HemaSphere
Powered by EHA

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Case Report
OPEN ACCESS

SARS-CoV-2 Interstitial Pneumonia Treated With Tocilizumab in a Patient Affected by Classical Hodgkin Lymphoma

Chiara Rusconi[1], Giulio Cassanello[2], Anna Guidetti[1], Chiara Oltolini[3], Vincenzo Marasco[2], Lucio Morabito[4], Matteo Della Porta[4], Rodolfo Lanocita[5], Gabriele Papagni[6], Cristiana Carniti[1], Paolo Corradini[1,2]

Correspondence: Chiara Rusconi (e-mail: chiara.rusconi@istitutotumori.mi.it).

The World Health Organization on March 2020 declared the novel coronavirus SARS-CoV-2 pandemic. Corona Virus Infectious Disease 19 (COVID-19) affects a wide range of patients, from asymptomatic to seriously compromised ones, displaying very heterogeneous clinical features. Severe cases may present with multiple organ dysfunctions, among which acute respiratory distress syndrome (ARDS) represents the principal cause of death. Excessive immune responses leading to a cytokine storm play a crucial role in lung damage progression, with interleukine 6 (IL-6) being one of the pivotal cytokines involved.[1] Hence, blockade of IL-6 signaling might represent a promising approach to treat COVID-19-related ARDS. Tocilizumab, a humanized monoclonal antibody against IL-6 receptor (IL-6R), has been previously described as a potential effective treatment option in seriously non-cancer COVID-19 patients.[2,3] Cancer patients are considered at higher risk of SARS-CoV-2 infection than general population, and their prognosis has been described as poorer.[4] In the oncological setting, hematological cancer patients are expected to be particularly susceptible to infections, due to malignancy-and therapy-related immunodeficiencies. A recent report highlights a very high mortality in an heterogeneous hematological cohort.[5] Very few preliminary data are available on the efficacy of tocilizumab for COVID-19 treatment in solid and hematological cancer patients.[5-7] We therefore report a case of SARS-CoV-2 interstitial pneumonia in a patient with classical Hodgkin Lymphoma (cHL) successfully treated with tocilizumab.

[1]Division of Hematology and Stem Cell Transplantation, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy
[2]Department of Oncology and Hemato-oncology, University of Milano, Italy
[3]Department of Infectious Diseases, San Raffaele Scientific Institute, Milano, Italy
[4]IRCCS Humanitas Research Hospital and Humanitas University, Rozzano-Milan, Italy
[5]Interventional Ultrasound Unit, Division of Radiology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy
[6]Intensive Care Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.
The authors have no conflicts of interest to disclose.

HemaSphere (2020) 4:5(e472). http://dx.doi.org/10.1097/HS9.0000000000000472.
Received: 13 May 2020 / Accepted: 23 July 2020

A 62 year-old man was diagnosed with cHL in March 2019; Ann Arbor stage was IIB. Comorbidities consisted of hypertension, *in situ* melanoma and papillary renal cell cancer, both surgically eradicated. Six ABVD (doxorubicine, bleomycin, vinblastine, and dacarbazine) cycles were administered from April to November 2019; complete metabolic response according to Lugano criteria[8] was achieved after 2 cycles and confirmed at the end of chemotherapy by ^{18}FDG-PET. Consolidation radiotherapy to bulky mediastinal mass was completed on February 3rd 2020. On March 17, a total body CT scan, planned for cHL assessment, showed a ground-glass opacity at the lower right pulmonary lobe but no evidence of lymphoma relapse (Fig. 1). Since no typical influenza-like illness symptoms were reported and radiological pattern was not consistent with post-radiotherapy toxicity, late bleomycin lung disease was alleged. Six days later, on March 23, the patient was febrile with a tympanic temperature of 38°C but no viral RNA was detected in his nasopharyngeal swab (NPS) by SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR). Laboratory tests showed lymphocitopenia and slightly increased inflammatory indexes. Levofloxacine 500 mg p.o. daily was initiated in outpatient setting. On March 26, patient's clinical conditions rapidly worsened and hospital admission to the COVID-19 ward was required. At hospital admission, a second SARS-CoV-2 NPS test resulted positive. At admittance, body temperature was 38.5°C and oxygen saturation was 88% on room air, requiring oxygen supplementation (4L/min). Modified Early Warning Score (MEWS)[9] was calculated for clinical severity assessment and resulted at point 3. Based on the fifth edition of the China Guidelines for the Diagnosis and Treatment of Novel Coronavirus (2019-nCoV) Infection,[10] the present case was classified as severe. Laboratory tests showed persistent lymphocitopenia and inflammatory indexes sharply increased (Table 1). Chest CT worsened, becoming bilateral and with multiple ground-glass opacities increased in number and extension (Fig. 1), as expected since the patient shifted from a subclinical to a symptomatic disease phase.[11] COVID-19 therapy was administered according to local protocols: hydroxychloroquine 200 mg bid, lopinavir/ritonavir 400/100 mg bid, enoxaparin 8000 U subcutaneously daily. Despite treatment, on March 27 higher fever (39°C), further worsening of inflammatory laboratory tests (Table 1) and increased oxygen supplementation (Fig. 1) were observed, and patient's MEWS increased to point 6. A first dose of tocilizumab 8 mg/kg i.v. was administered, together with Ceftriaxone 2 gr i.v.

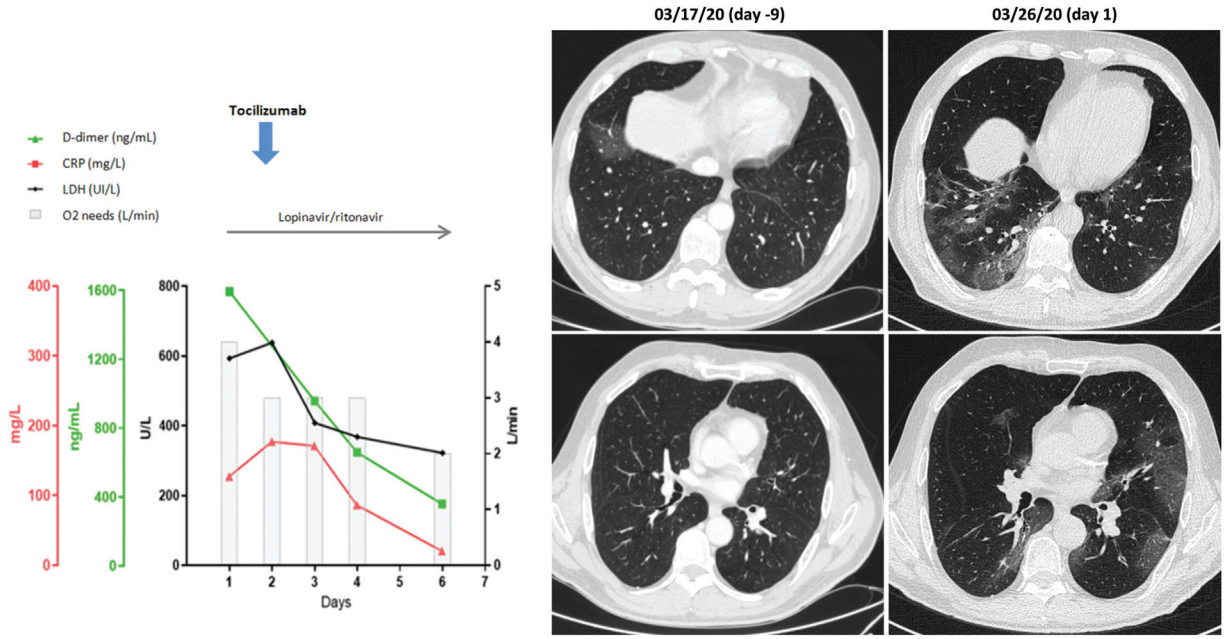

Figure 1. Trend of inflammatory indexes, O_2 needs and chest computed tomography scan.

daily. The following day, a rapid clinical improvement was observed, and MEWS dropped to point 3 in 12 hours; thus, a second dose of tocilizumab was not administered. Patient was afebrile since March 29, and oxygen supplementation was gradually reduced and stopped on March 31. Inflammatory indexes decreased accordingly to clinical course. On April 2nd the patient was discharged because fully recovered. Two negative NPS were obtained on April 23 and 24. IgG antibodies to SARS-CoV-2 in whole blood were detected using a COVID-19 rapid immunochromatographic (PRIMA LAB SA, Switzerland) on May 6.

Patients with hematological malignancies are variably immunocompromised, and therefore at elevated risk of severe COVID-19 and poor prognosis in case of ARDS development. Hyperinflammatory pulmonary symptoms in the contest of SARS-CoV-2 infection are associated with a cytokine storm involving interleukins and chemokine dysregulation. Interleukin 6 axis seems to play a major role, and can be inhibited by tocilizumab. Lung injury in COVID-19 patients probably reflects different pathophysiology patterns, and efficacy of tocilizumab is expected to be higher if ARDS is cytokine mediated; however, a reliable biomarker for differential diagnosis has not been identified yet. Considering the lack of standardized treatment for COVID-19 and actual uncertainties about effectiveness of antiviral and steroids, tocilizumab has been tested in small series of non-cancer COVID-19-infected patients with promising results. So far, 2 cancer patients, one affected by multiple myeloma and one by renal sarcoma, successfully treated with tocilizumab have been extensively reported.[6,7] More recently, a series of hematological cancer patients SARS-CoV-2 infected has been described: 3 out of 25 patients received tocilizumab, in 2 cases together with steroids, and a successful outcome has been reported for two of them.[5] The patient described in this report was affected by 3 different tumors before SARS-CoV-2 infection, all considered of good prognosis.

Table 1

Inflammatory Indexes Trend Before and After Tocilizumab Treatment.

		Results				
Laboratory Parameter	**Normal Range**	**26 Mar**	**27 Mar[a]**	**28 Mar**	**29 Mar**	**31 Mar**
WBC count, $\times 10^9$/L	4.0–10.0	8.7	9.5	6.1	2.0	2.2
Neutrophil count, $\times 10^9$/L	2.0–7.0	7.0	9.0	5.6	1.4	1.5
Lymphocyte count, $\times 10^9$/L	1.0–4.0	0.7	0.3	0.3	0.3	0.3
Haemoglobin, g/dL	13.5–16.5	14.4	13.6	12.6	13.4	13.5
Platelet count, $\times 10^9$/L	150–400	168	161	157	166	181
Creatinine, mg/dL	0.67-1.17	1.27	1.19	1.17	1.13	1.05
Fibrinogen, mg/dL	160–400	735	–	676	–	–
D-dimer, ng/mL	200–350	1570	–	941	646	349
C-reactive protein, mg/L	<5	127	177	171	86	20
Procalcitonin, ng/mL	0.05–0.5	–	0.47	0.50	0.28	0.12
Lactate dehydrogenase, U/L	<248	593	638	408	368	322
IL-6, pg/mL	<6.4	–	–	1080	406	403
Ferritin, ng/mL	23.9–9336.2	537	–	494	535	451

[a] Single dose Tocilizumab administration, 8 mg/Kg; - = not available, IL = Interleukin, WBC = white blood cell.

Classical HL proved to be chemo-sensitive, and the complete metabolic response documented by ^{18}FDG-PET performed after 2 cycles predicted a 5-years progression-free survival of approximately 90%.[12] Among the tumors this patient is affected by, cHL is considered the major driver of immunosuppression and, consequently, the main adverse prognostic factor for COVID-19, even if a prognostic relevance of age and hypertension should be considered. Of note, the patient developed antibodies against SARS-CoV-2 despite he had recently received chemotherapy. The first cHL patient affected by COVID-19 has been described by O'Kelly and colleagues: at symptoms onset, a PD-1 inhibitors induced pneumonitis was suspected, and treatment against SARS-CoV-2 was started after NPS test resulted positive.[13] Similarly, our initial hypothesis of bleomycin related flogistic lung alteration demonstrates how challenging the differential diagnosis of interstitial pneumonia might be in the hematological setting, and indicates that other causes should be considered also during the SARS-CoV-2 pandemic. On the other hand, in case of a clinical and radiological frame suggestive for COVID-19, NPS testing should be repeated at least once after a first negative result. The present patient, as well as the one reported by O'Kelly, required high flow non-invasive oxygen ventilation to overcome SARS-CoV-2 induced respiratory distress; despite some concerns about previous bleomycin exposure, adverse events after ventilation were not reported.[13]

Clinical and radiological deterioration of the patient's conditions observed during hydroxychloroquine and antiviral treatment, together with his inflammatory status, revealed by increased values of lactate dehydrogenase and C-reactive protein, prompted us to consider early administration of tocilizumab. We can speculate that treatment with tocilizumab within 48 hours from severe coronavirus pneumonia onset presumably changed disease course allowing a fast clinical recovery. Notably, in the present case no concomitant steroids were used, while some potential benefits of the concomitantly medications administered according to current local protocol cannot be excluded, even if antiviral and hydroxychloroquine efficacy for treatment of COVID-19 is still unclear and under evaluation in largest studies. In our experience, inflammatory indexes can be considered reliable indicators of lung damage severity: their quick and continuous rise was observed during respiratory deterioration and increased oxygen supplementation, while their rapid drop was recorded after tocilizumab administration, concomitantly to clinical recovery. Unfortunately, baseline IL-6 level was not available, and presumably the peak observed the day after tocilizumab administration reflects IL-6 receptor blocking. In the present clinical case, as well as in two previously described cancer patients tocilizumab did not lead to bacterial or opportunistic superinfection.[6,7] This finding is consistent with available data on infection risk in lymphoma patients who required tocilizumab due to severe cytokine release syndrome post CAR-T administration.[14] To the best of our knowledge, this is the first extended report on successful tocilizumab treatment for a lymphoma patient affected by COVID-19; immunocompromised subjects may mount an antibody response and overcome SARS-CoV-2 infection, even in case of severe interstitial pneumonia. As usual, data from a single case report should be interpreted with caution, and future randomized controlled trials are encouraged and expected, even in the difficult and adverse pandemic scenario, to determine safety, efficacy and optimal timing of tocilizumab administration, both in general and cancer COVID-19 patients.

Acknowledgement

The authors wish to thank all their Italian colleagues and healthcare operators for the unconditional selfless dedication and commitment to caring for patients during the COVID-19 pandemic. RC thanks Anna Maria De Filippo for linguistic revision.

References

1. Zhou Y, Fu B, Zheng X, et al. Pathogenic T-cells and inflammatory monocytes incite inflammatory storms in severe COVID-19 patients. *National Sci Rev.* 2020;7:998–1002.
2. Luo P, Liu Y, Qiu L, et al. Tocilizumab treatment in COVID-19: A single center experience. *J Med Virol.* 2020;92:814–818.
3. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci.* 2020;117:10970–10975.
4. Landman A, Feetham L, Stuckey D, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol.* 2020;21:335–337.
5. Malard F, Genthon A, Brissot E, et al. COVID-19 outcomes in patients with hematologic disease. *Bone Marrow Transplant.* 2020;6:1–5.
6. Michot J-M, Albiges L, Chaput N, et al. Tocilizumab, an anti-IL6 receptor antibody, to treat Covid-19-related respiratory failure: a case report. *Ann Oncol.* 2020;31:961–964.
7. Zhang X, Song K, Tong F, et al. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. *Blood Adv.* 2020;4:1307–1310.
8. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of hodgkin and non-hodgkin lymphoma: The lugano classification. *J Clin Oncol.* 2014;32:3059–3067.
9. Subbe CP, Kruger M, Rutherford P, et al. Validation of a modified Early Warning Score in medical admissions. *QJM.* 2001;94:521–526.
10. Lin L, Li TS. Interpretation of "guidelines for the diagnosis and treatment of novel coronavirus (2019-nCoV) infection by the National Health Commission (Trial Version 5). *Zhonghua Yi Xue Za Zhi.* 2020;7:100.
11. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis.* 2020;20:425–434.
12. André MPE, Girinsky T, Federico M, et al. Early positron emission tomography response-adapted treatment in stage I and II hodgkin lymphoma: final results of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol.* 2017;35:1786–1796.
13. O'Kelly B, McGettrick P, Angelov D, et al. Outcome of a patient with refractory Hodgkin lymphoma on pembrolizumab, infected with SARS-CoV-2. *Br J Haematol.* 2020;190:e1–e38.
14. Frigault MJ, Nikiforow S, Mansour M, et al. Tocilizumab not associated with increased infection risk after CAR T - Implications for COVID-19? *Blood.* 2020;136:137–139.