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Annals of Case Reports

Gareca M, et al. Ann Case Report 14: 478.

DOI: 10.29011/2574-7754.100478

Case Report

A Case Report of a COVID-19 Patient Treated with the Selective Inhibitor of Nuclear Export (SINE) Drug, Selinexor

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Citation: Gareca M, Baga L, Herr D (2020) A Case Report of a COVID-19 Patient Treated with the Selective Inhibitor of Nuclear Export (SINE) Drug, Selinexor. Ann Case Report 14: 478. DOI: 10.29011/2574-7754.100478

Received Date: 14 September, 2020; **Accepted Date:** 22 September, 2020; **Published Date:** 28 September, 2020

Abstract

A patient with hypertension who tested positive for SARS-CoV-2 infection received selinexor treatment for Coronavirus Disease 2019 (COVID-19). Upon admission to the ICU on Day 5 after hospitalization, the patient was receiving 60-70% FiO2 via nasal high flow therapy, and was afebrile, lethargic, and confused. Selinexor therapy began on Day 8 following initial hospitalization and his oxygen saturation improved through discharge on Day 15. Platelet counts increased progressively throughout treatment and improvement in transaminase elevations was observed by reductions in both ALT and AST. Here, we report the first successful use of oral selinexor to treat COVID-19 in a hypertensive subject. Randomized trials are underway to determine if the observed effects on inflammatory markers may extend to the broader COVID-19 population.

Keywords: COVID-19; exportin-1; selinexor; SARS-CoV-2; SINE compounds

Abbreviation: ALT: Alanine Transaminase (SGPT); AST: Aspartate Transaminase (SGOT); BNP: Brain Natriuretic Peptide; BUN: Blood Urea Nitrogen; BPM: breaths per minute; CBC: Complete Blood Count; COVID-19: Coronavirus Disease 2019; CRP: C-Reactive Protein; DNA: Deoxyribonucleic Acid; FIO_2: The Fraction of Inspired Oxygen; GFR: Glomerular Filtration Rate; ICU: Intensive Care Unit; IL-1: Interleukin-1; IL-6: Interleukin-6; KEAP: Karyopharm Expanded Access Program; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Haemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; MPV: Mean Platelet Volume; Na: Sodium; NC: Nasal Cannula; NHF: Nasal High Flow; NF-κb: Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; O_2: Oxygen; RBC: Red Blood Cell; RDW: Red Cell Distribution Width; RNA: Ribonucleic Acid; RR: Respiratory Rate; SaO_2: Oxygen Saturation; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; SINE: Selective Inhibitor of Nuclear Export; Tnfα: Tumor Necrosis Factor Alpha; US FDA: The United States Food And Drug Administration; WBC: White Blood Cell; XPO1: Exportin 1

Introduction

SARS-CoV-2 infection has evolved into a global health crisis and pandemic. SARS-CoV-2 infection can be accompanied by a marked inflammatory response which is associated with multi-organ dysfunction, respiratory failure, and death [1]. Both the SARS-CoV-2 lifecycle and pro-inflammatory transcription factors require functional host nuclear export mediated by Exportin 1 (XPO1), which was recently identified as a "hub" host protein for SARS-CoV propagation [2]. Selinexor is a potent, oral, selective inhibitor of nuclear export (SINE) compound that specifically blocks XPO1 [3]. SINE compounds reduce inflammation through inhibition of the NF-κB pathway, thereby reducing cytokines including IL-1, IL-6, and TNFα, which are associated with COVID-19 pathogenesis [4-6]. SINE compounds also block essential interactions between SARS-CoV-2 proteins and human XPO1 [7]. Selinexor demonstrates anti-SARS-CoV-2 activity in vitro with 90% inhibition of new virus production at 100nM (manuscript in preparation).

In addition, selinexor and related SINE compounds protect mice from endotoxin- and viral-induced lung injury by reducing pro-inflammatory cytokines and improving survival [8,9]. Selinexor received accelerated approval from the US FDA in combination with dexamethasone as a treatment for patients with advanced multiple myeloma, and >3,200 patients have received selinexor alone or in combination with other anti-neoplastic agents in clinical studies with adequate tolerability [10]. Given the urgency of the COVID-19 pandemic, the preclinical efficacy, and safety and tolerability observed in multiple early-phase clinical trials, selinexor may confer both anti-viral and anti-inflammatory activity in SARS-CoV-2 infected patients. Here, we report the first case of a COVID-19 patient treated with low dose selinexor (20

mg three times weekly) and his early clinical response following dosing.

Case Description

AA 69-year-old Hispanic male (80.2kg, 1.75m, ~1.95 m^2) with a past medical history of hypertension presented to Lehigh Valley Hospital Allentown, PA on April 21, 2020 with complaints of increasing weakness, confusion, decreased appetite, and shortness of breath. The patient was found to be SARS-CoV-2 positive on April 13, 2020, which was confirmed during hospital admission on Day 1 and Day 3. The family reported that the patient had been febrile for 10 days and treated at home by his primary care physician with ivermectin. The patient was living with three additional family members reported to be ill. Upon arrival to the emergency room (Day 1), the patient was afebrile, tachypneic with a respiratory rate of 30-33 breaths per minute (bpm), blood pressure of 102/89mmHg, and heart rate of 133-88 beats per minute. He was hypoxic on room air, requiring 2L/min O_2 via Nasal Cannula (NC) to maintain his oxygen saturation (SaO_2 via pulse oximetry) >90%.

Laboratory tests showed an elevated white blood cell count (WBC, 13×109/L), creatinine (1.31μmol/L), Na (129mEq/L), and transaminitis with AST (101 U/L) and ALT (99 U/L). On Day 2 of the hospital admission, the patient became increasingly confused and was placed on 6 L/min O_2 via NC to maintain SaO2 >90%. He developed progressive confusion and worsening hypoxia later that day and was switched to 70% FiO_2 via facemask. On Day 3 the patient's respiratory rate was 21-25 bpm and the chest x-ray showed stable hazy bilateral infiltrates. On Day 4, the patient was more alert on 70% FiO_2 via facemask with the following vital signs: temperature 99.1°F, heart rate 99 beats per minute, blood pressure 146/89mmHg, respiratory rate 20bpm, and SaO_2 94%. The patient subsequently decompensated and was transferred to the ntensive Care Unit (ICU) on Day 5, where he received 65-70% FiO_2 via Nasal High Flow (NHF) therapy (Optiflow, NC) to maintain SaO_2 >90%. The patient became increasingly lethargic but did not require vasopressors or mechanical ventilation.

Methods

For analysis, the patient's medical records - including clinical characteristics and treatment, laboratory parameters, chest X-rays, and treatment - were collected. This case study was approved by the institutional review board of the Lehigh Valley Health Network, and informed consent was obtained.

Selinexor Dosing

The patient received 6 doses of 20 mg oral selinexor over a period of 2 weeks.

Results

Upon admission to the ICU on hospital Day 5, the patient was receiving 60-70% FiO_2 via NHF therapy, and was afebrile, lethargic, and confused. The patient was ineligible for the clinical trial Evaluation of Activity and Safety of Oral Selinexor in Participants With Severe COVID-19 Infection (Coronavirus) (XPORT-CoV-1001, NCT04349098) due to a serum sodium level <135mmol/L (an exclusion criteria), and was subsequently enrolled on the Karyopharm Expanded Access Program (KEAP). The patient was characterized to a medium-risk group of developing critical illness among patients with COVID-19 based on 10 variables measured on admission [11]. On Day 8, the patient began oral selinexor 20mg three times per week (every other day). That afternoon, he improved sufficiently to receive 10L/min O_2 via NC. The patient's O_2 requirement decreased to 8L/min NC O_2 on Day 9, further decreasing to 6L/min NC before transfer from the ICU to the COVID-19 hospital ward. The respiratory rate was 20-23 bpm on Day 8 and improved to <20 bpm on Day 9. His condition continued to improve and he became more interactive and ambulatory by Day 10, with O_2 requirements decreased to 5L/min NC and then 4L/min NC.

Three days after the first dose of selinexor (Day 11), the patient was transferred to a regular floor and was able to talk and eat without desaturating while receiving 3L/min NC. In the evening of Day 11, with no assistance, his SaO_2 was 94-96% through discharge on Day 15, within 7 days after initiating selinexor treatment. Prior to starting therapy, the patient had elevated inflammatory markers which improved rapidly and significantly after starting selinexor. Most notably, C-Reactive Protein (CRP) decreased from 196.0mg/L upon admission (Day 1) to 13.9mg/L after 2 doses of selinexor (Day 10), with a further reduction to 5.5mg/L on Day 12. Comparable effects were observed for IL-6: 11pg/mL on Day 8 prior to selinexor dosing to <5pg/mL on Day 10, and ferritin (5,735ng/mL to 1,214ng/mL) (Table 1). Other significant substantial improvements following initiation of selinexor included platelet count, which increased progressively throughout treatment from 203 × 10^9/L to 466 × 10^9. The transaminase elevations associated with severe COVID-19 present at hospital admission also improved with reductions in both ALT (99 U/L to 38 U/L) and AST (101 U/L to 32 U/L) (Table 2).

Days from hospital admission	Selinexor dose	RR (bpm)	O_2 Requirement (L/min NC)	Ferritin (ng/mL)	CRP (mg/L)	IL-6 (pg/mL)	Fibrinogen (mg/dL)
Day 1		30-33		5735	196		
Day 3		21-25		5100	140		
Day 8	20mg	20-23	10 → 8 → 6			11	1065
Day 9		<20					
Day 10	20mg		5	1150	13.9	<5	
Day 11		18	4				
Day 12	20mg		1	1214	5.5		
Day 13							
Day 14	20mg						
Day 15					<3.0		582
bpm: Breaths Per Minute; CRP: C-Reactive Protein; IL-6: Interleukin-6; RR: Respiratory Rate							

Table 1: Respiratory and inflammatory assessments.

	Day 1 (Admission)	Day 8	Day 11	Day 15 (Discharge)
CBC				
Hemoglobin (g/dL)	14	14.6	13	14.5
Hematocrit (%)	42	43.3	38.2	42.5
WBC ($X10^9$ cells/L)	13	6.5	3.5	5.1
RBC (million/mm^3)	4.6	4.59	4.06	4.6
Platelet Count ($X10^9$ cells/L)	203	523	460	Clumped platelets
MPV (fL)	8.6	8.9	9.3	Test not performed
MCV (fL)	92	94	94	93
MCH (pg)	31.3	31.8	32.1	31.6
MCHC (g/dL)	33.9	33.7	34.2	34.2
RDW (%)	13.1	13.6	13	13
CHEMISTRY				
Glucose (mg/dL)	198	102	114	105
BUN (mg/dL)	14	32	24	19
Creatinine (mg/dL)	1.31	1.02	0.88	1
Sodium (mEq/L)	129	140	131	130
Potassium (mEq/L)	4.9	4.2	5.2	5.1
Chloride (mEq/L)	101	107	100	101
Carbon Dioxide (mEq/L)	22	24	28	22

Anion Gap (mEq/L)	6	9	3	7
GFR, Calculated (mL/min/1.73 m^2)	55	75	88	76
Albumin (g/dL)	2.5	2.4	2.5	2.7
Calcium (mg/dL)	8.1	9.5	8.8	8.6
Protein, Total (g/dL)	7.1	7.6	7.2	6.9
Bilirubin, Total (mg/dL)	0.7	0.7	0.3	0.6
AST (Units/L)	101	36	32	38
ALT (Units/L)	99	49	38	54
Alkaline Phosphatase (IU/L)	2.5	115	100	93

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BNP: Brain Natriuretic Peptide; BUN: Blood Urea Nitrogen; CBC: Complete Blood Count; GFR: Glomerular Filtration Rate; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; MPV: Mean Platelet Volume; RBC: Red Blood Cell; RDW: Red Cell Distribution Width; WBC: White Blood Cell

Table 2: Laboratory results during course of hospitalization.

Discussion

Selinexor and related SINE compounds have shown potent in vitro and in vivo anti-viral activity against a broad range of RNA and DNA viruses. Here we report a case of a patient with severe COVID-19 and progressive hypoxia and at high risk for progressive respiratory failure who responded to low dose selinexor without any reported adverse effects. The changes observed following administration of selinexor-particularly the dramatic clinical improvements in a patient who was rapidly decompensating with profound hypoxia and mental status changes, as well as reductions in CRP and ferritin-suggest that selinexor may confer both anti-viral and anti-inflammatory activity and may be a feasible approach to reducing overall disease burden and improving prognosis in patients with severe COVID-19.

Conclusion

This is the first report to demonstrate the possible activity of selinexor in a SARS-CoV-2-infected patient. Combined with the established safety and tolerability, these data may translate to the broader application of selinexor to the COVID-19 patient population. The safety and adverse event profile of selinexor in patients with severe COVID-19 is currently being assessed in a placebo-controlled randomized global trial (NCT04349098).

Acknowledgments

This study was supported by research funding from Karyopharm Therapeutics, Inc. JetPub Scientific Communications LLC, supported by Karyopharm Therapeutics, Inc., assisted in the preparation of this manuscript, in accordance with Good Publication Practice (GPP3) guidelines.

Conflict of Interest

The authors declare no competing financial interests.

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