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 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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Cite this article as: Bi J, Ma H, Zhang D, et al. Does chemotherapy reactivate SARS-CoV-2 in cancer patients recovered from prior COVID-19 infection?. Eur Respir J 2020; 56: 2002672 [https://doi.org/10.1183/13993003.02672-2020].

https://doi.org/10.1183/13993003.02672-2020 Eur Respir J 2020; 56: 2002672
| Patient | Sex  | Age  | 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   | Lung neuroendocrine carcinoma | 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   | Breast cancer    | T4N3M0  | Hypertension     | 3 cycles of abraxane + lobarplatin | 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 + pertuzumab | 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, 10 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, 4 Jun, 6 Jul | 0                | 14 Apr, 18 May, 10 Jun, 6 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
| Patient | Sex | Age | 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 +bevacizumab                   | 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, 24 Jul, 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 (F1G0) | 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 (F1G0) | 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               | 2 cycles of gemcitabine +anlotin+PD-1 inhibitor                                  | 5 Jun, 3 Jul               | 0                    | 20 May, 3 Jun, 4 Jun, 29 Jun |
| 39      | Male  | 41  | 1  | Glioblastoma           | None    | 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+S-fluorouracil+leucovorin; FOLFIRI: irinotecan+5-fluorouracil+leucovorin; EP: etoposide+cisplatin; XELOX: oxaliplatin+capecitabine; AC: adriamycin+cyclophosphamide; RT: radiotherapy; PP: pemetrexed+cisplatin; DP: paclitaxel+cisplatin; DC: docetaxel+carboplatin; GP: 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-naive. 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 Bi1,8, Hong Ma2,8, Dongsheng Zhang3,8, Jing Huang2, Dongqin Yang4, Yajie Wang5, Vivek Verma1, Tao Zhang2, Desheng Hu1, Qi Mei6,9, Guang Han1,9 and Jian Li7
1Dept of Radiation Oncology, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. 2Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. 3Dept of Oncology, Hubei University of Medicine, Suizhou Hospital, Suizhou, China.
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

Received: 7 July 2020 | Accepted after revision: 26 Aug 2020

Acknowledgements: We thank Tian Tang (Renmin Hospital of Wuhan University, Wuhan, China) for her assistance in the study and we thank all patients involved in the study.

Author contributions: All authors had full access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: J. Bi and G. Han. Collection of clinical data: J. Bi, H. Ma, D. Zhang, J. Huang, D. Yang and Y. Wang. Data analysis and interpretation: J. Bi, H. Ma, D. Zhang, D. Yang, Y. Wang and G. Han. Preparation of the paper: J. Bi, H. Ma and G. Han. Study supervisors: G. Han, T. Zhang and D. Hu. Final manuscript revisions: V. Verma, T. Zhang, Q. Mei, G. Han and J. Li.

Conflict of interest: None declared.

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https://doi.org/10.1183/13993003.02672-2020