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Imran K. Tailor

Department of Adult Hematology and Bone Marrow Transplantation, King Fahad Medical City, Riyadh, Saudi Arabia, doctorimran77@yahoo.co.uk

Nawal F. Alshehry

Department of Adult Hematology and Bone Marrow Transplantation, King Fahad Medical City, Riyadh, Saudi Arabia

Syed Z. Zaidi

Department of Adult Hematology and Bone Marrow Transplantation, King Fahad Medical City, Riyadh, Saudi Arabia

Mohammed A. Marei

Department of Adult Hematology and Bone Marrow Transplantation, King Fahad Medical City, Riyadh, Saudi Arabia

Ibraheem H. Motabi

Department of Adult Hematology and Bone Marrow Transplantation, King Fahad Medical City, Riyadh, Saudi Arabia

See next page for additional authors

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Authors

Imran K. Tailor, Nawal F. Alshehry, Syed Z. Zaidi, Mohammed A. Marei, Ibraheem H. Motabi, Mansour Alfayez, and Syed Y. Altaf

LETTER TO EDITOR

Outcome of Myeloma Patients with COVID-19 on Active Lenalidomide-Based Therapy: Does Lenalidomide Protect From Severe COVID-19?

Imran K. Tailor^{*}, Nawal F. Alshehry, Syed Z. Zaidi, Mohammed A. Marei, Ibraheem H. Motabi, Mansour Alfayez, Syed Y. Altaf

Department of Adult Hematology and Bone Marrow Transplantation, King Fahad Medical City, Riyadh, Saudi Arabia

To the Editor

Patients with haematological cancers and concurrent coronavirus disease 2019 (COVID-19) reportedly have poor outcomes as indicated by high hospitalisation rates, high case fatality rates in mechanically ventilated patients, and a high mortality rate of $\geq 10\%$ [1–3]. A recent small study reported a high mortality rate among patients with myeloma and concurrent COVID-19 infection [4]. Interestingly, one large study reported that active or recent chemotherapy was not a predictor of severe disease, whereas checkpoint inhibitor therapy and age over 65 years were associated with adverse outcomes [1]. Here we describe the outcomes of three consecutive patients with myeloma and concurrent COVID-19 infection admitted at our tertiary care centre between April and June 2020, whilst on lenalidomide-based therapy, two of whom underwent autologous stem cell transplant, with at least 30 days of follow-up.

Clinical features, laboratory characteristics, and other outcomes of the three patients with myeloma are listed in Table 1.

Outcomes of patients with solid tumours and haematological cancers and concurrent COVID-19 infection are poor with high rates of hospitalisations, higher need for ventilatory support, and increased mortality rates [1–4,6,7]. Our study demonstrated excellent outcomes of three consecutive patients with myeloma whilst on lenalidomide-based therapy, with none of them developing severe disease despite being in an immunocompromised state.

Patients with myeloma have an increased risk of developing bacterial (7-fold) and viral infections (10-fold) [5]. In our series, two patients underwent stem cell transplant and two of them had significant comorbidities. Although no conclusions can be drawn, our study raises a very interesting question: does active chemotherapy or immunomodulatory treatment have any protective role against severe COVID-19?

One large study involving over 400 patients with cancer, including haematological cancers, and concurrent COVID-19 infection reported that recent chemotherapy was not associated with adverse outcomes, whereas checkpoint inhibitor therapy (which acts by harnessing and activating the immune system) was a predictor of poor outcome [1]. Other smaller studies also made similar observation that there was no correlation between active treatment with chemotherapy and outcome among patients with haematological cancers [6]. Acute respiratory distress syndrome (ARDS) is the most common cause of death among patients with COVID-19 and develops secondary to cytokine storm [8,10]. Cytokine storm is characterised by disproportionate response to infection or inflammation inducing significant increase in cytokines, such as interleukin (IL)-1, IL-2, IL-6, granulocyte colony-stimulating factor, interferon δ , and tumour necrosis factor (TNF) α , which interact with the complement system and coagulation system and may lead to disseminated intravascular coagulation, multiorgan failure, and death in some patients [9].

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* Corresponding author.
E-mail address: doctorimran77@yahoo.co.uk (I.K. Tailor).

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Table 1. Clinical and Laboratory Characteristics of Patients.

Characteristic	Patient 1	Patient 2	Patient 3
Age	57	43	49
Sex	Female	Male	Male
Diagnosis	Relapsed light chain myeloma post bortezomib/autologous stem cell transplant/lenalidomide/daratumumab	Ig A myeloma post bortezomib/autologous stem cell transplant/lenalidomide	Newly diagnosed light chain myeloma with plasma cell leukaemia with recent history of acute kidney injury
Previous autologous stem cell transplant	Yes	Yes	No
Comorbidities	Diabetes, hypertension, ischemic heart disease, chronic kidney disease	Learning difficulties, care home resident	None
ECOG performance status at presentation	2	1	1
Therapy at the time of presentation	Lenalidomide, dexamethasone	Lenalidomide, dexamethasone	Lenalidomide, bortezomib, dexamethasone
Active treatment for myeloma at COVID-19 diagnosis or in the past 4 wk	Yes	Yes	Yes
Symptoms	Fever, cough, shortness of breath	Cough	Fever, cough
Chest x-ray	Infiltrates present	Not performed	Normal
Oxygen requirement	2 L/min	None	None
Laboratory findings	Mild anaemia, leukopenia, moderate thrombocytopenia; Normal coagulation/D-dimers, Chemistry Increased CRP, ferritin, and LDH	Not done	Mild anaemia only
Noninvasive ventilation	No	No	No
Mechanical ventilation	No	No	No
Treatment	Antibiotics and supportive care	Supportive care	Supportive care
IVIG therapy in previous 4 wk	Yes	No	No
Hospitalisation (d)	13	No (care home isolation only)	25 (till negative COVID swab)
Time taken for negative COVID-19 from initial positive	14	Not tested	25
Outcome	Recovered	Recovered	Recovered
Follow-up (d)	30	59	83

Note. CRP = C-reactive protein; D = day; ECOG = Eastern Cooperative Oncology Group; IVIG = intravenous immunoglobulin; LDH = lactate dehydrogenase; min = minute; wk = week.

COVID-19 is associated with excessive cytokine levels and ARDS; however, there is no consensus if viral replication and/or cytokine storm are responsible for ARDS [9]. This forms the basis of use of many anti-inflammatory drugs in COVID-19, including tocilizumab (IL-6 inhibitor), Bruton tyrosine kinase inhibitors (e.g., ibrutinib), and Janus kinase-2 inhibitors (e.g., ruxolitinib), which have shown favourable outcomes in small series of patients [8,11]. Dexamethasone, an immunosuppressive agent, has shown to reduce COVID-19-related mortality rate in oxygenated and ventilated patients by 20% and 35%, respectively, in one of the largest randomised controlled trials conducted till date for COVID-19 patients [12].

Lenalidomide, an immunomodulatory agent, is one of the backbones in the treatment of myeloma leading to great outcomes; it is used at various stages of management including at induction, in relapsed setting, and as maintenance therapy [13]. Its immunomodulatory action inhibits the production of proinflammatory cytokines, such as TNF- α , IL-1, IL-6, and IL-12, and elevates the production of anti-inflammatory cytokine IL-10, and this has been implicated in clinical efficacy in myeloma [14]. This particular effect of lenalidomide may be playing a protective role in preventing the catastrophic cytokine storm, thereby dampening the immune system which may well be helpful in patients with COVID-19.

Based on aforementioned observations, although our study is a small series, we hypothesise that lenalidomide may play a protective role in myeloma patients and prevent developing severe form of disease; however, this warrants further testing. Second, it raises another important question: should immunomodulatory drugs such as lenalidomide be continued during active COVID-19 infection? This theory also supports the notion that initiation or continuation of chemotherapy or immunosuppressive therapy should not be delayed or stopped in patients with haematological cancers even if they are deemed to be stable or low risk, lest it should alter overall outcome, just for the fear of pandemic. Moreover, this may have an implication in other autoimmune conditions too, wherein use of immunomodulatory drugs is the norm; stopping a therapy may be associated with adverse outcomes from not

only severe COVID-19 but also progression of autoimmune disease.

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