

SARS-CoV-2 in Myelodysplastic Syndromes: A Snapshot From Early Italian Experience

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Myelodysplastic syndrome patients are subjects of advanced age, vulnerable and frail, whose outcome is heavily influenced by pre-existing comorbidities worsening the hematologic condition. Infections are a rather common cause of death (around 30%), especially, but not only, for IPSS-R higher risk patients.¹⁻³ In MDS there is a significant impairment of lymphopoiesis, resulting in lymphopenia ($ALC < 1.0 \times 10^9/l$) in around 38% of MDS patients and poor prognosis.⁴ Data on innate and adoptive immune systems (either disease related or due to immunosenescence) and the subsequent supposed susceptibility and incidence of viral infections in MDS are scarce.⁵

With all these considerations in mind, at Coronavirus outbreak in Italy, the spread of the COVID-19 pandemic was so extremely rapid that we were expecting to face in short times a very large number of severely symptomatic MDS patients and tried to rapidly learn from the earlier and more severely hit areas.⁶ As per April 28, date until which we collected our data, and in full emergency, the number of diagnosed cases of SARS-Cov2 in Italy was 199.470 with 25.215 deaths.⁷ In the same period, in the general population around 10% of tested cases were actually infected.⁸

Collection of data in the national MDS Registry (FISiM) and the regional Registry for Rome and surrounding area (GROM) has been approved by local Ethical Committees. Through these 2 networks we collected data regarding laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in MDS patients symptomatic and tested from February 24 to April 28, 2020. Data have been obtained from 50 Centers. Total number of MDS patients followed up in that period was 5326 as per April 28, median age 73 years. As per national guidelines, oropharyngeal and nasal swab with PCR was performed in regional laboratories for all suspected cases: 305/5326, tested irrespective of gravity of symptoms, and the presence of true SARS-CoV-2 infection sent for confirmation in the national reference central laboratory (Istituto superiore di sanità -ISS). Confirmed SARS-CoV-2 was diagnosed in 63/305 tested cases (20.6%), globally in 63/5326 (1.18%) MDS patients, in the time frame indicated above. Median age of affected MDS patients was 78 years. We evaluated the distribution of SARS-CoV-2 cases dividing the Country into three macro-regions, considering adhering Centers and the epidemiology and cumulative incidence of COVID-19 in Italy:⁷ 3 Regions of Northern Italy (Lombardia, Piemonte and Emilia Romagna, SARS-CoV-2 > 500 cases /100.000 inhabitants, as per April 28), Rome and surroundings (specific GROM Registry), and Rest of Italy (Table 1). The majority of SARS-CoV-2 cases and cumulative incidence among MDS patients was localized in the 3 Regions of Northern Italy (LPE) (1.6%), consistent with the data of COVID-19 epidemic in the general population of the area (62.4% of total Italian cases),⁷

while in Rome and Rest of Italy it was < 1%, (0.3 and 0.85% respectively). Median age of affected MDS patients in LPE Regions was 81 years, in Rome 71 years and in the rest of Italy 77 years.

At the time of analysis, only 33/63 patients were alive, indicating a lethality rate significantly higher than that of non-MDS population (same age range 70-79 years: 28.9% deceased, lethality 24%).⁷

Available details on demographics, clinical characteristics and treatment of 63 MDS patients with SARS-CoV-2 are indicated in Table 2. It is evident that SARS-CoV-2 affected prevalently male subjects, confirming the observation in non-MDS Italian affected population aged 70 to 79 yrs. In particular, although numbers are extremely small, the lethality rate was higher in male MDS patients (73% of total deaths). To note, the same trend was noted for male patient in the general population infected (lethality for male 29.5% vs 16.7% for female aged 70-79 years),⁷ while survival of MDS patients was not apparently influenced by age (median age 78 years in both groups). Reported cause of death for all 30 cases was respiratory failure, in 82% of cases COVID-19 was complicated by bacterial pneumonia and 5% cardiac failure. ARDS was indicated in 50% of deceased cases. Regarding IPSS-R risk categories, the majority of patients who recovered were lower risk ones (62%), while deceased patients were in the great majority IPSS-R higher risk ones (17/30). There is no statistically significant difference for infection, gravity of infection or survival according to the type of treatment received, in part due to the small figures when we come to the granularity of therapies. A higher proportion of patients was in treatment with azacitidine, consistent with their diagnosis of IPSS-R higher risk MDS. The totality of the MDS patients who were diagnosed with SARS-CoV-2 had multiple severe comorbidities (> 3 comorbidities 80% of cases).

A few patients received only supportive care for COVID-19 infection, either for milder clinical presentation (3/33) or, on the contrary, for a rapid and extremely aggressive onset leading to early death (3/30). In the majority of cases, MDS specific therapies were suspended.

The impact of SARS-CoV-2 on the frail MDS population was evaluated in a limited time frame during the peak of the pandemic in Italy and the strict national lockdown. Incidence of symptomatic infection was not as relevant as expected in MDS patients for whom neutropenia, lymphopenia, stress erythropoiesis and iron overload could have determined a substantial susceptibility to and gravity of SARS-CoV-2. Similar observations were recently reported, in a much younger population of beta thalassemic patients.⁹ Median age of SARS-CoV-2 MDS patients was higher than that of the affected Italian MDS population, and this, together with comorbidities, may account for the high lethality rate observed.¹⁰ This report is limited and

Table 1

Distribution of SARS-CoV-2 Positive MDS Patients Diagnosed from February 24th to April 28th 2020, Respect to Number of MDS Patients in Treatment in 50 Italian Hematology Centers.

Region	N° of MDS Patients Registered	SARS-CoV-2 Positive MDS Patients (%)
LPE Regions*	2689 (51%)	44/63 (70%)
Rome and surroundings	767 (14%)	3/63 (5%)
Rest of Italy	1870 (35%)	16/63 (25%)
Total	5326 (100%)	63 (100%)

According to the Centers that provided data, Italian territory was subdivided into 3 macroregions, following the differences in cumulative incidence of COVID-19 infection in general population. Regions with a cumulative incidence of SARS-Cov-2 > 500/100.000 inhabitants, as per April 28th,⁷ that is Lombardia, Piemonte, and Emilia Romagna *(LPE) were analyzed separately. Globally 1.18% of MDS patients under treatment or observation in the period indicated was affected by SARS-Cov-2, 20.6% of patients who underwent molecular testing, with a median age of 78 years.

Table 2**Demographics and Clinical Characteristics of MDS Patients Diagnosed with SARS-CoV-2 and Available Data on MDS and COVID-19 Treatment.**

		N° of MDS patients alive 33/63	N° of MDS patients deceased 30/63
Age (median)	Years	78	78
Sex	M/F	42/21	22/8
IPSS-R	Very low	0/33	2/30
	Low	19/33	4/30
	Intermediate	8/33	7/30
	High	2/33	11/30
	Very High	2/33	6/30
MDS Therapy	NA	2/33	0/30
	ESA	16/33	4/30
	HMA	4/33	15/30
	HMA+ venetoclax	1/33	-
	BSC	8/33	5/30
	BSC+ chelation	1/33	-
	Lenalidomide	-	1/30
	Danazol	-	2/30
	W/W	3/33	3/30
	COVID 19 Therapy	Antibiotics	26/33
Hydroxychloroquine		24/33	28/30
Steroids		4/33	4/30
Lmw Heparin		6/33	10/30
Lopinavir/Ritonavir		1/33	1/30
Darunavir/Cobicistat		3/33	10/30
ICU		12/33	17/30
Supportive therapy only		3/33	3/30
Antivirals (not specified)		1/33	1/30
	Tocilizumab	2/33	6/30

preliminary (early landmark date), produced during the health emergency. Here we share the international problem of general epidemiology of SARS-CoV-2. In fact, we do not have data for asymptomatic infected MDS patients, for whom diagnostic procedures were not performed, and still complete data are lacking. At present, after resolution of the health emergency, routine serology evaluation of COVID-19 antibodies is ongoing for MDS patients managed in our Centers.

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