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CASE REPORT

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Cancer patients and targeted therapy during COVID-19 pandemic: A descriptive case series study

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Abstract

To evaluate the effectiveness of targeted therapy on preventing or treating COVID-19, in this study, we want to share our experience about 14 patients (nine women, five men; average age, 59 years) who were treated with targeted therapy due to their underlying malignant disorders in our center.

KEYWORDS

case series, COVID-19, immunotherapy, malignant disease, targeted therapy

1 | INTRODUCTION

It was believed that patients with active cancer receiving systemic treatment like chemotherapy are at greater risk of complications associated with COVID-19. Compared to the general population, broad prospective data sets from the CCC-19 consortium and the UKCCMP group have recently reported the elevated mortality rates of cancer patients.[1,2] Systemic treatment (e.g., chemotherapy) put patients at greater risk of infection and lead to worse results after COVID-19 infection.[3] In a cohort of 1590 COVID-19 patients by Liang et al., 18 cancer patients were evaluated. In this population, the prevalence of COVID-19 was higher than the general population, according to their results, and cancer patients who were infected had worse outcomes.[4] The risk associated with biological therapies is less evident, as some of them could battle the COVID-19 inflammatory storm.[5] Biologic medication has been found to be beneficial in cancer as well as in psoriasis, eczema, and sepsis.[6,7] Targeted therapy currently plays a key role in the treatment of hematology-oncology diseases, and there is little evidence on its effectiveness on treating patients with COVID-19. On the other hand, physicians are always doubtful whether to continue or not these drugs in the phase of infection. In 2012, during acute viral infections, Erickson et al. identified a high expression in the lower respiratory tract of PD-1 and PDL-1. As well, they argued that poor CD + 8 T-cell functions and chronic viral infections were produced by lower human respiratory system.[8] Immune checkpoint blockade (ICB) therapy—specifically antibodies targeting programmed death receptor 1 (PD-1) and its ligand programmed death ligand 1 (PDL1)—has significantly expanded the therapeutic effects for some recurrent or metastatic malignancies.[9,10] Ibrutinib is an oral covalent Bruton tyrosine kinase inhibitor (BTK), which is considered as an important enzyme in the signaling of B-cell receptors.[11,12] In a study of Ibrutinib monotherapy, with a median follow-up of 5 years, the overall response rate was estimated as 87% among patients with previously untreated CLL and as 89% among those with relapsed or

refractory disease.[11] In a highly important lethal flu animal model, the ability of Ibrutinib in inhibiting pulmonary inflammatory cytokines, lung damage, and death were shown.[13] The findings of the Roschewski's study implied that treating cytokine storm with a BTK inhibitor may be considered as a therapeutic approach in severe cases of COVID-19.[14] Ruxolitinib, which is the oral JAK 2 receptor inhibitor, is currently approved for the treatment of myelofibrosis patients[15] (Figure 1). A recent clinical trial was conducted on six patients with Waldenstrom macroglobulinemia who were taking the Ibrutinib and subsequently diagnosed with COVID-19. These six patients had only mild symptoms linked to COVID-19.[16] In one study, two patients with metastatic melanoma treated with Nivolumab and Ipilimumab were reported who developed pneumonitis during COVID-19 and continued drug treatment.[17] In another study, two patients with metastatic melanoma who were treated with Nivolumab underwent rapid recovery during COVID-19 and then continued drug treatment.[18] To evaluate the effectiveness of these drugs on preventing or on treating COVID-19, we decided to follow-up the patients who have been treating with these drugs due to the underlying disease.

2 | CASE DESCRIPTION

This was a descriptive case series study. The patients receiving Ibrutinib, both Nivolumab and Ruxolitinib due to their underlying malignant disorders, were monitored in our center from February 2020, when COVID-19 appeared in Iran, until the end of January, 2021. At the beginning of the study, the symptoms of COVID-19 were explained to the patients and were monitored based on the symptoms and followed up monthly based on telephone calls. For COVID-19 symptomatic patients, RT-PCR; CXR; and laboratory tests such as ESR, CRP, and CBC were performed and the confirmed cases were then monitored. The above-mentioned drugs were not discontinued when infected by this disease (by considering the supervision of an infectious and hematology-medical oncology specialist). COVID-19 diagnosis was performed by an infectious disease specialist, and the patients were followed up for underlying disease by a skilled hematology-medical oncologist.

2.1 | Case presentation

In this study, 14 patients (nine women, five man; average age, 59 years) receiving targeted therapy due to their underlying malignant disorders were monitored in our center. The patients were of Iranian ethnic origin. *None* of the study participants *had* received any specific *vaccines* against SARS-COV-2 before or during the entire *study period*. Only two patients were found to be infected with COVID-19. Targeted therapy was not discontinued due to the lack of severity of COVID-19 in these cases. In this study, five patients received Nivolumab, five cases received Ruxlotinib, and four cases received Ibrutinib. The details of the patients are given in Table 1. None of the patients treated with Ruxolitinib had suspicious symptoms during the period. One of the patients was treated with Nivolumab and one with Ibrutinib as follows:

1. Patient treated with Nivolumab (Patient 1): A 57-year-old woman who was under observation with metastatic melanoma (liver) since 2 years ago before

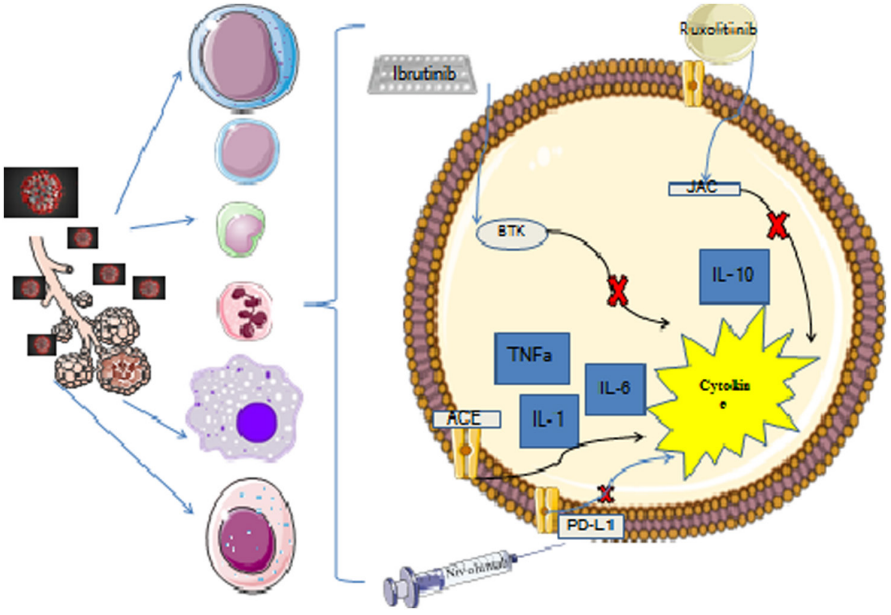

FIGURE 1 COVID-19 activates the cytokine release pathway through the ACEII receptor, Ibratinib, Nivolumab, and Ruxolitinib inhibit cytokine through the inhibit of BTK, PD-L1 and JAK2 receptor, respectively. ACEII, angiotensin-converting enzyme II; BTK, Bruton's tyrosine kinase; JAK2, Janus Kinase II; PD-L1, Programmed death-ligand 1.

TABLE 1 Patient characteristics

	Ruxolitinib					Ibrutinib				Nivulomab				
	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 1**	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 1**	**Patient 2**	**Patient 3**	**Patient 4**	**Patient5**
Age	71	73	27	45	72	61	42	64	61	57	77	65	64	48
Sex	M	F	F	F	M	M	F	F	M	F	F	F	M	F
COVID-19	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Positive	Positive	Negative	Negative	Negative	Negative
Underlying disease	Myelofibrosis	Myelofibrosis	MDS-MPD	Myelofibrosis	Myelofibrosis	CLL	CLL	CLL	CLL	Melanoma	Melanoma	Lung cancer	Lung cancer	RCC
Outcome	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Death	Alive	Alive	Alive	Alive	Alive

Abbreviations: CLL, chronic lymphocytic leukemia; F, female; M, male; MDS-MPN, myelodysplastic syndrome/myeloproliferative neoplasm; RCC, renal cell carcinom.

being treated with Nivolumab. Since the previous year, her underlying disease became stable. The patient referred 1 month ago with symptoms of weakness, low-grade fever and cough as well as positive COVID-19 RT-PCR. Lung CT was performed for the patient and little ground glass opacity (GGO) was seen. So, Nivolumab was continued and the RT-PCR resulted was negative after 2 weeks. During these 2 weeks, only symptomatic treatments including acetaminophen were used for the patient. Lung CT after 4 weeks was done again and GGO was cleared.

2. Patient treated with Ibrutinib (Patient 4): A 61-year-old man with CLL Rai at stage III since 2.5 years ago. He has diabetes mellitus from 10 years ago and treating with metformin and glibenclamide. He was previously treated in another center, and then referred to our center 1 year ago. Accordingly, due to the active disease, he was a candidate for receiving Ibrutinib. Unfortunately, due to the economic situation, he was not able to obtain the drug, approximately 5 months ago. The patient's disease became stable, and leukocytosis, thrombocytopenia, and anemia have improved with the administration of Ibrutinib. He was diagnosed with COVID-19 with fever, shortness of breath, and positive RT-PCR 1 month ago. Because of his background disease, risk factors, and probability of COVID-19 progression, the patient was admitted to the hospital. At the admission time, his O_2sat without oxygen was 87%. Lung CT was performed for the patient and multiple ground glass opacity (GGO) was seen. The patient was discharged after 10 days with continued Ibrutinib and supportive treatment, such as Corticosteroid treatment, under a good condition. Lung CT after 6 weeks was done again and GGO was cleared. During the three-month follow-up, the CBC was normal with no organomegaly and he had shown no constitutional symptom. After 3 month, the patient presented to the emergency room with chest pain. Thereafter, he was hospitalized with a diagnosis of extensive myocardial infarction. Despite getting a PCI, he died as a result of an arrhythmia. Notably, RT-PCR at the time of admission was negative.

Other 12 patients in this period had no suspicious symptoms related to COVID-19.

3 | DISCUSSION

A controversial issue is the roles of targeted therapy and immunotherapy in the treatment of cancer, which play roles in the treatment of COVID-19. Accurate statistics are not available to assess the incidence of people

treated with these drugs, whether these patients have a higher or lower incidence rate compared to other normal people in the community. Even so, immunotherapy has proved to be a double-edged sword: the same mechanism that benefits the patient can kill him. Immune-related toxicities are less frequent than chemotherapy toxicities but potentially mortal. The underlying mechanism is the release of the break to the immune system and the recognition of self-antigens as foreign. This way, a boosted immunity system attacks different organs, leading to thyroiditis, hypophysitis, hepatitis, colitis, etc. Most of these adverse events usually improve after a course of corticoid therapy; however, a small percentage will need more intense immunosuppressive treatment. Some of these potential toxicities have a high mortality rate, as encephalitis, myocarditis, or pneumonitis, so early and powerful immunosuppression is required.[19,20] Questions related to disease recurrence following discontinuation of therapy may clarify the greater interest in the continuity of BTKi, at least in part. There is also a potential advantage of BTKi in attacking macrophages and/or inhibiting proinflammatory cytokines in blunting the hyperinflammatory level of COVID-19 disease.[21] In the patients treated with Ibrutinib, only one person developed COVID-19. During the time of the patient's hospitalization due to COVID-19, Ibrutinib was not interrupted, and the patient later died of myocardial infarction after 3 months. In the case report of Lin et al., Ibrutinib was re-administered for the patient who recovered reasonably in D-dimer levels and absolute lymphocyte count. Notably, the recovery is difficult to relate directly to Ibrutinib because of the use of Tocilizumab and other drugs.[22] Our patient was treated with drugs such as Dexamethasone, Interferon, and Remedsivir, and complete improvement in patient could not be attributed to Ibrutinib. In the Cao et al.'s analysis, a significant chest computed tomography improvement, a faster recovery from lymphopenia, and favorable side-effect profile in the Ruxolitinib group were observed.[23] Additionally, in the Walz's meta-analysis and Cao's study, emphasis was on positive clinical outcome of JAK inhibitors in COVID-19 infection.[24,25] In the Robilotti's study, the association among checkpoint inhibitor immunotherapies (such as Nivolumab), as a risk factor for causing severe outcomes in patients treated with these drugs, was shown. According to the results of other studies regarding treating the underlying diseases with Nivolumab during the current COVID-19 pandemic, there still are some controversies.[18,26] In our research, there were no cases of COVID-19 in the Ruxolitinib received group and among the patients treated with Nivolumab, one developed COVID-19, but her symptom rapidly improved with no complications. This was a descriptive case series and the important limitations of this study were the small number of patients and not eliminating other factors that could have affected the protection of COVID-19.

4 | CONCLUSIONS

This article cannot investigate the therapeutic effect of these drugs on the treatment of COVID-19. It's not logical to stop targeted therapy just because of the fear of getting infected with COVID-19. It seems reasonable to continue targeted therapy in patients with Hematology-Oncology disease in COVID-19 pandemic because these treatments were shown to have a significant impact on the prognosis of these patients. Another notable point is that the side-effects of these treatments, such as pneumonitis and thyroiditis, should be considered more carefully when other treatments like interferon, are additionally used for patients with COVID-19. Importantly, caution is recommended in the case of Nivolumab. Studies with more data are needed to reach a definitive conclusion.

AUTHOR CONTRIBUTIONS

KK and MM chose the case, supervised manuscript preparation, reviewed the published literature, and wrote the case report manuscript. RM reviewed the published literature, interviewed the patient, and collected the patient past medical history. KK, MM, and RM edited the written manuscript. KK was the corresponding author and submitting the manuscript. All the authors read and approved the final manuscript.

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CONFLICT OF INTEREST

There are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICAL APPROVAL

This study was approved by the institutional ethics review boards of our university (approval number IR.ZUMS.REC.1399.423).

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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REFERENCES

1. Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet*. 2020;395(10241):1907-1918.
2. Lee LY, Cazier JB, Starkey T, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. *Lancet*. 2020;395(10241):1919-1926.
3. Zhang L, Zhu F, Xie L, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. *Ann Oncol*. 2020;31(7):894-901.
4. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol*. 2020;21(3):335-337.
5. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis*. 2020;20(4):400-402.
6. Devaraj NK. Antibiotic resistance: a real menace. *Oman Med J*. 2017;32(6):531.
7. Devaraj NK. A recurrent cutaneous eruption. *BMJ Case Rep*. 2019;12(2):e228355.
8. Erickson JJ, Gilchuk P, Hastings AK, et al. Viral acute lower respiratory infections impair CD8+ T cells through PD-1. *J Clin Invest*. 2012;122(8):2967-2982.
9. Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2016;375:1856-1867.
10. Armand P, Engert A, Younes A, et al. Nivolumab for relapsed/refractory classic Hodgkin lymphoma after failure of autologous hematopoietic cell transplantation: extended follow-up of the multicohort single-arm phase II CheckMate 205 trial. *J Clin Oncol*. 2018;36(14):1428-1439.
11. O'Brien S, Furman RR, Coutre S, et al. Single-agent ibrutinib in treatment-naïve and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. *Blood*. 2018;131(17):1910-1919.
12. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med*. 2014;371(3):213-223.
13. Florence JM, Krupa A, Booshehri LM, Davis SA, Matthay MA, Kurdowska AK. Inhibiting Bruton's tyrosine kinase rescues mice from lethal influenza-induced acute lung injury. *Am J Physiol Lung Cell Mol Physiol*. 2018;315(1):L52-L58.
14. Roschewski M, Lionakis MS, Sharman JP, et al. Inhibition of Bruton tyrosine kinase in patients with severe COVID-19. *Sci Immunol*. 2020;5(48):eabd0110.
15. Yang LP, Keating GM. Ruxolitinib. *Drugs*. 2012;72(16):2117-2127.
16. Treon SP, Castillo J, Skarbnik AP, et al. The BTK-inhibitor ibrutinib may protect against pulmonary injury in COVID-19 infected patients. *Blood*. 2020;135:1912-1915.
17. Souza IL, Fernandes Í, Taranto P, Buzaid AC, Schvartsman G. Immune-related pneumonitis with nivolumab and ipilimumab during the coronavirus disease 2019 (COVID-19) pandemic. *Eur J Cancer*. 2020;135:147-149.
18. Di Giacomo AM, Gambale E, Monterisi S, et al. SARS-COV-2 infection in patients with cancer undergoing checkpoint blockade: clinical course and outcome. *Eur J Cancer*. 2020;133:1-3.
19. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018;378(2):158-168.
20. Haanen J, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28:iv119-iv142.
21. Ní Gabhann J, Hams E, Smith S, et al. Btk regulates macrophage polarization in response to lipopolysaccharide. *PLoS One*. 2014;9(1):e85834.
22. Lin AY, Cuttica MJ, Ison MG, Gordon LI. Ibrutinib for chronic lymphocytic leukemia in the setting of respiratory failure from severe COVID-19 infection: case report and literature review. *EJHaem*. 2020;1(2):596-600.
23. Cao Y, Wei J, Zou L, et al. Regarding Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): a multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol*. 2020;146(1):137-146.e3.
24. Walz L, Cohen AJ, Rebaza AP, et al. JAK-inhibitor and type I interferon ability to produce favorable clinical outcomes in COVID-19 patients: a systematic review and meta-analysis. *BMC Infect Dis*. 2021;21(1):1-10.
25. Cao Y, Wei J, Zou L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): a multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol*. 2020;146(1):137-146.e3.
26. Robilotti EV, Babady NE, Mead PA, et al. Determinants of COVID-19 disease severity in patients with cancer. *Nat Med*. 2020;26(8):1218-1223.

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