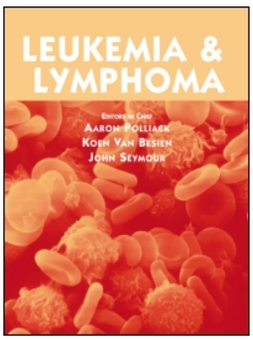

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LETTER TO THE EDITOR

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# Worsening of COVID-19 after chemotherapy in patients considered to have recovered from a SARS-CoV-2 infection

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Given the increased risk of infection after chemotherapy, hematological societies have proposed postponing chemotherapy, when feasible, during the COVID-19 pandemic [1], despite initial studies showing no increase in the incidence of COVID-19 among hematological patients [2]. However, immune deficiency in these patients may impair viral clearance and recent data suggest that hematologic malignancies are associated with increased mortality due to COVID-19 [3,4]. Nevertheless, the pathophysiology and disease presentation differs in these patients compared to non-hematological patients [5]. Several cases of asymptomatic or symptomatic SARS-CoV-2 infection with persistence of virus in the respiratory tract have been reported [6,7]. However, the appropriate timing of administration of chemotherapy after a patient has clinically recovered from COVID-19 still remains unclear. Here, we report three cases involving patients with aggressive lymphoma treated with chemotherapy following recently recovered COVID-19.

A 75-year-old male with a history of hypertension, dyslipidemia, and prostate cancer treated with brachytherapy seven years ago was diagnosed in July 2020 with diffuse large B-cell lymphoma (DLBCL), stage IVB (testicular involvement, no central nervous system (CNS) or medullary involvement), R-IPI 4, CNS IPI 3, GC phenotype, (not double-HIT). The patient was treated with chemotherapy (R-CHOP-21). The last chemotherapy before SARS-CoV-2 infection was the fifth cycle (October 26$^{th}$).

On October 31$^{st}$, the patient was admitted to the emergency department for diarrhea and cough without fever. He was not neutropenic and SARS-CoV-2 polymerase chain reaction (PCR) was positive on naso-pharyngeal swab (NPS) (cycle threshold value (Ct): 6.7/32). The patient was discharged with a diagnosis of mild COVID-19 and became rapidly asymptomatic. Our hospital had chosen a strategy to assess viral clearance based on the symptoms rather than on testing and no PCR control for SARS-CoV-2 on NPS was performed, in accordance with local guidelines.

On November 16$^{th}$, he received his 6th R-CHOP cycle while completely asymptomatic and without any signs of inflammation in the blood. He was admitted to the hospital on November 24$^{th}$ for febrile neutropenia and treated empirically with piperacillin-tazobactam. Blood and urine cultures were negative. However, SARS-CoV-2 PCR on NPS tested positive (Ct: 8.8/32), and SARS-CoV-2 serology was negative. The patient's clinical situation rapidly deteriorated and he was admitted to the intensive care unit (ICU) for severe acute respiratory distress syndrome (ARDS). Computed-tomography (CT)-scan of the lung showed "crazy paving" and diffuse ground glass opacities. Bronchoalveolar lavage (BAL) viral culture was positive for SARS-CoV-2. No other pathogen except for HSV1 was identified by microscopy, culture, or multiplex PCR. The patient received 10 days of treatment with remdesivir [8] and two transfusions of 200 ml of convalescent plasma [9]. He was treated with isavuconazole for probable invasive aspergillosis (N-galactomannan and PCR positive on BAL) 9 days after ICU admission, but died 5 days later due to multiple organ failure with an RT-PCR on NPS still yielding a low Ct positive result (12.12/32).

A 65-year-old male with a history of DLBCL, stage IVB, R-IPI: 4, CNS-IPI: 4, medullary involvement but no CNS involvement, non-GC phenotype, was treated with R-CHOP-21 chemotherapy. The last chemotherapy before SARS-CoV-2 infection was the third cycle (October 16$^{th}$).

On November 2$^{nd}$, the patient was asymptomatic but SARS-CoV-2 PCR was positive (Ct: 29) on NPS performed routinely before a Positron emission tomography (PET)-scan. PET-CT showed complete hematological response and bilateral hypermetabolic pulmonary infiltrates.

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The patient was hospitalized for COVID-19 pneumonia with hypoxemia on November 12th and treated with 10 days of dexamethasone 6 mg/d and 7 days of piperacillin-tazobactam for a possible bacterial suprainfection. His respiratory status rapidly improved and he was weaned from oxygen. Since we were already 15 days behind schedule with his chemotherapy, and to maintain dose-intensity for this aggressive lymphoma, the decision was made to administer the fourth cycle of chemotherapy with a 15 day delay, on November 20th.

On December 2nd, the patient was admitted again for hypoxemia. He was not neutropenic. A chest CT-scan showed exacerbation of ground glass opacities and bilateral patchy shadowing. The patient received empiric antibiotic treatment with cefepim and clarithromycin. Microbiological work-up on BAL was solely positive for SARS-CoV-2 by multiplex syndromic PCR and viral culture. SARS-CoV-2 serology was negative. He rapidly deteriorated and required invasive ventilation for moderate ARDS. He didn't receive specific treatment for COVID-19. His respiratory status improved and he was weaned from mechanical ventilation after 15 days, but is still currently in a rehabilitation facility.

A 73-year-old male with a history of thrombo-embolic disease (G20210A mutation of prothrombin) and systemic anaplastic T cell lymphoma, Stage IIIA, IPI 2, ALK negative, CD30 positive, received his third cycle of brentuximab-CHP on October 15th before COVID-19 infection.

On October 22nd, the patient was admitted to the emergency department for cough, fever, and anosmia. The diagnosis of mild COVID-19 was made based on a positive SARS-CoV-2 PCR on NPS (Ct: 13) and absence of hypoxemia; the patient was sent home. He subsequently became asymptomatic and received his fourth (November 5th) and fifth cycles of chemotherapy (November 26th).

On December 4th, the patient was admitted with febrile neutropenia with hypoxemia and received empiric antibiotherapy with piperacillin-tazobactam. Blood and urinary cultures were negative. Thoracic CT-scan showed bilateral ground glass opacities. SARS-CoV-2 PCR was positive on NPS and serology was negative. No contact with a COVID-19 case was documented. BAL was solely positive for SARS-CoV-2 by syndromic multiplex PCR (Ct: 23,8) and viral culture. He was treated with 10 days of remdesivir, one transfusion of convalescent plasma and 6 days later with SARS-CoV-2 monoclonal antibodies (REGN-COV2) [10] followed by rapid clinical improvement. Two consecutive PCR on NPS performed 1 week apart could not detect SARS-CoV2.

We report three cases of COVID-19 during treatment for aggressive lymphoma, two of them deemed to have recovered and one improved following an initial SARS-CoV-2 infection episode but showed clinical worsening of COVID-19 following chemotherapy administration. The clinical worsening was attributed to COVID-19 because patients were still shedding SARS-CoV-2 that was grown on cell culture they presented typical images on chest CT-scan suggestive of COVID-19, and no other pathogens were found identified by microbiological work-up.

In a meta-analysis from Vijenthira *et al.*, recent chemotherapy was not associated with an increased risk of death [3], but this is a different situation than the cases we have presented as patients had received chemotherapy before being infected. In another study, no reactivation was documented following chemotherapy in patients previously infected with SARS-CoV-2, but all patients had negative SARS-CoV-2 PCR on NPS and positive SARS-CoV-2 serology before receiving chemotherapy [11]. Hueso *et al.* recently described a patient who developed symptomatic COVID-19 following chemotherapy following a previous documented infection 8 weeks earlier [9].

It is noteworthy that all three patients had negative serology for SARS-CoV-2 more than one month after their first positive PCR for SARS-CoV-2, suggesting that these patients were not able to develop a humoral immune response against SARS-CoV-2. Although we do not have data concerning the cellular immunity of these patients against SARS-CoV-2, we can hypothesize that it was impaired due to the underlying malignancies and chemotherapy.

It stays unclear whether these cases were relapses or reinfections. For example, the third patient was diagnosed more than 1 month before being admitted for severe COVID-19. The Genotyping of the consecutive SARS-CoV-2 ARN could theoretically help us differentiate between these two situations. However, it will be difficult to determine whether patients experienced an aggravation of the original SARS-CoV-2 infection due to chemotherapy or a new SARS-CoV-2 infection because viral mutations, either spontaneous or due to treatment pressure, have been reported [5].

Guidelines from the European Society for Medical Oncology propose delaying chemotherapy until SARS-CoV-2 viral clearance for patients with lymphoma and COVID-19 infection [12]. However, evaluation of viral clearance is ambiguous as SARS-CoV-2 PCR can remain positive for months [13], and resolution or absence of symptoms does not rule out persisting infection, as illustrated by our three cases and described by others [5,14]. Furthermore, in cases of aggressive neoplasia, delaying therapy is associated with an increased risk of relapse or progression of disease [15,16]. Therefore, specific guidelines should be discussed regarding, definition of viral clearance demonstration, and indications for specific use of convalescent plasma and/or monoclonal antibodies. A thorough evaluation of the balance between the risk of viral reactivation/relapse and the benefit of maintaining a dose-intensity for that type of aggressive lymphoma when administering chemotherapy is of paramount importance for these patients. Humoral immune response against SARS-CoV2 has to be assessed (using specific IgG antibody titer), and if missing, either chemotherapy has

to be postponed or patients have to be vigorously monitored for SARS-CoV2 reactivation or new onset infection.

Moreover, we believe that monoclonal antibodies and convalescent plasma could represent an effective treatment for these patients presenting with SARS-CoV2 along with a humoral immunity deficiency due to an underlying condition and/or its treatment.

In conclusion, we report three cases of worsening COVID-19 after chemotherapy in lymphoma patients who were clinically cured after a first episode of SARS-CoV-2 infection. These cases highlight the importance of viral clearance assessment before chemotherapy, as patients may reactivate SARS-CoV-2 infection, resulting in severe COVID-19 disease.

## Acknowledgement

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## Ethical statement

First patient was not able to sign a written informed consent, his wife have accepted that his medical information's was published. Two others patients signed a written informed consent.

The use of data was approved by Erasme University Hospital ethics committee

## Author contributions

AP: Conceptualization, writing original draft, GV, NY, CM: Data curation, reviewing MH, DG, VDW, MC: reviewing, editing.

## Disclosure statement

The authors declare no conflict of interest

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