more evidence-based management recommendations for these patients. Until more data arise, the recommendations we provide herein can be used based on clinicians' best judgment.

CONFLICTS OF INTEREST

The authors report no conflicts of interest relevant to this work.

FUNDING INFORMATION

None.

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DOI 10.1002/ajh.25857

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Received: 12 May 2020 | Accepted: 13 May 2020

DOI: 10.1002/ajh.25870

Granulocyte-colony stimulating factor in COVID-19: Is it stimulating more than just the bone marrow?

To the Editor:

Granulocyte-colony stimulating factor (GCSF) is routinely administered in cancer patients as prophylaxis or treatment of neutropenia. Although the safety profile of GCSF use in patients with symptomatic COVID-19 disease is unclear, lung findings from autopsies of patients showed neutrophil extravasation in the alveolar space.[1] It is known that severe cases of COVID-19 have been reported to have a higher absolute neutrophil count (ANC)-absolute lymphocyte count (ALC) ratio[2]; both reported findings raise questions about the appropriate timing of administering growth factors to neutropenic patients with SARS-CoV-2 infection.

Although clear causal evidence of GCSF administration leading to worse outcomes in COVID-19 patients does not yet exist, there

are concerns regarding the potential for increased pulmonary inflammation and macrophage activation with GCSF use in this setting.[3] Currently, there are no standardized treatments or medications available to treat COVID-19, so it is crucial to identify factors such as GCSF that may lead to a more severe outcome in COVID-19 patients.

Herein, we describe three patients who received GCSF and developed severe disease from COVID-19 within 72 hours of administration. All patients were admitted to the hospital in late March 2020 for symptomatic COVID-19 infection, proven by qualitative RNA PCR assay. All three patients had a severe infection with SARS-CoV-2 and received hydroxychloroquine 400 mg twice a day for the first day, followed by 200 mg twice a day for four days, for a total five day course in accordance with hospital criteria that were in place at that time.

Patient 1: A 65-year-old male with relapsed acute myeloid leukemia, on a regimen of azacitidine and venetoclax, with last dose one month prior to admission, had persistent neutropenia of one month duration prior to his admission for fever of 38.7°C and neutropenia. The ANC was 0.3 K/mcl and pulse oximetry was 99% on room air. Chest X-ray performed on the day of admission (hospital day 0) showed diffuse bilateral patchy lung opacities (Supplementary Figure 1). Upon hospital admission, he was empirically treated with aztreonam and vancomycin and received 480 mcg of filgrastim (GCSF) subcutaneously (SC) for neutropenia.

On hospital day 2 (twenty-four hours after his dose of GCSF), the patient had worsening oxygen requirements necessitating intubation and transfer to the intensive care unit (ICU). Repeat chest X-ray showed increased bilateral lung opacities (Supplementary Figure 1). Laboratory workup revealed an increase in ANC to 2.2K/mcL (Table 1).

On day 3 of hospitalization, he developed new atrial fibrillation and increasing vasopressor requirements. His ANC rose to 4.3K/mcL with rapidly rising ANC/ALC ratio. His hospital course was further complicated by recalcitrant shock, metabolic acidosis, and rising oxygen requirements. Discussion of goals of care with the family led to his terminal extubation. The patient expired on hospital day 12; on the day of death, the ANC/ALC ratio reached a maximum value of 11.

Patient 2: A 35-year-old female, had mediastinal diffuse large B-cell lymphoma who underwent autologous stem cell transplant in January 2020, was admitted for fever and dry cough. Upon admission, she was hemodynamically stable except for a fever of 38.1°C. Her oxygen saturation was 99% on room air. Workup on admission revealed a normal chest X-ray and ANC of 4.1 K/mcL. During the first 2 days of hospitalization, the patient remained febrile, but otherwise hemodynamically stable and without an oxygen requirement. On hospital day 3, she developed worsening leukopenia with nadir ANC of 0.6 K/mcl. She remained febrile and was treated with piperacillin-tazobactam empirically for fever and neutropenia. Chest X-ray on day 3 revealed bilateral patchy lung opacities. On hospital day 5, she received a dose of GCSF 480 mcg SC and her ANC increased to 10.7 K/mcl 2 days later. The ANC decreased again to 0.6 K/mcl on day 12 of hospitalization for which she received a second dose of GCSF 480 mcg SC; the following day her ANC increased to 20.2 K/mcl.

On day 14 (forty-eight hours after her second dose of GCSF), the patient developed increasing shortness of breath with rapid oxygen desaturation (nadir 78% on room air) requiring oxygen supplementation via a non-rebreather mask at 15 L/min. She had a rapidly rising ANC/ALC ratio in relation to clinical decline with maximal value of 22.63. Her chest CT revealed increased bilateral opacities at which time she also developed hypotension and tachycardia. Her oxygen requirements increased necessitating high flow oxygen. She slowly improved and was discharged on day 33 of hospitalization with a lower ANC/ALC ratio.

Patient 3: A 58-year-old woman with invasive ductal carcinoma of the breast on doxorubicin and cyclophosphamide (last dose 10 days prior to admission) was admitted with fever and neutropenia (ANC on admission 0.6K/mcl). On admission, she was febrile to 39.2°C She was hemodynamically stable with an oxygen saturation of 99% on room air. She denied cough, chest pain or shortness of breath on admission.

She was treated with cefepime at 2 g every 8 hours for neutropenic fever. Chest X-ray revealed faint bilateral opacities. She received GCSF at 480 mcg SC on the day of her admission.

On day 2 of hospitalization, her ANC increased to 7.5 K/mcl but she still received a second dose of GCSF 480 mcg SC on this day. On hospital day 3, she became increasingly tachypneic (respiratory rate 30 breaths/minute) and was placed on 2 L oxygen by nasal cannula. Her laboratory workup revealed an elevation in her ANC to 16.5 K/mcl (hospitalization day 3) with a peak ANC/ALC ratio of 75. Repeat chest X-ray demonstrated worsening bilateral multifocal opacities.

On day 5 of hospitalization, she was transferred to the ICU for worsening respiratory distress and was intubated on the same day. On hospital day 7, she developed acute respiratory distress syndrome and multiple organ failure and remained intubated for twenty days. Chest X-ray on day 13 revealed worsening lung findings. She was extubated on hospital day 25, and currently remains hospitalized but in stable condition. Later in her hospital course, she was noted to have a progressive decrease in the ANC/ALC ratio, correlating with clinical improvement in her respiratory symptoms.

Data regarding outcomes in cancer patients with COVID-19 infection across the world are evolving. Febrile neutropenia is a major risk factor for infection related morbidity in cancer patients. Increased morbidity and mortality have been described in COVID patients with cancer as well as in those with comorbid medical conditions.[4]

To our knowledge, this is the first report describing the course of COVID-19 infection in selected cancer patients who received GCSF for neutropenic fever in the United States. All three patients developed a rising NLR >3 at 24 hours after GCSF administration. At 72 hours after administration of GCSF, all three patients had NLR >5 and suffered respiratory decline. The increase in ratio correlated with clinical decompensation as defined by worsening respiratory failure (Supplementary Figure 2). Of these, two patients with age >50 years and comorbid medical conditions developed decline severe enough to require mechanical ventilation.

TABLE 1 Demographics table outlining pertinent clinical characteristics, laboratory values and clinical course.

Variable	Patient 1	Patient 2	Patient 3
Age – year	65	35	58
Gender	Male	Female	Female
Weight kg	98.4	60.8	122.8
BMI kg/m^2	29.1	22.1	46.8
Comorbidities	Hypertension, diabetes mellitus type 2, hepatitis C	None	Obesity
Smoking history	Never smoker	Never smoker	Never smoker
Cancer type and stage	Metastatic prostate cancer Relapsed acute myeloid leukemia on therapy	Diffuse large B-cell lymphoma status post autologous stem cell transplant 1/2020	Invasive ductal breast carcinoma on doxorubicin and cyclophosphamide
COVID 19 symptoms	Fever, myalgias, dyspnea, diarrhea	Fever, cough	Fever
GCSF total dose Dose day (480microgram vial)	4.8microgram/kg Admission day	7.8microgram/kg One dose each on days 5 + 8	3.9microgram/kg One dose each on days 1 + 2
ANC (K/mcL)		(Post dose 2)	(Post dose 2)
Admission	0.3	4.1	0.6
GCSF day ("Day 0")	0.3	0.6	7.5
Day +1	2.2	20.2	16.2
Day +2	4.8	18.1	10.2
Day +3	4.3	7.5	5.4
ALC (K/mcL)		(Post dose 2)	(Post dose 2)
Admission	0.7	0.5	0.3
GCSF day ("Day 0")	0.4	0.4	0.1
Day +1	1.3	1	0.3
Day +2	0.9	0.8	0.6
Day +3	0.4	0.6	0.3
Anti-infective treatment	Hydroxychloroquine Aztreonam Vancomycin	Hydroxychloroquine Piperacillin-tazobactam	Hydroxychloroquine Cefepime
Clinical Course Day +1 Day +2 Day +3	Increasing hypoxia Intubation Shock, increasing hypoxia	(Post dose 2) Shortness of breath Hypoxia: 78% room air Hypotension, no intubation	(Post dose 2) Tachypnea 2L oxygen Worsening hypoxia Day +5 intubation
IL6 (pg/mL) 48h post -GCSF	68.2	13.5	82.1
CRP (mg/dL) 48h post-GCSF	6.09	0.49	15.45
D dimer (mcg/mL) 48h post-GCSF	0.36	0.32	0.66
IL-10 (pg/mL) 48h post-GSF	164	<9	26
Procalcitonin (ng/mL) 48h post G-CSF	0.12	0.03	0.4
Ferritin (ng/mL) 48h post G-CSF	2790	56	2056

Normal range for above laboratory findings: IL6 [0-16.4 pg/mL], CRP <10mg/dL, D-dimer <0.50 mg/L, IL10 [4.8-9.8 g/mL], Procalcitonin [0.10-0.49 ng/mL], Ferritin [12-300 ng/mL].

These two patients also had high IL 6 levels. Although increasingly described, the genesis of the cytokine release state in COVID-19 remains poorly understood.

Data from China has shown that in patients over age 49.5 years and with ANC/ALC ratio >3.3, 46.1% of COVID-19 patients with mild disease will develop severe disease and that the mean time to such development

is 6.3 days.[5] This case series draws attention to the fact that GCSF can cause rapidly rising NLR ratio >3 within 24 hours of administration.

In the setting of COVID-19 illness, further rapid rise in neutrophilia with NLR ratio >5 may portend respiratory deterioration to the point of mechanical ventilation within the next 72 hours, especially in those patients who are older than age 50 and have comorbid medical conditions.

Limitations exist in our case series. This represents only a small number of patients who specifically came to our attention because they declined within 72 hours after receiving GCSF. Another limitation is missing data points regarding pre GCSF IL6 and other such markers, as these laboratory investigations were not performed on patients who initially had normal oxygenation on room air at admission.

Larger scale studies are needed to delineate the relationship between GCSF administration and progression of COVID-19 infection from mild to severe stage in high risk patients.

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DOI 10.1002/ajh.25870

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Received: 15 March 2020 | Accepted: 21 April 2020

DOI: 10.1002/ajh.25849

From Hematologist's desk: The effect of COVID-19 on the blood system

To the Editor:

Fan *et al*. critically studied the difference in hematological parameters between the ICU vs non-ICU COVID-19 cases.[1] The study underscores the pertinent hematological parameters, which might help the treating physicians to anticipate ahead of time regarding the potential need of the intensive level of care. COVID-19 is a rapidly evolving and emerging disease, and AJH readers would certainly benefit from further discussion and refinement.

Concern over coagulation abnormalities in COVID-19 patients: Fan et al did not discuss the coagulation parameters of their patient series.[1] Currently, the exact significance of coagulopathy in COVID-19 patients is yet to be determined. But preliminary results from recent studies have shown that a high D-dimer value correlates with ICU requirement and a higher mortality, when compared to individuals with normal/mild elevation of the D-dimer levels.[2] Tang et al recently reviewed 183 cases of COVID-19 patients and studied their coagulation pattern.[3] They found that the non-survivors had significantly higher D-dimer values ($P < .001$), fibrin degradation product (FDP) values ($P < .001$), longer prothrombin time ([PT in seconds] $P < .001$) when compared to survivors at admission. Fibrinogen levels ([g/L], $P = .149$), antithrombin activity (AT [%], $P = .096$), and activated partial thromboplastin time ([APTT in seconds], $P = .096$) were not significantly different between the two groups. Also, at follow up during the hospital stay, Tang et al found 71.4% of non-survivors end up having disseminated intravascular coagulation (DIC) as compared to only 0.6% of survivors.

Lack of data of thrombosis in COVID-19 patients: Thrombosis is another hematological challenge while managing sick patients. Did any