Does chemotherapy reactivate SARS-CoV-2 in cancer patients recovered from prior COVID-19 infection?

To the Editor:

Cancer patients are particularly vulnerable to coronavirus disease 2019 (COVID-19) [1–3]. These individuals are not only more susceptible to this infection, but also more frequently develop severe pneumonia during the disease course [1–3]. One factor associated with an increasing risk for developing severe events in this population is oncologic therapy, especially cytotoxic chemotherapy. Therefore, some oncologists and societies recommend that chemotherapy should generally not be started until COVID-19 symptoms have completely resolved and viral testing becomes negative [3, 4]. Additionally, some cancer patients who have recovered from infection are recommended to withhold, postpone, or switch to alternative routes of chemotherapy (*e.g.* oral instead of intravenous infusion) until the end of the COVID-19 pandemic [3, 4].

However, implications of the aforementioned recommendations remain uncertain in routine clinical practice. First, given the highly fluid state of our understanding of the viral biology of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the precise time interval between resolution of infection and initiating/restarting chemotherapy requires further evaluation. This is especially important in nations with continually rising coronavirus cases, where prolonged interruption of anti-tumour treatment may cause both patient anxiety as well as disease progression. Second, the delivery of immunosuppressive chemotherapy in recovered COVID-19 patients risks reactivation of disease. This concept is especially important because reports have highlighted that SARS-CoV-2 can re-emerge in recovered (with negative viral RNA) patients [5]. This may potentiate the burgeoning notion of a "second wave" of the pandemic. As of 31 May, 2020, a total of 271 cancer patients recovered from prior COVID-19 infection were screened in Hubei Cancer Hospital. The majority of patients (192, 71%) had stage III or IV disease and therefore required urgent chemotherapy-based treatment. Thus, it became important to investigate whether chemotherapy can cause reactivation of SARS-CoV-2 in cancer patients with prior COVID-19 infection.

In this study, we collected and analysed data from 39 cancer patients with SARS-CoV-2 infection history (negative for viral RNA and positive for serum antibodies) who received subsequent chemotherapy from seven hospitals within Hubei Province, China, including Hubei Cancer Hospital, Union Hospital, Suizhou Hospital, Renmin Hospital of Wuhan University, The Fifth Hospital of Wuhan, People's Hospital of Dongxihu District, and Tongji Hospital. All serum samples were tested for specific antibodies against SARS-CoV-2 by the colloidal gold immunoassay (Innovita, Tangshan, Hebei, China) prior to intravenous infusion chemotherapy. The patients harbouring positive SARS-CoV-2 specific antibodies were screened for SARS-CoV-2 RNA in throat swabs by real-time RT-PCR. This investigation was approved by the institutional ethics board of Hubei Cancer Hospital of Huazhong University of Science and Technology in Wuhan, China (number LLHBCH2020LW-006).

The median age was 57 years (interquartile range (IQR) 46–63 years) and the median follow-up from initial administration of chemotherapy was 116 days (IQR 100–125 days). Prior to chemotherapy administration, all patients were negative for SARS-CoV-2, and all had at least one positive result for anti-SARS-CoV-2 antibodies. In total, five (13%) patients were negative for immunoglobulin G (IgG^-) and positive for immunoglobulin M (IgM^+), 30 (77%) were IgG^+ IgM^-, and 4 (10%) were IgG^+ IgM^+. Among this cohort, lung cancer was the most frequent neoplasm (nine patients, 23%), followed by breast cancer

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TABLE 1 Clinical characteristics of cancer patients receiving systemic therapy with prior severe acute respiratory syndrome coronavirus 2 infection

Patient	Sex	Age years	PS	Cancer diagnosis	Staging	Chronic diseases	Systemic therapy	Time of systemic therapy	Grade of neutropenia	Time of nucleic acid testing
1	Female	56	1	NSCLC	T3N2M1	Diabetes	2 cycles of paclitaxel +nedaplatin	21 Apr, 14 May	2	20 Apr, 13 May, 9 Jun
2	Male	70	1	NSCLC	T4N2M0	COPD	4 cycles of vinorelbine +anlotinib	3 Apr, 30 Apr, 22 May, 16 Jun	0	21 Feb, 2 Apr, 28 Apr, 15 May, 15 Jun
3	Female	33	1	NSCLC	T4N3M1	None	2 cycles of PP, 3 cycles of PP+bevacizumab	20 Mar, 13 May, 4 Jun, 25 Jun, 16 Jul	0	18 Mar, 2 Apr, 12 May, 1 Jun, 22 Jun, 14 Jul
4	Female	67	1	NSCLC	T4N0M0	Hypertension and diabetes	2 cycles of GP	7 Apr, 13 May	2	6 Apr, 20 Apr, 11 May, 10 Jul
5	Male	59	1	NSCLC	T3N1M0	None	4 cycles of DP	4 Apr, 11 May, 3 Jun, 26 Jun	1	3 Apr, 8 May, 27 May, 24 Jun
6	Male	73	1	NSCLC	T3N2M0	None	4 cycles of abraxane +nedaplatin	11 Apr, 5 May, 3 Jun, 25 Jun	2	9 Apr, 4 May, 1 Jun, 23 Jun
7	Female	59	1	NSCLC	T3N3M1	None	2 cycles of docetaxel +nedaplatin and 1 cycle of GP	13 Mar, 18 Apr, 18 Jun	2	10 Mar, 15 Apr, 26 May, 10 Jun, 15 Jun, 8 Jul, 13 Jul
8	Male	72	1	NSCLC	T3N1M0	Hypertension, cardiovascular disease and COPD	2 cycles of abraxane and 2 cycles of abraxane +nedaplatin+PD-1 inhibitor	25 Mar, 6 May, 6 Jun, 1 Jul	3	23 Mar, 1 Apr, 3 Apr, 5 May, 3 Jun, 29 Jun
9	Male	64	1	Lung neuroendocrine carcinoma	T4N3M0	Hypertension	3 cycles of abraxane +lobaplatin	21 Apr, 19 May, 18 Jun	4	19 Apr, 18 May, 15 Jun
10	Female	64	1	Breast cancer	T3N1M0	Diabetes	3 cycles of capecitabine and 2 cycles of docetaxel	10 Apr, 1 May, 23 May, 12 Jun, 4 Jul, 24 Jul	1	9 Apr, 14 Apr, 23 Apr, 16 May, 8 Jun, 2 Jul, 21 Jul
11	Female	49	2	Breast cancer	T2N0M1	None	5 cycles of capecitabine +letrozole	18 Mar, 15 Apr, 30 May, 22 Jun, 23 Jul	0	17 Mar, 20 Mar, 14 Apr, 28 May, 22 Jul
12	Female	45	1	Breast cancer	T2N2M1	None	6 cycles of capecitabine +trastuzumab +partuzumab	15 Apr, 5 May, 28 May, 17 Jun, 7 Jul, 28 Jul	0	14 Apr, 29 Apr, 11 May, 26 May, 12 Jun, 6 Jul, 27 Jul
13	Female	37	1	Breast cancer	T3N2M0	None	3 cycles of capecitabine and 2 cycles of AC	26 Mar, 16 Apr, 25 May, 17 Jun, 18 Jul	2	25 Mar, 15 Apr, 22 May, 15 Jun, 16 Jul
14	Female	30	1	Breast cancer	T2N0M0	None	4 cycles of AC and 1 cycle of docetaxel	28 Mar, 22 May, 9 Jun, 30 Jun, 22 Jul	3	27 Mar, 7 Apr, 21 May, 6 Jun, 26 Jun, 20 Jul
15	Female	63	1	Breast cancer	T1N1M0	Hypertension	4 cycles of docetaxel	15 Mar, 19 Apr, 13 May, 19 Jun	1	13 Mar, 18 Apr, 10 May, 23 May, 17 Jun
16	Female	53	1	Breast cancer	T4N3M1	Hypertension	5 cycles of capecitabine	18 Mar, 14 Apr, 13 May, 4 Jun, 1 Jul	1	17 Mar, 13 Apr, 12 May, 26 May, 30 Jun
17	Female	40	1	Breast cancer	T2N2M0	None	1 cycle of capecitabine and 4 cycles of AC	13 Mar, 20 Apr, 12 May, 3 Jun, 26 Jun	2	12 Mar, 23 Mar, 17 Apr, 11 May, 27 May, 25 Jun, 15 Jul
18	Female	61	1	Rectal cancer	T2N1M1	Hypertension	2 cycles of FOLFOX and 2 cycles of DC	12 May, 26 May, 16 Jun, 16 Jul	1	24 Apr, 27 Apr, 11 May, 12 Jun, 14 Jul
19	Male	52	1	Rectal cancer	T4N1M0	Diabetes	4 cycles of capecitabine	16 Apr, 19 May, 12 Jun, 6 Jul	0	14 Apr, 18 May, 10 Jun, 3 Jul
20	Female	51	1	Rectal cancer	rT0N0M1	None	4 cycles of XELOX+PD-1 inhibitor	18 Apr, 7 May, 1 Jun, 3 Jul	4	16 Apr, 5 May, 29 May, 1 Jul

Continued

TABLE 1 Continued

Patient	Sex	Age years	PS	Cancer diagnosis	Staging	Chronic diseases	Systemic therapy	Time of systemic therapy	Grade of neutropenia	Time of nucleic acid testing
21	Female	37	1	Colon cancer	T3N1M1	None	7 cycles of FOLFIRI +bevacizumab	21 Mar, 8 Apr, 8 May, 28 May, 15 Jun, 1 Jul, 20 Jul	2	19 Mar, 7 Apr; 5 May, 27 May, 12 Jun, 29 Jun, 16 Jul
22	Male	37	1	Colon cancer	T4N2bM1	None	4 cycles of FOLFIRI +bevacizumab	15 May, 31 May, 15 Jun, 6 Jul	2	14 May, 29 May, 12 Jun, 2 Jul, 29 Jul
23	Male	47	1	Colon cancer	T2N1M0	None	2 cycles of capecitabine and 2 cycles of XELOX	12 Apr, 10 May, 3 Jun, 25 Jun	1	8 Apr, 11 Apr, 9 May, 23 May, 1 Jun, 24 Jun
24	Male	63	1	Colon cancer	T3N1M1	Hypertension	5 cycles of XELOX +bevacizumab	3 Apr, 1 May, 22 May, 17 Jun, 7 Jul	1	2 Apr, 30 Apr, 15 May, 15 Jun, 3 Jul
25	Male	58	1	NPC	T3N2M0	None	2 cycles of DP; RT and 1 cycle of cisplatin	8 Apr, 1 May, 11 Jun	2	6 Apr, 30 Apr, 23 May, 8 Jun, 26 Jun
26	Male	41	1	NPC	T3N2M0	None	2 cycles of GP+PD-1 inhibitor; RT and 2 cycles of cisplatin+PD-1 inhibitor	26 Mar, 19 Apr, 15 May, 7 Jun	2	25 Mar, 17 Apr, 29 May
27	Male	62	1	NPC	T4N2M0	None	3 cycles of abraxane +nedaplatin	9 Mar, 1 Apr, 18 Jun	2	8 Mar, 31 Mar, 28 May, 15 Jun
28	Female	59	1	NPC	rT0N1M0	None	2 cycles of GP and 2 cycles of GP+PD-1	19 May, 9 Jun, 1 Jul, 24 Jul	2	21 Apr, 15 May, 3 Jun, 6 Jun, 30 Jun, 20 Jul
29	Male	40	1	NPC	T3N2M0	None	2 cycles of DP; RT and 2 cycles of cisplatin	17 Apr, 8 May, 1 Jun, 23 Jun	2	15 Apr, 6 May, 26 May
30	Male	59	1	Oesophagus cancer	T4N2M0	None	3 cycles of docetaxel+S1	1 May, 29 May, 25 Jun	2	30 Apr, 6 May, 28 May, 22 Jun
31	Male	67	2	Oesophagus cancer	T3N1M1	None	2 cycles of TP	18 Mar, 12 May	1	17 Mar, 11 May, 26 May
32	Male	57	1	Oesophagus cancer	T4aN2M0	Hypertension and diabetes	3 cycles of capecitabine +nedaplatin+PD-1 inhibitor	23 Mar, 8 Jun, 3 Jul	1	20 Mar, 1 Jun, 2 Jul
33	Male	64	1	Gastric cancer	T3N2M1	None	3 cycles of EP	22 May, 11 Jun, 7 Jul	1	15 Apr, 20 May, 8 Jun, 4 Jul
34	Male	55	**1**	Gastric cancer	T3N3M1	None	3 cycles of oxaliplatin+S1	25 Mar, 18 Apr, 10 May	0	24 Mar, 16 Apr, 9 May, 22 May
35	Female	48	1	Cervical cancer	IIB (FIGO)	None	3 cycles of DP	22 May, 12 Jun, 7 Jul	1	22 Apr, 20 May, 10 Jun, 3 Jul
36	Female	60	1	Ovarian cancer	IIIc (FIGO)	None	4 cycles of etoposide +apatinib	23 Mar, 21 Apr, 6 May, 29 May	2	23 Mar, 20 Apr, 5 May, 28 May
37	Female	62	1	Ampullary carcinoma	T4N0M1	None	1 cycle of capecitabine +temozolomide and 1 cycle of abraxane	2 Apr, 1 Jun	1	31 Mar, 28 May, 5 Jun
38	Male	71	1	Soft tissue sarcoma	T3N0M0 G3	None	2 cycles of gemcitabine +anlotinib+PD-1 inhibitor	5 Jun, 3 Jul	0	20 May, 3 Jun, 4 Jun, 29 Jun
39	Male	41	1	Glioblastoma		None	3 cycles of temozolomide	24 Apr, 22 May, 19 Jun	0	23 Apr, 19 May, 17 Jun

PS: performance status; NPC: nasopharyngeal cancer; NSCLC: non-small cell lung cancer; GP: gemcitabine+cisplatin; FOLFOX: oxaliplatin+5-fluorouracil+leucovorin; FOLFIRI: irinotecan +5-fluorouracil+leucovorin; EP: etoposide+cisplatin; XELOX: oxaliplatin+capecitabine; AC: adriamycin+cyclophosphamide; RT: radiotherapy; PP: pemetrexed+cisplatin; TP: paclitaxel +cisplatin; DC: docetaxel+carboplatin; DP: docetaxel+
cisplatin; S1: tegafur gimeracil oteracil potassium capsule.

(eight, 21%) and colorectal cancer (seven, 18%). 15 (38%) patients had stage IV disease with distant organ metastasis. 27 (69%) patients had received chemotherapy prior to initially developing COVID-19, and 12 (31%) patients were chemotherapy-naïve. 33 (85%) patients received multi-agent chemotherapy or a combination of chemotherapy and targeted therapies (including five patients with intravenous chemotherapy plus a PD-1 inhibitor); six (15%) received either orally administered drugs or a combination of targeted drug therapies (table 1).

At the time of last follow-up, all patients remained negative for SARS-CoV-2, without suspicious changes on chest computed tomography. 22 (56%) patients experienced altered immunoglobulin test results; specifically, 12 (31%) patients who were initially IgG^+ IgM^- became IgG^- IgM^- after the median 57 days (IQR 36–66 days) from initial administration of chemotherapy. Among the four (10%) patients who were initially IgG^+ IgM^+, three patients became IgG^- IgM^+, and one became IgG^+ IgM^- respectively after 54, 65, 101 and 23 days of chemotherapy. Two (5%) patients who were initially IgG^+ IgM^- became IgG^+ IgM^+ after 55 and 72 days of chemotherapy. Three patients who were initially IgG^- IgM^+ became IgG^- IgM^- after 59, 94 and 101 days of chemotherapy, and only one patient initially IgG^- IgM^+ became IgG^+ IgM^-.

Treatments were tolerated well in this cohort. At least one therapy-associated adverse event was registered in 31 (79%) patients and all adverse events were of grades I or II, except for four cases of grade III–IV neutropenia which returned to normal after treatment with granulocyte colony-stimulating factor (G-CSF).

Potential re-emergence of COVID-19 in recovered patients receiving immunosuppressive chemotherapy is a major oncologic and public health concern. Concerns of reactivation of a prior infection are not limited to COVID-19. Previous studies have shown that reactivation of hepatitis B virus occurs in nearly 20% of cancer patients undergoing chemotherapy, and may result in varying degrees of liver damage [6, 7]. There has also been a report that chemotherapy may cause reactivation of tuberculosis [8]. Additionally, many studies have illustrated (in the recovered COVID-19 population) that chemotherapy is associated with a higher risk of developing severe events (*e.g.* pneumonitis), as compared to cancer patients without receipt of recent chemotherapy [1, 2]. However, not all studies have supported such conclusions; some have found no significant effect on mortality for patients having undergone chemotherapy within the prior 4 weeks [9, 10]. Those studies mainly addressed whether chemotherapy could predict for hospitalisation, severe disease and mortality in cancer patients with COVID-19 infection. However, limited information is known about the outcome of chemotherapy for cancer patients with prior COVID-19 infection. To address this knowledge gap, this study's findings suggest that administering chemotherapy to this population is associated with a very low short-term risk of SARS-CoV-2 reactivation. Further work is required to prospectively follow these subjects in the longer term.

Many studies have indicated that patients with COVID-19 have varying degrees of multiple organ dysfunction [11–13], especially those who are critically ill [13]. The rate of liver dysfunction, acute kidney injury, and cardiac injury were as high as 29%, 29% and 23%, respectively [13]. To date, it is unknown whether chemotherapy would make cancer patients with prior COVID-19 infection more vulnerable to organ damage. Although our data demonstrate that this population does not demonstrate an overtly increased susceptibility to organ dysfunction in the short term, corroboration with longer-term prospective data is required for firmer conclusions.

Our study has several limitations. First, according to the updated COVID-19 Diagnostic Criteria (7th Edition) [14], viral serum antibody-based tests are indeed valid for diagnosis; however, false-positive and false-negative test results can occur. The sensitivity and specificity of the colloidal gold immunoassay utilised herein for IgG, IgM and IgG/IgM was 83%/74%/84% and 99%/97%/95%, respectively [15]. Second, the number of cases in this study is relatively small, and retrospective assessment can never exclude biases in patient selection. Third, the duration of follow-up in this study was relatively short and it may take a longer period of time to determine immune-related alterations caused by chemotherapy in cancer patients who have recovered from COVID-19 infection. Nevertheless, when conservatively interpreted, our study indicates no overt short-term increase in the risk for SARS-CoV-2 reactivation following immunosuppressive chemotherapy in this uniquely vulnerable population.

To our knowledge, this is the first study reporting that recovered COVID-19 cancer patients remain negative in the short-term for SARS-CoV-2 after delivery of chemotherapy. The knowledge/experience gained from this study may aid guidelines on delivering chemotherapy to cancer patients recovered from COVID-19 infection during this pandemic as well as to address potential "second waves" in the future.

Jianping Bi[1,8], Hong Ma[2,8], Dongsheng Zhang[3,8], Jing Huang[2], Dongqin Yang[4], Yajie Wang[5], Vivek Verma[1], Tao Zhang[2], Desheng Hu[1], Qi Mei[6,9], Guang Han[1,9] and Jian Li[7]

[1]Dept of Radiation Oncology, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. [2]Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. [3]Dept of Oncology, Hubei University of Medicine, Suizhou Hospital, Suizhou, China.

[4]Dept of Oncology, The Fifth Hospital of Wuhan, Wuhan, China. [5]Dept of General Surgery, People's Hospital of Dongxihu District, Wuhan, China. [6]Dept of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. [7]Institute of Medical Information, Biometry, and Epidemiology, Ludwig-Maximilian-University Munich, Munich, Germany. [8]Jianping Bi, Hong Ma and Dongsheng Zhang contributed equally as first authors. [9]Guang Han and Qi Mei contributed equally to this article as lead authors and supervised the work.

Correspondence: Guang Han, Dept of Radiation Oncology, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430079, China. E-mail:hg7913@hotmail.com

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