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Special considerations in the management of patients with myelodysplastic myndrome / myeloproliferative neoplasm overlap syndromes during the SARS-CoV-2 pandemic

To the Editor:

The ongoing pandemic with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and resultant coronavirus disease 2019 (COVID-19) is resulting in high mortality and morbidity worldwide.[1,2] While the exact impact of SARS-CoV-2 in cancer patients remains to be defined, early reports, especially from China, suggest an increased mortality in those older than 60 years, those with pulmonary compromise or hematological malignancies.[3] The virus SARS-CoV-2 uses the angiotensin converting enzymes-related carboxypeptidase (ACE2) receptor to gain entry into cells, with these receptors widely expressed in the cardiopulmonary system, monocytes and monocyte-derived macrophages.[4] Monocytes and macrophages frequently interact with ACE2-expressing cells in various tissues, and ACE2 is also expressed by cells of the bone marrow (BM) niche, where it associates with the granulocyte-colony stimulating factor (G-CSF) receptor to negatively regulate hematopoietic progenitor cells mobilization (supplemental material for complete reference list in Data S1).

The cytokine profile of patients with COVID-19 resembles that of patients with secondary hemophagocytic lymphohistiocytosis (HLH), with the excess production of interleukin 2 (IL-2), IL-6, G-CSF, interferon gamma inducing protein 10, monocyte chemoattractant protein-1 and tumor necrosis factor (TNF) alpha, among others.[5,6] Severe manifestations of SARS-CoV-2 are largely cytokine mediated and include cytokine release syndrome (CRS), respiratory failure secondary to acute respiratory distress syndrome (ARDS), and multiorgan dysfunction syndrome (MODS) (Figure S1).[1,2,5] Note, IL-6 is a prominent secreted cytokine and plays a critical role in the inflammatory cascade seen.[6] This has led to the use of IL-6 and IL-6 receptor (IL-6-R)-directed monoclonal antibodies such as siltuximab (IL-6) and tocilizumab/sarilumab (IL-6-R) in the management of CRS and ARDS in patients with COVID-19.

The 2016 iteration of the World Health rganization (WHO) classification of myeloid neoplasms identifies four distinct sub-types of adult onset myelodysplastic syndromes/myeloproliferative neoplasms (MDS/MPN), namely chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia, *BCR/ABL*-negative (aCML), MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T), and MDS/MPN, unclassifiable (MDS/MPN-U).[7] Among these, proliferative variants of CMML, MDS/MPN-U and aCML tend to have persistent leukocytosis along with circulating immature myeloid cells.[8] Proliferative CMML in particular has a proinflammatory phenotype with elevated serum levels of cytokines including IL-6, TNF-alpha, monocyte colony stimulating factor (M-CSF) and IL-1RA[9]; with CMML cells demonstrating an intrinsic hypersensitivity to GM-CSF that is more prominent in RAS-mutant samples.[10] Case series have described exaggerated leukemoid reactions, CRS, ARDS and MODS in CMML patients who have undergone surgery, or in response to infections/inflammation; given the abundance of ACE2 receptors experessed on monocytes and macrophages, we hypothesize that these patients are particularly susceptible to the cytokine-related complications of SARS-CoV-2.[11]

We describe a 69-year-old man with symptomatic (constitutional symptoms), proliferative, *ASXL1*, *NRAS*, *TET2* mutated- CMML-0 with a normal karyotype, who had a stable white blood cell count (WBC) of ~35×10^9/L for 6 months, regulated on hydroxyurea. A donor search for allogenic hematopoietic cell transplant had been initiated. Further dose increments in hydroxyurea to try to better control his leukocytosis were not tolerated, due to anemia and thrombocytopenia. The patient was admitted with high grade fever and hypoxic respiratory failure to his local hospital. His WBC on admission was 90×10^9/L with neutrophilic series left-shift and he went on to develop ARDS and MODS, necessitating assisted ventilation. He was diagnosed with SARS-CoV-2 and died prior to the administration of anti-cytokine directed therapies.

Given the paucity of evidence for the management of hematological malignancies during this pandemic and the proinflammatory milieu of proliferative MDS/MPN overlap neoplasms, we formed an ad hoc expert panel to help draft consensus emergency recommendations for the management of COVID-19 in these patients. The committee also reviewed available cytokine-directed clinical trials for SARS-CoV-2 and summarized details of therapies of particular interest to patients with proliferative MDS/MPN-overlap neoplasms (Table 1).

Permissive leukocytosis in these pateints to a degree that may be reasonable in other settings may put patients at increased risk for complications in the COVID-19 era, and tighter regulation of the WBC is a worthwhile consideration. This has to be carefully balanced with the potential need for additional blood draws and clinic visits, including blood product transfusions for worsening cytopenias. In a clinically suspected case of SARS-CoV-2 in an MDS/MPN patient, frequent monitoring of CBC, with use of additional doses of hydroxyurea to control an evolving leukemoid reaction may be beneficial, though this is unclear. The use of corticosteroids as antinflammatory agents is somewhat controversial, given concerns of potentially increasing ACE-2 expression and viral replication/decreasing viral clearance, and should be used with caution. In the event of CRS or ARDS, treating

TABLE 1 Cytokine signaling-associated clinical trials for COVID patients

NCT number	Drug name	Mechanism of action	Phase	Enroll #	Arms	Dosage	Location	Recruitment status
NCT04322773	Tocilizumab vs. Sarilumab	IL-64 antagonists	2	200	Tocilizumab	Single Dose 400 mg (IV)	Denmark	Yes
					Tocilizumab	Single Dose 2 × 162 mg (sc)		
					Sarilumab	Single Dose 1 × 200 mg (sc)		
NCT04324073	Sarilumab	IL-6R antagonist	2,3	240	Sarilumab	Single Dose 1 × 400 mg (IV)	France	Yes
NCT04327388	Sarilumab	IL-6R antagonist	2,3	300	Sarilumab	Single Dose 1 concentration (IV)	Canada, France, Italy, Spain	Yes
					Sarilumab	Single Dose 2 concentration (IV)		
NCT04341870	Sarilumab	IL-6R antagonist	2,3	60	Sarilumab in combo with ([a]):	Single Dose 400 mg (IV) on D1	France	Not open yet
					[a]Azithromycin	Oral, 500 mg on D1, 250 mg D2-D5		
					[a]Hydroxychloroquine	Oral, 600 mg QD (200 mg TID) on D1-D10		
					Sarilumab alone	Single Dose 400 mg IV		
NCT04315298	Sarilumab	IL-6R antagonist	2,3	400	Sarilumab	Single Dose (IV) low dose	US	Yes
					Sarilumab	Single Dose (IV) high dose		
					Placebo	Single Dose (IV) to match Sarilumab		
NCT04329650	Siltuximab	IL-6 antagonist	2	100	Siltuximab	Single Dose (IV) 11 mg/Kg	Spain	Not open yet
					Methylprednisolone	250 mg/24 h (IV) × 3 d followed by 30 mg/24 h × 3 d		
NCT04331795	Tocilizumab	IL-6R antagonist	2	50	Tocilizumab (with risk factors)	Single Dose 200 mg (IV)- 2nd dose if needed	US	Yes
					Tocilizumab (without risk factors)	Single Dose 80 mg (IV)- 2nd dose if needed		
NCT04315480	Tocilizumab	IL-6R antagonist	2	38	Tocilizumab	Single Dose (IV) 8 mg/kg	Italy	Active, not recruiting
NCT04335071	Tocilizumab	IL-6R antagonist	2	100	Tocilizumab	Single Dose (IV) 8 mg/kg	Switzerland	Not open yet
						Placebo	Single Dose (IV) 100 mL of NaCl 0.9%	
NCT04320615	Tocilizumab	IL-6R antagonist	3	330	Tocilizumab	Single Dose by IV	US, Canada, Denmark, France, Germany, Italy, UK, Spain	Yes
					Placebo	Single Dose by IV		
NCT04317092	Tocilizumab	IL-6R antagonist	2	400	Tocilizumab	Single Dose 8 mg/kg (IV)	Italy	Yes
NCT04332094	Tocilizumab	IL-6R antagonist	2	276	Tocilizumab in combo with ([a]):	Two Doses on Day 1: 162 mg (sc) 12 h apart	Spain	Yes
					[a]Azithromycin	Oral, 500 mg on D1-D3		
					[a]Hydroxychloroquine	Oral, 400 mg/12 h D1,200 mg/12 h for D2-D6		

TABLE 1 (Continued)

NCT number	Drug name	Mechanism of action	Phase	Enroll #	Arms	Dosage	Location	Recruitment status
					Azithromycin with ([a]):	Oral, 500 mg on D1-D3		
					[a]Hydroxychloroquine	Oral, 400 mg/12 h D1, 200 mg/12 h for D2-D6		
NCT04335305	Tocilizumab with Pembrolizumab	IL-6R antagonist (Toc); Immune check point block (Pem)	2	24	Tocilizumab with ([a]):	Single Dose 8 mg/kg (IV)		Not open yet
					[a]Pembrolizumab	Single Dose 200 mg (IV)		
NCT04339712	Anakinra vs. Tocilizumab	IL-1R antagonist (Ana)	2	20	Tocilizumab	In case of immune dysregulation: single dose 8 mg/kg (IV)	Greece	Not open yet
		IL-6R antagonist (Toc)			Anakinra	Incase of MAS: 200 mg × 3 daily for 7 d (IV)		
NCT04330638	Anakinra, Anakinra with Siltuximab, Tocilizumab, Tocilizumab with Anakinra	IL-6 antagonist (Sil); IL-1R antagonist (Ana); IL-6R antagonist (Toc);	3	342	Anakinra	Daily 100 mg (sc) for 28 d	Belgium	Yes
					Siltuximab	Single Dose 11 mg/kg (IV)		
					Anakinra with ([a]):	Daily 100 mg (sc) for 28 d (or until discharge)		
					[a]Siltuximab	Single Dose 11 mg/kg (IV)		
					Tocilizumab	Single Dose 8 mg/kg (IV)		
					Anakinra with ([a]):	Daily 100 mg (sc) for 28 d		
					[a]Tocilizumab	Single Dose 8 mg/kg (IV)		
NCT04341584	Anakinra	IL-1R antagonist	2	240	Anakinra	2 × 200 mg (IV) on D1-D3, 2 × 100 mg (IV) on D4, 1 × 100 mg (IV) on D5	France	Not open yet
NCT04324021	Emapalumab or Anakinra	IFN-γ inhibitor (Ema); IL-1R antagonist (Ana)	2,3	54	Emapalumab	D1: 6 mg/kg (IV), D4, D7, D10, D13 3 mg/kg (IV)	Italy	Yes
					Anakinra	400 mg/kg (V) 4 × daily for 15 d		
NCT04337216	Mavrilimumab	GM-CSFR α monoclonal	2	10	Mavrilimumab	Single Dose (IV)	US	Not open yet
NCT04326920	Sargramostim	Recombinant GM-CSF	4	80	Sargramostim	Inhalation via nebulizer (125μg) for 5 d -continue with IV if patient requires mechanical ventilation	Belgium	Yes
NCT04331899	Peginterferon Lambda-1 alpha	IFN-α mimetic	2	120	Peginterferon Lambda-1 alpha	Single Dose (sc) 180μg	US	Not open yet
NCT04320238	rHu interferon α-1b with or without thymosin alpha 1	rHu IFN-α1b Immune modulator(Thy)	3	2944	rHu IFN-α1b	Nasal drops: 2-3 per nostril × 4 times a day	China	Yes
					rHu IFN-α1b with ([a]): thymosin alpha 1	Nasal drops: 2-3 per nostril × 4 times a day sc 1 × per week		
NCT04280588	Fingolimod	Sphingosine-1-phosphate receptor modulator	2	50	Fingolimod	Oral 0.5 mg daily × 3 d	China	Yes

(Continues)

TABLE 1 (Continued)

NCT number	Drug name	Mechanism of action	Phase	Enroll #	Arms	Dosage	Location	Recruitment status
NCT04275245	Meplazumab	humanized anti-CD147 Ab	2	20	Meplazumab	10 mg (IV) × 2 d, once per day	China	Yes
NCT04268537	PD-1 blocking Ab	Immune check point block	2	120	PD-1 blocking Ab Thymosin	Single Dose 200 mg (IV) 1.6 mg sc qd, × 5 d	China	Not open yet
NCT04317040	CD24Fc	Inflammatory cytokine inhibitor	3	230	CD24Fc	Single Dose 480 mg (IV)	US	Yes
NCT04333472	Piclidenoson	Inflammatory cytokine inhibitor	2	40	Piclidenoson	Oral, 2 mg every 12 hs for up to 21 d	Israel	Not open yet
NCT04338802	Nintedanib	Tyrosine kinase inhibitor	2	96	Nintedanib	Oral, 150 mg 2 × daily for 8 weeks	China	Not open yet
NCT04340232	Baricitinib	JAK inhibitor	2,3	80	Baricitinib	Oral, 2 mg once daily for 14 d	US	Not open yet
NCT04320277	Baricitinib in combo with Ritonavir	JAK inhibitor (Bar) anti-viral (Rit)	3	60	Baricitinib (mild cases) Baricitinib (moderate cases)	Oral, 4 mg once daily × 2 weeks; Ritonavir 600 Oral, 4 mg once daily × 2 weeks; Ritonavir 600	Italy	Yes
NCT04331665	Ruxolitinib	JAK inhibitor	NA	64	Ruxolitinib	Oral, 10 mg twice daily D1-D14, 5 mg twice daily D15-D16, 5 mg once daily on D17	Canada	Not open yet
NCT04338958	Ruxolitinib	JAK inhibitor	2	200	Ruxolitinib	Oral, 2 × 10 mg per day with defined response adapted dose escalation up to 2 × 20 mg for 7 d	Germany	Not open yet
NCT04334044	Ruxolitinib	JAK inhibitor	1,2	20	Ruxolitinib	Oral 2 × 10 mg per day for 14 d	Mexico	Not open yet
NCT04332042	Tofacitinib	JAK inhibitor	2	50	Tofacitinib	Oral, 10 mg twice daily for 14 d	ITaly	Not open yet
NCT04321993	Baricitinib Sarilumab Hydroxychoroquine sulfate Lopinavir/ritnavir	JAK inhibitor (Bar) IL-6R antagonist (Sar) Inflammatory cytokine inhibitor (Hyd) Protease inhibitor (Lop)	2	1000	Baricitinib Sarilumab Hydroxychoroquine sulfate Lopinavir/Ritnavir	Oral, 2 mg once a day for 10 d Single Dose 200 mg (sc) Oral, 2 × 200 mg daily for 10 d Oral, 2 × 200 mg/50 mg daily for 10 d	Canada	Not open yet
NCT04341675	Sirolimus	mTOR inhibitor			Sirolimus	Oral, 6 mg once on D1, 2 mg once a day D3-D13	US	Not open yet
FDA approved compassionate use	Lenzilumab	anti-GM-CSF antibody	Pre-3		Approved Apr 2, 2020	Sponsor: Humanigen, Inc.	US	https://apnews.com/ACCESS WIRE/738d3526740dee777dacee2b6b8a836f

Abbreviations: Terminology Key: NCT, national clinical trial; IV, intravenously; sc, subcutaneous injection; IL-6, interleukin-6; IL-6R, interleukin-6 receptor; IFN-γ, interferon gamma; GM-CSFR α, granulocyte-macrophage colony-stimulating factor receptor alpha; rHu, recombinant human; IFN-α1b, interferon alpha 1b; CD147, cluster of differentiation 147; Ab, antibody; JAK, janus kinase; D1, Day 1; NaCl, sodium chloride; mg/kg, milligram per kilogram; MAS); μg, microgram; qd, once a day; bid, twice a day.

[a]All trials were identified from https://www.clinicaltrials.gov using filter criteria: COVID, 2019-nCOV, SARS-CoV-2.

physicians should consider potential early access to clinical trials or off-label use of anti-IL-6 therapies (Table 1). This recommendation is of particular importance in CMML, given that *TET2*, which is the most frequently mutated gene in CMML (60%), encodes a protein involved in the negative regulation of *IL6* gene expression. This suggests that *TET2*-mutant patients may not be able to down-regulate IL-6 once the inflammatory cascade has been initiated.[12]

IL-6 signals through three pathways: (a) cis signaling in immune cells, where it binds to membrane-bound IL-6-R in a complex with gp30 and activates JAK-STAT3, (b) trans signaling, where IL-6 binds to soluble IL-6-R and then forms a complex with gp130 on potentially all cell surfaces, especially the endothelium, activating JAK-STAT3 (cytokine storm and endothelial dysfunction), and (c) trans presentation, where IL-6-R binds to gp130 on T-helper cells (Th17) leading to accentuated T cell signaling.[13] Current evidence points towards IL-6-R antagonists' being superior to IL-6 neutralizing antibodies, due to the ability of the former in blocking trans presentation of IL-6, an important mechanism in the development of acute lung injury and ARDS.[13] Preliminary data from China in SARS-CoV-2 with tocilizumab seems encouraging, with oxygen requirements being reduced in 75% of tocilizumab-treated patients (n = 21). Clinical trials with sarilumab and siltuximab continue to accrue.

Given the inherent hypersensitivity of CMML cells to GM-CSF (granulocyte macrophage), additional anti-cytokine therapy using anti-GM-CSF monoclonal antibodies such as lenzilumab may also be considered. Of note, lenzilumab has been shown to abrogate neurotoxicity and CRS by neutralizing GM-CSF in chimeric antigen receptor T-cell mice models.[14] In addition, a recent phase 1 study of lenzilumab in CMML demonstated clinical benefit in 27% of patients, without any drug-related grade 3 or 4 adverse events.[10] Mavrilimumab, a GM-CSF receptor alpha directed mononclonal antibody is also being considered for the management of CRS in SARS-CoV-2. Additional cytokine-directed clinical trials that might have value in the context of SARS-CoV-2 induced CRS include studies with anakinra (IL-1beta receptor antagonist), empalumab (monoclonal antibody to interferon gamma, currently approved for HLH) and JAK inhibitors (ruxolitinib, pacritinib) (Table 1). We continue to closely watch these studies for safety and efficacy signals. We recommend that all providers consider documenting any patients with hematological malignancies infected with SARS-CoV-2 in the American Society of Hematology (http://www.ashresearchcollaborative.org/covid-19-registry) and COVID19 and Cancer Consortium (CCC19 http://ccc19.org) registries.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

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Care of patients with hemoglobin disorders during the COVID-19 pandemic: An overview of recommendations

To the Editor:

The outbreak of Coronavirus Disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a global health emergency.[1] Compared to the general population, patients with hemoglobin disorders such as sickle cell disease (SCD) or thalassemia are expected to be more severely affected by COVID-19 due to their preexisting chronic morbidities.[2] The Centers for Disease Control and Prevention does not report any specific indications for patients with hemoglobinopathies. However, it can be hypothesized that the rapid spread of the virus may render these patients fragile when fighting the infection.

SCD, a hematological condition with functional asplenia, puts patients at a greater risk to develop acute pulmonary complications, including viral infections.[2] A study by Hussain et al reported four SCD cases that tested positive for COVID-19.[3] These cases initially presented to the emergency department for a typical vaso-occlusive crisis (VOC), and the clinical course of their SARS-CoV-2 infection was rather mild. Patients had a history of respiratory complications, such as acute chest syndrome (ACS), asthma, or pulmonary embolism, which may be potential risk factors for progressive COVID-19 pulmonary disease in patients with SCD.[3] A series of isolated cases of ACS in SCD patients positive for COVID-19 has been recently reported.[4,5] Therefore, very little clinical experience of infected patients with SCD currently exists. For this reason, we believe that certain recommendations must be followed by healthcare professionals treating any SCD patient infected with SARS-CoV-2.

First, it is important to recognize the clinical manifestations suggestive of rapidly progressive ACS, including multi-organ failure, hepatic dysfunction, thrombocytopenia, and acute kidney injury. Healthcare professionals should differentiate between pneumonia or ACS, and the more diffuse ground glass appearance that is commonly associated with SARS-CoV-2 infection. Caution should be taken towards increased pulmonary pressures and right heart failure as symptoms suggestive of pulmonary hypertension, which can increase the risk of complications of a SARS-CoV-2 infection. Pulmonary and cardiac specialists should be consulted in case of suspicion of pulmonary hypertension. It is also important to recognize the high risk of life-threatening sepsis among SCD patients, whose functional hyposplenism renders them vulnerable to superimposed bacterial infections.

In terms of the therapeutic options for these patients, we recommend early aggressive simple or exchange blood transfusions for SCD patients diagnosed with COVID-19 and manifesting fever and cough, have worsening anemia, evidence of hypoxia and/or lung imaging changes. Exchange transfusions should be initiated in case of progressively worsening hypoxemia and clinical deterioration. Blood products shortage is anticipated during the pandemic, so pre-established transfusion thresholds should be adjusted to include mainly patients with severe anemia or with complications, namely ACS or stroke. There currently exists no evidence that being on hydroxyurea would increase SARS-CoV-2 infection risk. However, it is advisable to avoid the routine use or increasing doses of hydroxyurea to reduce the need for repeated phlebotomy and hospital visits.[2,6] In areas where severe blood shortages are expected due to the pandemic, a low dose of hydroxyurea is recommended in all pediatric patients with sickle cell anemia, who receive regular blood transfusion therapy for primary or secondary stroke prevention.[7] In the absence of regular blood transfusion therapy, hydroxyurea treatment will also decrease the incidence rates of acute vaso-occlusive pain and ACS events.[7] Noteworthy, a treatment with one single dose of tocilizumab (8 mg/kg) was successfully used to treat an adult SCD patient with