected and analyzed by enzyme-linked immunosorbent assay (ELISA) to detect anti-SARS-CoV-2 spike receptor-binding domain [14]. After the reaction of ELISA, optical density at 450 nm (OD450) was determined with a multifunctional microplate reader. The cutoff for IgM was

0.30, and IgG was 0.20, determined by calculating the mean OD450 of a negative serum sample plus 3 SDs. Duration of SARS-CoV-2 antibody among the patients were recorded, and the patients selected in this study were alive before the cutoff date (March 31, 2021). Informed consent was obtained from all the participants, and all methods were carried out in accordance with relevant guidelines and regulations.

Single-cell RNA sequencing. Peripheral blood mononuclear cells (PBMCs) were collected from one representative chemotherapy patient using a Ficoll–Hypaque density solution according to the standard density gradient centrifugation methods. This 57-year-old male patient was diagnosed with non-small-cell lung cancer (stage: IIIA) and SARS-CoV-2 infection on February 25, 2020. After recovered from COVID-19, the first blood collection for single-cell RNA sequencing (Singeron) was conducted on April 16, 2020. The patient underwent four chemotherapy cycles (500mg/m2 pemetrexed combined with 75 mg/m2 Nedaplatin) from August to September 2020. The second blood collection for single-cell RNA sequencing was conducted on February 28, 2021. After quality control, we used Seurat v3.8 to do data normalization, dimensional reduction, clustering and calculated differentially express genes (DEGs) among clusters. We identified cell types (15, 015 cells) base on DEGs and CellMarker database.

Statistics. Statistical analysis in Fig. 1 was performed using Prism 7 software (GraphPad La Jolla, USA). Two-way analysis of variance (ANOVA) followed by the two-tailed Student t-test were used, p value less than 0.05 was considered to be statistically significant. Linear regression model in Table 2 was performed by the lme4 and lmerTest packages in R version 3.6.1, p value less than 0.05 means statistically significant.

Study approval. This retrospective study was approved by the ethics committee of Wuhan Tongji Hospital (2020370) and Zhongnan Hospital of Wuhan University (2020039).

Declarations

Conflict of interest statement The authors have declared that no conflict of interest exists.

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Figures

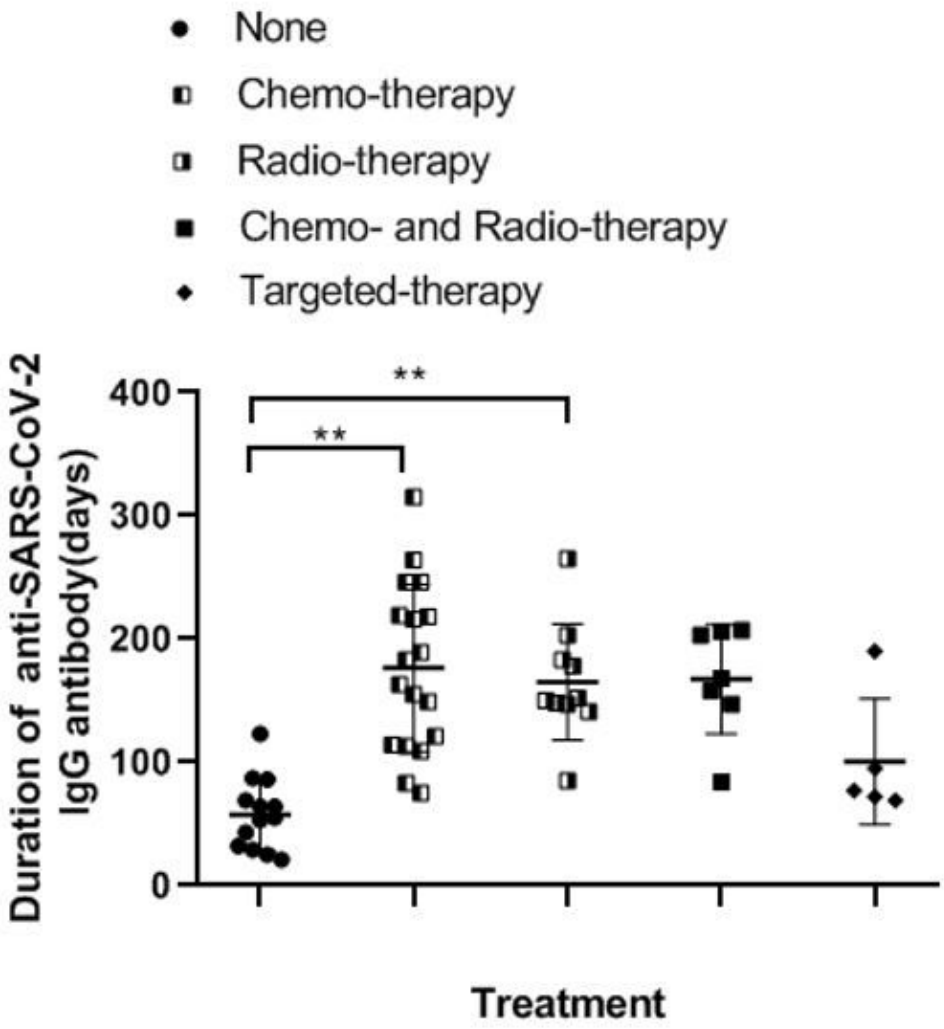

Figure 1

The duration of anti-SARS-CoV-2 IgG antibody in the cancer patients recovered from COVID-19 under different treatments. Two-way analysis of variance (ANOVA) followed by the two-tailed Student t-test were used (*0.01 < p<0.05; **p<0.01).

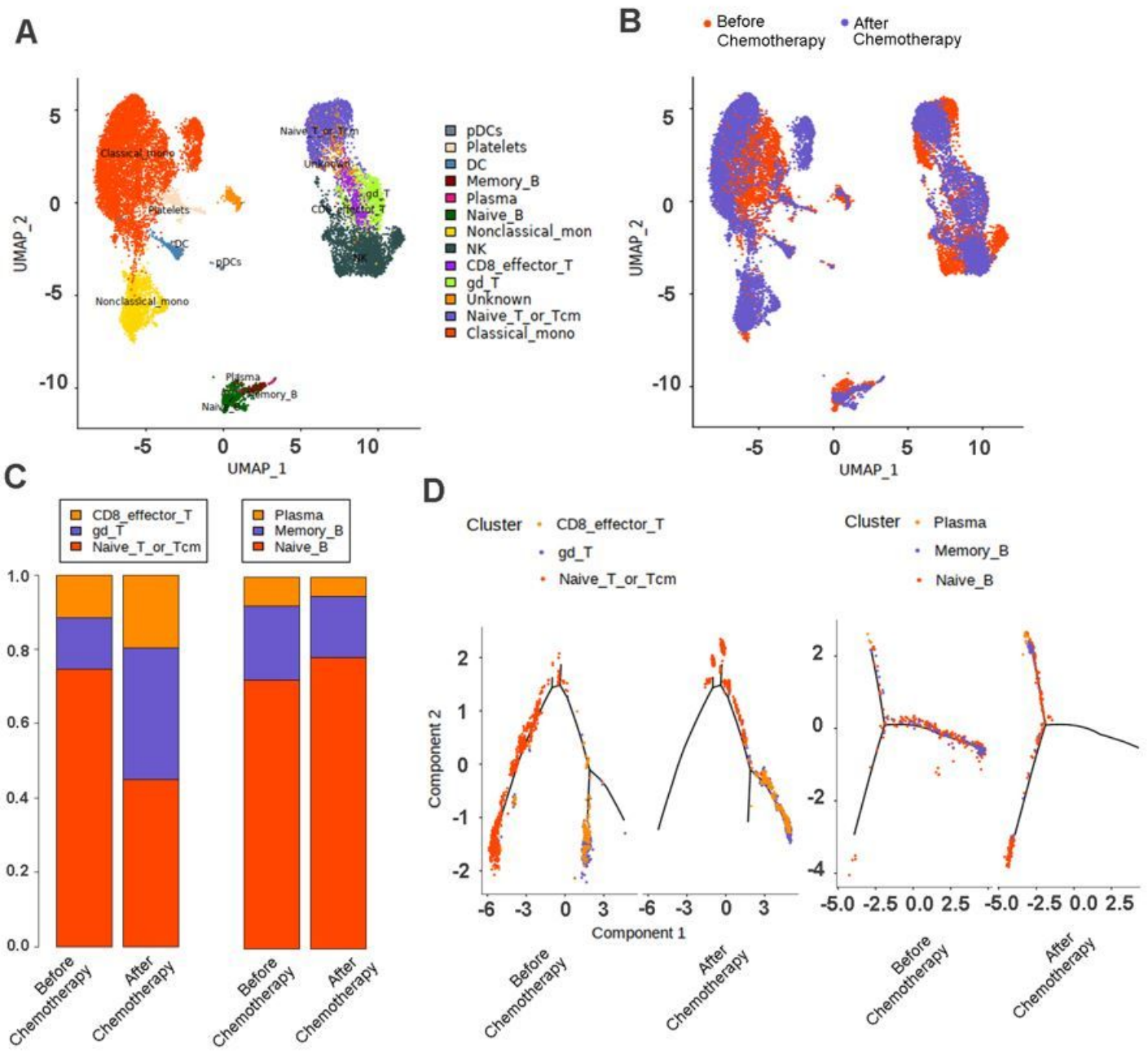

Figure 2

Dynamic study for the immunologic features in a representative patient infected by SARS-CoV-2 for more than one year. This 57-year-old male patient was diagnosed with non-small-cell lung cancer (stage: IIIA) and SARS-CoV-2 infection on February 25, 2020. After recovery from COVID-19, he underwent four chemotherapy cycles (500mg/m2 pemetrexed combined with 75 mg/m2 Nedaplatin) from August to September 2020. The single-cell sequencing blood collections were conducted both before the chemotherapy (April 16, 2020) and after the chemotherapy (February 28, 2021). (A) UMAP projection of clusters by cell type (15, 015 cells), different colors corresponding to different cell types. (B) UMAP projection of clusters by sample source, red: before chemotherapy; blue: after chemotherapy (February 28, 2021). (C) Percentage of cell composition of each sample before and after chemotherapy; left: proportion of different T cell subset; right: proportion of different

B cell subsets. (D) The Monocle 2 trajectory plot showing the dynamics of T cells (left) and B cells (right) in the patient before and after chemotherapy.

Supplementary Files

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- Supplementarymaterials.pdf