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Outcome of COVID-19 in multiple myeloma patients in relation to treatment

Katharina Helene Susek[1] | Charlotte Gran[1,2] | Hans-Gustaf Ljunggren[3] | Evren Alici[1,4] | Hareth Nahi[1,4]

[1]Center for Hematology and Regenerative Medicine, Department of Medicine, Karolinska Institute, Stockholm, Sweden

[2]Department of Clinical Chemistry, Karolinska University Laboratory, Stockholm, Sweden

[3]Center for Infectious Medicine, Department of Medicine, Karolinska Institute, Stockholm, Sweden

[4]Hematology Center, Karolinska University Hospital, Stockholm, Sweden

Correspondence
Katharina Helene Susek, Center for Hematology and Regenerative Medicine, Department of Medicine, Huddinge, Karolinska Institutet, Alfred Nobels Allee 8, 141 86 Stockholm, Sweden.
Email: katharina.susek@ki.se

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Abstract

COVID-19 has emerged as a global pandemic. Cancer patients have been reported to be at higher risk for adverse outcome of COVID-19. Studies are ongoing to decipher the risk factors and risk groups among cancer patients as well as strategies to refine treatment approaches. Here, we report eight patients with multiple myeloma that underwent immunomodulatory therapies with daratumumab or lenalidomide-based combination treatments and one patient with smoldering multiple myeloma, all of which presented with symptomatic COVID-19. We report that patients that succumbed to COVID-19 presented with either progressive tumor disease under daratumumab treatment or were in remission under lenalidomide-dexamethasone treatment.

KEYWORDS
infectious diseases, immunology, multiple myeloma, plasma cell neoplasms

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by the coronavirus SARS-CoV-2, has become a global pandemic since its first emergence in late 2019. The clinical presentation varies among individuals with patients reporting only mild respiratory symptoms to severe lethal respiratory disease and multi-organ damage.[1] Risk factors for a severe course of the disease and adverse outcome are increased age, male gender, obesity, and other comorbidities.[2] Cancer patients are at higher risk to develop a severe form of COVID-19.[3] It is yet unclear whether the increased risk is associated with the malignancy, treatment strategies, or other possible iatrogenic factors.[4]

The introduction of new therapeutic agents, such as immunomodulatory drugs (IMIDs), proteasome inhibitors (PI), and monoclonal antibodies in the treatment of multiple myeloma (MM), lead to increased survival rates.[5] However, several of these novel treatments are associated with an increased risk of infectious complications.[6] We recently reported that MM patients receiving daratumumab were at increased risk for bacterial and viral infections.[7] Pathogenesis of MM results in the suppression of the adaptive immune system and leads to low levels of immunoglobulin production. Reduction of immunoglobulin levels is seen in more than 70% of patients with MM.[8] Such immunoparesis (hypogammaglobulinemia) is correlated with shorter overall survival (OS) and progression-free survival (PFS).[9]

Katharina Helene Susek and Charlotte Gran contributed equally.

Treatment guidelines of cancer patients during the COVID-19 pandemic have been published by several consensus groups such as the European Myeloma Network (EMN).[10] More studies are needed to define the risk groups among MM patients and to refine treatment recommendations. We therefore, here, assessed a cohort of patients that were previously diagnosed with MM or smoldering MM (SMM) and developed COVID-19 during March to May 2020 in Stockholm.

Novelty Statement

1. We suggest that MM patients are observed for increased vulnerability to adverse COVID-19 outcomes during progression or under certain immunomodulatory therapies.
2. Patients with progressive disease under daratumumab treatment and patients in remission on lenalidomide treatment may be at higher risk for mortality from COVID-19.
3. Patients with progressive MM under daratumumab treatment or in remission under lenalidomide treatment may need a closer clinical follow-up during the current COVID-19 pandemic.

2 | METHODS AND RESULTS

The characteristics of the nine patients followed are summarized in Table 1. Of the patients, eight had MM and one patient had SMM. Six of the MM patients were on daratumumab-based treatment and two of the patients were treated with lenalidomide-dexamethasone (RD). All patients presented with fever and eight out of nine patients additionally reported dry cough. Other symptoms were dyspnea, arthralgia, diarrhea, and ageusia (loss of taste). Upon symptom onset, the MM treatments were discontinued. All patients were confirmed with COVID-19 by PCR from nasopharyngeal swabs within 14 days after symptom debut. Four out of nine patients died within three weeks after initial symptoms (Table 1). Of the deceased patients,

TABLE 1 Patient characteristics, treatments, COVID-19-related outcomes as well as additional laboratory and clinical data

Pat. ID	1	2	3	4	5	6	7	8	9
Patient characteristics, treatments and COVID-19 related outcomes									
Diagnosis	MM	MM	MM	MM	MM	MM	MM	MM	SMM
Age, y	58	77	70	70	43	83	94	71	68
Gender	M	M	F	M	F	F	M	M	M
Sub-type	IgAλ	κ	IgAλ	IgGκ	IgAκ	IgAλ	IgDλ	IgGκ	IgGλ
ISS[a]	III	III	III	II	–	II	III	–	II
Previous lines of MM treatment	5[b]	0	4[c]	0	1[d]	1[e]	0	1[f]	–
Current line of MM treatment	dD-Veneto	dVD	dD	dRD	dKD	dD	RD	RD	None
Months on current MM treatment	2	3	7	49	5	16	3	17	–
MM response to current line	PD	PD	MR	CR	VGPR	VGPR	PR	VGPR	–
MM disease progression	Yes	Yes	No	No	No	No	No	No	No
COVID-19 related risk factors	DM2	No	No	No	DM2, HT	DM2, HT	DM2	No	HT
BMI	30	23	20	21	24	34	25	24	23
Anticoagulants	No	No	No	Yes	No	No	Yes	Yes	No
Death due to COVID-19	Yes	Yes	No	No	No	No	Yes	Yes	No
Laboratory values at verification of COVID-19 (PCR)									
CRP, mg/L	79	16	38	136	<1	65	–	6	–
Hemoglobin, g/dL	71	104	93	100	112	100	114	132	126
Leukocytes, 10^9/L	1.2	10.5	6.1	4.9	2	4.3	4	1.8	5.2
Neutrophils, 10^9/L	0.5	8	–	4.5	–	3.2	–	1.4	–
Lymphocytes, 10^9/L	0.5	–	–	0.3	–	0.7	–	0.2	–

(Continues)

TABLE 1 (Continued)

Pat. ID	1	2	3	4	5	6	7	8	9
Creatinine, µmol/L	102	47	68	60	55	116	72	83	118
eGFR, mL/min/1.73 m^2	63	>90	>90	78	>90	37	60	67	51
M-protein spike, g/L	68	—	16	0	1	2	—	1	54
IgG, g/L	1.8	2.2	0.83	5	3.0	4.9	5.7	8.1	0
IgA, g/L	0	<0.08	0	0.42	1.1	0.30	2.1	2.5	0.23
IgM, g/L	<0.1	<0.08	<0.1	0.96	<0.1	0.24	0.34	0.39	0.21
Immunoparesis[g]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Clinical symptoms in the course of COVID-19									
Fever, >38.5°C	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dry cough	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dyspnoea	Yes	No	No	No	No	Yes	Yes	No	np
Other COVID-19 related symptoms[h]	No	No	No	Yes	Yes	No	No	Yes	No
Saturation, lowest level	93%	ND	ND	95%[i]	ND	89%	79%	70%	ND
Oxygen demanding	No	No	No	Yes	No	Yes	Yes	Yes	No
Hospitalization	No[j]	No[j]	No[k]	Yes	No[k]	Yes	Yes[l]	Yes	No[k]
PCR and COVID-19 specific IgG response									
Post-COVID-19-positive PCR, d	NE	NE	ND	34	28	10	NE	NE	7
IgG antibody response to COVID-19, d	NE	NE	ND	46 (pos)	15 (neg)	10 (neg)	NE	NE	78 (neg)

Abbreviations: CR, complete response; dD, (daratumumab-dexamethasone); dD-Veneto, (daratumumab-dexamethasone-venetoclax); dKD, (daratumumab-carfilzomib-dexamethasone); DM2, Diabetes mellitus type 2; dRD, (daratumumab-lenalidomide-dexamethasone); dVD, (daratumumab-bortezomib-dexamethasone); HDT, (high-dose treatment); HT, hypertension; KD, (carfilzomib-dexamethasone); KPD, (carfilzomib-pomalidomide-dexamethasone); MR, minimal response; ND, not determined; NE, not evaluable due to exitus; PD, (pomalidomide-dexamethasone); PD, progressive disease; PR, partial response; RD, (lenalidomide-dexamethasone); VCD, (bortezomib-cyclophosphamide-dexamethasone); VGPR, very good partial response; VRD, (bortezomib-lenalidomide-dexamethasone); VTD, (bortezomib-thalidomide-dexamethasone).

[a]As defined by the International Myeloma Working Group.

[b]1st line VCD + HDT 2nd line RD 3rd line KPD 4th line dD 5th HDT.

[c]1st line VTD 2nd line RD 3rd line PD, 4th line KD.

[d]1st line VRD + HDT.

[e]1st line VCD.

[f]1st line VCD.

[g]Reduction below the lower normal limit of one or two uninvolved immunoglobulins, IgG < 6.7 g/L, IgA < 0.88 g/L, IgM < 0.27 g/L.

[h]Either of diarrhea, arthralgia, loss of taste.

[i]Saturation on 5 L oxygen.

[j]Hospitalization was judged not to be beneficial, because of end-stage disease.

[k]Mild symptoms, admission to hospital not required.

[l]Received oxygen treatment at home from advanced homecare teams.

two had progressive disease while on daratumumab, three weeks prior to initial symptoms. The other two deceased patients had received RD and were in remission at the time of COVID-19 diagnosis. Among the patients that survived, the patient with SMM developed COVID-19-specific IgM antibodies within one week after the onset of the symptoms. However, no seroconversion to IgG occurred. Of the three other patients with MM that received daratumumab, only one patient developed an IgG response. All alive patients resolved their COVID-19 symptoms and resumed their daratumumab-based treatments, despite remaining SARS-CoV-2 PCR positive.

3 | DISCUSSION

Immunoparesis is associated with worse overall survival, which is not generally related to an increased risk of infections.[9,11] A

report on patients with MM and COVID-19 did not find a correlation between immunoparesis and increased risk of adverse COVID-19 outcome.[12] However, in another report, higher mortality was reported in cases of severe IgG hypogammaglobulinemia, but not with immunoparesis.[13] In the present cohort, we observed immunoparesis in all daratumumab treated patients, but did not see a correlation with COVID-19 outcome. Additional treatments, including previous high-dose melphalan and autologous stem cell transplantation (ASCT), have not been associated with COVID-19 severity.[12] Previous reports did not show a correlation between daratumumab or IMID-based systemic therapy and adverse COVID-19 outcome.[13,14] Only cardiovascular comorbidities were correlated with an increased odds ratio for hospitalization, ICU-admission, mechanical ventilation, or death in the context of MM.[12,13] With mortality rates varying between 24% and 55%, patients with MM are more vulnerable to death from COVID-19 compared to patients in the general population.[12-14] With the limitation of a low study subject number, we observed that patients with progressive disease seem to be at higher risk for mortality from COVID-19 as were patients in remission on RD treatment. If confirmed by larger cohorts, this might be due to the dysregulation of the immune system during MM progression or the nature of immunomodulatory therapies. To address this, a detailed biomarker analysis including characterization of immune and inflammatory cell populations as well as pro-inflammatory cytokines in patients with MM will be necessary.

In summary, based on previous reports and this study, patients with MM show a high risk for mortality from COVID-19 infection which seems not to be associated with immunoparesis but rather immune dysregulation under progression or certain treatments such as RD. The exact underlying mechanisms are so far not understood. As there is currently no vaccine or specific treatments available, it is necessary to carefully consider clinical management and treatment of patients with MM in the context of COVID-19.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

CG and HN collected the data. KHS, CG, and HN analyzed the data. All authors wrote and revised the manuscript.

ORCID

Katharina Helene Susek https://orcid.org/0000-0003-2430-0748
Charlotte Gran https://orcid.org/0000-0002-6069-6615
Hans-Gustaf Ljunggren https://orcid.org/0000-0003-0908-7387
Evren Alici https://orcid.org/0000-0001-5307-6648
Hareth Nahi https://orcid.org/0000-0003-4711-5094

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