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CORRESPONDENCE

COVID-19 outcomes in patients with hematologic disease

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To the Editor:

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel coronavirus of zoonotic origin that emerged in China at the end of 2019. The infection, named Coronavirus Disease 2019 (COVID-19), is now spreading worldwide. As of April 16, 2020, the virus had affected more than 2,000,000 individuals and resulted in over 125,000 deaths worldwide. Mortality can be as high as 15% in elderly patients, and/or in patients with comorbidities [1, 2]. Based on the current available data, the incubation period (time from exposure to symptom development) is estimated as between 2 and 14 days [3]. At present, there are no approved treatment options in Europe and no available vaccine. Avoiding exposure by adhering to recommended hygiene procedures, isolation of infected persons and social distancing are the only prevention strategies recommended by the WHO [4].

Risk factors for COVID-19 severity and death include older age, along with comorbidities such as diabetes, hypertension, or cardiac disease [1, 2]. In addition, data from China suggest that patients with cancer have a significantly higher incidence of severe events (including intensive care unit admission, need of assisted ventilation, death) after contracting the virus (39% versus 8% in patients without cancer) [5]. Another study reported that cancer patients appear to be twice as likely to contract infection with SARS-CoV-2 [6]. Importantly, that study suggests that hospital admission and recurrent hospital visits, inherent to cancer patients' management, are potential risk factors for SARS-CoV-2 infection [6]. To date, very few data are available on COVID-19 outcomes in patients with hematologic diseases. Only one 47-year-old patient with a lymphoma has been included in a previous report [5], and two articles have reported on the course of COVID-19 infection in a 39-year-old patient with chronic lymphocytic leukemia [7] and in a 60-year-old patient with multiple myeloma (MM) [8]. All three patients had a favorable outcome. Nevertheless, these were relatively young, unlike the overall patient population with hematologic neoplasms which is usually aged, comorbid and highly immunosuppressed. These patients are therefore expected to be a particularly vulnerable group for COVID-19. A better characterization of those infected with the virus is important. Here we describe the demographic characteristics, coexisting conditions, imaging findings, and outcomes among patients with hematologic disease and COVID-19 infection.

We included all consecutive adult patients with a hematologic disease admitted to the Hematology Department (inpatient and outpatient admissions) of the Saint-Antoine-Hospital, AP-HP, Paris, France, with laboratory-confirmed COVID-19 infection between March 9 and April 4, 2020 and with at least 10 days of follow-up. A confirmed case of COVID-19 was defined by a positive result on a real-time RT-PCR assay of a specimen collected on a nasopharyngeal swab. We reviewed medical records to collect demographic, clinical, and treatment data and outcomes of COVID-19. All laboratory tests and radiologic assessments, including plain chest radiography and computerized chest tomography, were performed at the discretion of the treating physician.

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COVID-19 was suspected and screened by PCR in 48 patients with a hematologic disease and the infection was identified in 25. Clinical details on hematologic and treatment history and COVID-19 infection are listed in Table 1. The median patient age was 72 (range, 40–96) years, 68% were male. The median duration of symptoms before the COVID-19 PCR assay was performed, was 4 (range, 0–22) days. None of the patients had recently traveled to a country with known transmission such as China, Iran, or Italy, but five had direct contact with a COVID-19 positive family member. Among the remaining patients, six were already hospitalized (none of them in the hematology department) at the time of viral infection symptoms' onset due to a fall episode ($n = 2$), MM diagnosis ($n = 3$) or accidental cardiac drug overdose ($n = 1$). Ten patients had one or more outpatient visits to the hematology department, suggesting a possible nosocomial origin of their infection. In the remaining four patients, the origin of COVID-19 infection was unknown.

The most common symptoms at diagnosis were fever ($n = 22$, 89%), cough ($n = 19$, 79%), and shortness of breath ($n = 19$, 79%). The majority ($n = 20$, 80%) of patients had a lymphoid malignancy, including 10 with MM (40%), and only 4 (16%) had a myeloid malignancy (myelodysplastic syndrome). One patient had paroxysmal nocturnal hemoglobinuria. Patients received a median of 1 (range, 0-6) line of treatment. Fourteen patients (56%) were being treated for their underlying disease at the time of COVID-19 diagnosis, with 10 (40%) receiving corticosteroids. Seven patients had a history of hematopoietic stem cell transplantation (autologous, $n = 5$, allogeneic, $n = 1$, and both, $n = 1$) and one had been treated with anti-CD19 CAR T cells 3 months before. Of note, the four patients with myelodysplastic syndrome received only supportive care, one patient with MM had just been diagnosed and had not initiated therapy, and one with stage A chronic lymphoid leukemia was on a 'wait and watch' strategy. In addition, all patients but two (92%) had additional chronic medical conditions. In particular, 17 (68%) patients had high blood pressure, 8 (32%) were obese, and 6 (25%) had diabetes mellitus. Fourteen (56%) patients had more than one coexisting condition besides the hematologic disease.

As reported elsewhere [1], lymphopenia was common at hospital admission ($n = 23$, 92%), with a median lymphocyte count of 760/μL (range, 150–5910). Only one patient had severe neutropenia at the time of COVID-19 diagnosis (median, 2,350/μL; range, 70–11,400). A computerized tomographic scan of the chest was performed in 14 patients and bilateral ground glass opacities were evident in all of them. A chest radiography was performed in seven additional patients and all radiographs showed bilateral pulmonary opacities.

As of April 16, 2020, with a median follow-up since symptom onset of 29 days (range, 14–40), 13 of the 18 patients (52%) developed acute respiratory distress syndrome (ARDS) [9] and 6 received mechanical ventilation (Supplementary Fig. 1). It was decided not to transfer the remaining seven patients with ARDS to the intensive care unit because of their age and hematological disease history. All patients who did not develop ARDS were alive at last follow-up. Of patients with ARDS, nine died, including two who received mechanical ventilation. The Kaplan–Meier estimate of overall survival at 1 month was 60%.

It is hypothesized that similarly to patients with solid malignancies, those with hematologic neoplasms are more susceptible to COVID-19 and develop severe forms. This study highlighted the following observations: patients with a hematologic malignancy harbored a higher risk of developing a severe form of COVID-19 with ARDS, requiring mechanical ventilation, compared to those in the general French population without an underlying medical condition [1]. This translated into a very high mortality (estimated as 40% at 1 month) which we can expect to be even higher with a longer follow-up. Furthermore, fewer than half of the patients were receiving active anti-neoplastic treatment before COVID-19, highlighting that vigilance must remain high in every patient given the long-term immunosuppressive effect of prior therapies. Interestingly, for the majority of the patients, a nosocomial origin was suspected, owing to their hospitalized status or to outpatient visits within the 14 previous days.

We observed an overrepresentation of patients with MM in our cohort (although MM is not overrepresented in our department), suggesting that such patients are particularly vulnerable, owning to the immunosuppression associated with the disease and its treatment, in particular steroids. In fact, the detrimental effect of steroids on patient outcome has been established during previous coronavirus outbreaks (SARS-CoV-1 and MERS-CoV) [10, 11], and a similar impact is expected in patients infected with SARS-CoV-2 [12]. Finally, we must emphasize that more than half of the patients were over 65 years of age, and 92% had at least one additional comorbidity, factors which have been associated with COVID-19 severity [1, 2], and which have possibly contributed to the seriousness of the infection and high mortality rate observed in our study.

Overall, patients with hematologic malignancies appear to be a population very vulnerable to COVID-19 infection. Therefore, hematology departments should remain COVID-19 free zones dedicated solely to hematologic treatment. Furthermore, patients should strictly comply with social distancing and hospital outpatient visits should be reduced to mitigate the risk of COVID-19.

Table 1 Clinical characteristics, treatments and outcomes of patients with hematological malignancies and SARS-CoV-2 infection.

Patient No	Age	Sex	BMI	Hemalogical disease	Hematological status	Hematological treatment	Ongoing corticosteroids	Number of treatment lines	Previous transplant	Comorbidities	Time between onset of symptoms and diagnosis (days)	Radiologic diagnosis	ARDS	Invasive mechanical ventilation	COVID-19 management	Follow-up since first symptoms (days)	Survival status
1	65	M	28.7	Myeloma	Complete remission	Ongoing isatuximab + DXM maintenance	Yes	2	Autologous	HBP	3	Positive CT	Yes	Yes	Best supportive care	17	Dead
2	73	F	30.2	Myeloma	Diagnosis	None	No	0	No	Diabetes, HBP, stroke, obesity	4	Positive X-ray	Yes	Yes	Best supportive care	13	Dead
3	65	M	24.3	Myeloma	Complete remission	Ongoing lenalidomide maintenance	No	1	Autologous	HBP	4	ND	No	No	HCQ/AZT + Tociluzumab	40	Alive
4	61	M	41.5	Lymphoma (DLBCL)	Complete remission	None, 3 months post CAR T-cell	No	4	Autologous and allogeneic	Diabetes, HBP, obesity	7	Positive CT	Yes	Yes	Best supportive care	38	Alive
5	61	F	31.6	Myeloma	Partial remission	Ongoing carfilzomib + lenalidomide + DXM	Yes	6	Autologous	Diabetes, HBP, stroke, obesity	7	Positive CT	No	No	Lopinavir-ritonavir	34	Alive
6	45	M	45.8	PNH	Partial remission	Ongoing eculizumab	No	1	No	Obesity	4	Positive CT	Yes	Yes	Best supportive care	32	Alive
7	40	F	26.7	ALL	Complete remission	None, 9 months post allo-HSCT	No	1	Allogeneic	No	0	Positive CT	Yes	Yes	Best supportive care	23	Alive
8	78	M	26.3	MDS	Progressive disease	Best supportive care	Yes	0	No	Glioma, stroke	1	Positive X-ray	Yes	No	Tociluzumab + corticosteroids	10	Dead
9	79	M	37.8	Lymphoma (hairy cell)	Complete remission	None, 12 years post Cladribine	No	2	No	HBP, obesity, CKD, MDS, MGUS	2	Positive X-ray	No	No	Lopinavir-ritonavir	26	Alive
10	62	F	24.2	LGL leukemia	Complete remission	None, 18 months post cyclophosphamide	No	1	No	No	1	Positive CT	No	No	Best supportive care	32	Alive
11	75	M	28.7	MDS	Progressive disease	Best supportive care	No	0	No	Diabetes, HBP	7	Positive CT	Yes	No	Best supportive care	27	Dead
12	81	M	21.3	Myeloma	Partial remission	Ongoing lenalidomide + DXM	Yes	1	No	HBP	3	Positive CT	Yes	No	Best supportive care	10	Dead
13	81	M	30.1	Lymphoma (Marginal zone)	Progressive disease	None, 14 months post rituximab + bendamustine	No	1	No	Diabetes, HBP, stroke, obesity, COPD	0	ND	No	No	Best supportive care	35	Alive
14	63	M	25.0	Lymphoma (hairy cell)	Complete remission	None, 5 years post rituximab	No	2	No	HBP	5	ND	No	No	Best supportive care	32	Alive
15	92	M	20.0	Myeloma	Progressive disease	Ongoing cyclophosphamide + prednisone	Yes	3	No	HBP	14	Positive X-ray	Yes	No	Best supportive care	14	Dead
16	89	M	23.6	Myeloma	Stable disease	Ongoing lenalidomide + DXM	Yes	2	No	CKD	6	Positive CT	Yes	No	Best supportive care	21	Dead
17	61	M	23.9	Myeloma	Complete remission	Ongoing bortezomib maintenance	No	2	Autologous	Cardiomyopathy	12	Positive X-ray	No	No	Best supportive care	29	Alive
18	86	M	22.3	CLL	Stable disease	Wait and watch	No	0	No	HBP, stroke, CKD	10	Positive X-ray	Yes	No	Lopinavir-ritonavir + corticosteroids	17	Dead
19	68	F	24.4	Myeloma	Partial remission	Ongoing daratumumab + lenalidomide + DXM	Yes	2	No	Diabetes, HBP	1	Positive CT	Yes	Yes	Lopinavir-ritonavir + corticosteroids + tociluzumab	17	Alive
20	72	F	31.5	Myeloma	Partial remission	Ongoing daratumumab + lenalidomide + DXM	Yes	1	No	HBP, obesity	0	Positive CT	No	No	Best supportive care	20	Alive

Table 1 (continued)

Patient No	Age	Sex	BMI	Hematological disease	Hematological status	Hematological treatment	Ongoing corticosteroids	Number of treatment lines	Previous transplant	Comorbidities	Time between onset of symptoms and diagnosis (days)	Radiologic diagnosis	ARDS	Invasive mechanical ventilation	COVID-19 management	Follow-up since first symptoms (days)	Survival status
21	76	M	19.3	MDS	Progressive disease	Best supportive care	No	1	No	CKD, COPD	3	Positive CT	No	No	Best supportive care	20	Alive
22	97	F	17.2	MDS	Progressive disease	Best supportive care	No	1	No	Pancreatic adenocarcinoma, CKD	2	ND	Yes	No	Best supportive care	4	Dead
23	71	M	24.1	Lymphoma (DLBCL)	Complete remission	Ongoing rituximab maintenance	No	2	Autologous	HBP, stroke	22	Positive CT	No	No	Anakinra	29	Alive
24	63	M	22.8	Lymphoma (Poppema)	Complete remission	Ongoing rituximab-CHOP	Yes	1	No	HBP	10	Positive X-ray	No	No	Best supportive care	19	Alive
25	75	F	41.4	Waldenström macroglobulinemia	Partial remission	Ongoing rituximab + cyclophosphamide + DXM	Yes	3	No	HBP, obesity, epidermoid carcinoma of the anal canal	1	Positive CT	No	No	Best supportive care	14	Alive

M male, *F* female, *BMI* body mass index (kg/m^2), *DLBLC* diffuse large B-cell lymphoma, *PNH* paroxysmal nocturnal hemoglobinuria, *ALL* acute lymphoblastic leukemia, *MDS* myelodysplastic syndrome, *LGL* large granular lymphocyte, *CLL* chronic lymphoid leukemia, *DXM* dexamethasone, *allo-HSCT* allogeneic hematopoietic stem cell transplantation, HBP high blood pressure, *CKD* chronic kidney disease, *MGUS* monoclonal gammopathy of undertemined significance, *COPD* chronic obstructive pulmonary disease, *CT* computed tomography, *HCQ* hydroxychloroquine, *AZT* azithromycine.

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Author contributions FM designed the study, recruited patients, collected, assembled, and analyzed the data, and wrote the manuscript. AG recruited patients, collected, assembled, and analyzed the data and helped writing the manuscript. EB, ZW, ZM, SI, AB, SL, SS, EC, AP, RA, FMB, and OL recruited patients, collected data, and approved the manuscript. ML performed statistical analysis and helped writing the manuscript. RD and MM designed the study, recruited patients, assembled, and analyzed the data, supervised research, and wrote the manuscript.

Compliance with ethical standards

Conflict of interest MM reports grants and/or lecture honoraria from Janssen, Sanofi, Maat Pharma, JAZZ pharmaceutical, Celgene, Amgen, BMS, Takeda, Pfizer, and Roche, all outside the submitted work. FM reports lecture honoraria from Therakos/Mallinckrodt, Biocodex, Janssen, Keocyt, Sanofi, JAZZ pharmaceutical and Astellas, all outside the submitted work. RD reports lecture honoraria from Keocyt, Sanofi, and Novartis, all outside the submitted work. The other authors declare no competing financial interests.

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References

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–20.
2. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020. In press.
3. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med. 2020. In press.
4. Koo JR, Cook AR, Park M, Sun Y, Sun H, Lim JT, et al. Interventions to mitigate early spread of SARS-CoV-2 in Singapore: a modelling study. Lancet Infect Dis. 2020. In press.
5. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21:335–7.
6. Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China. JAMA Oncol. 2020. In press.
7. Jin XH, Zheng KI, Pan KH, Xie YP, Zheng MH. COVID-19 in a patient with chronic lymphocytic leukaemia. Lancet Haematol. 2020;7:e351–2.
8. Zhang X, Song K, Tong F, Fei M, Guo H, Lu Z, et al. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. Blood Adv. 2020;4:1307–10.
9. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012;307:2526–33.

10. Lee N, Allen Chan KC, Hui DS, Ng EK, Wu A, Chiu RW, et al. Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. J Clin Virol. 2004;31:304–9.
11. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA, et al. Corticosteroid therapy for critically ill patients with middle east respiratory syndrome. Am J Respir. Crit Care Med. 2018;197:757–67.
12. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020;395:473–5.