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LETTER TO THE EDITOR

COVID-19 infection in children with cancer and stem cell transplant recipients in Turkey: A nationwide study

To the Editor:

Adults with cancer are reported to have a higher risk for coronavirus disease (COVID-19) infection and more severe disease and mortality than the general population.[1,2] Although children seem to be at a lower risk for COVID-19 than adults,[3–5] data specifically addressing children with cancer are limited.[6–12]

We conducted a retrospective, multicenter, cross-sectional study on behalf of the Turkish Pediatric Hematology Society (TPHD) and Turkish Pediatric Oncology Group (TPOG) Society to analyze the characteristics of COVID-19 in all patients with cancer and stem cell transplant (SCT) recipients in all centers in Turkey, during March 11-May 31, 2020. Approval for the study was obtained by Turkish Ministry of Health (MoH), Istanbul University COVID Scientific Research Committee, and Istanbul University Ethics Committee. The study was carried out through the analysis of a questionnaire with 62 questions, which was sent to all members of the TPOG and TPHD Societies working in all 66 pediatric hematology/oncology departments in university, state, and private hospitals in Turkey. All replied and 53 patients were reported from the 24 centers.

Following the national recommendations and guidelines of the MoH,[13,14] centers tested all symptomatic patients or patients with contact history or patients who were planned to undergo transplantation or surgery. All patients and caregivers were questioned at the entrance of the hospital/oncology center and if there were any symptoms or contact history they were sent to the special clinics within the hospital that were allocated for suspected/proven COVID-19 patients. If a patient was suspected of having COVID-19 and found positive while in the oncology clinic, she/he was transferred to the COVID clinic and all staff, patients, and accompanying persons with whom she/he was in contact were tested for COVID-19.

Samples from the naso-oropharyngeal swabs were tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by polymerase chain reaction (PCR). Confirmed cases were defined as PCR-positive patients. Probable cases were defined according to guidelines of World Health Organization[15] and MoH,[13] as those who had typical symptoms and chest CT findings, or who had typical symptoms and contact history but negative PCR. Patients were classified into four groups regarding the severity of infection as asymptomatic/mild, moderate, severe, and critical on the basis of the clinical, laboratory, and radiological features.[3,15] Patients were treated according to recommendations of the MoH.[13,14] Statistical analyses were performed by IBM SPSS Statistics version 21.0. For comparison of mean of numerical variables Mann-Whitney U test was used. Categorical nominal variables were compared with Fisher's exact tests.

There were 51 children with cancer, six of whom (four leukemia/lymphomas, two solid tumors) had undergone SCT (Table 1). The median age was 6 (0.3-17.8) years and 64.7% of the patients were male. Additional two patients with thalassemia major who underwent SCT were not included in the analyses. Chemotherapy courses were interrupted in 32 (62.7%) patients and delayed with a median of 15 (3-45) days. The most common presenting signs were fever and cough, while 37.25% of patients were asymptomatic. COVID-19 pneumonia was detected in 26 (50.9%) patients. Five of them had hypoxemia. Gastrointestinal system (17.6%) was the second most commonly involved site followed by central nervous, musculoskeletal systems and skin.

Twenty-five patients had asymptomatic/mild, 17 patients moderate/severe, and nine patients critical disease. Thirty-eight patients were hospitalized and treated according to the severity of illness, six of whom were already hospitalized for reasons such as surgery or diagnostic workup when diagnosed with COVID-19. Nine patients with critical disease were in the intensive care unit (ICU) and three were intubated. Treatment consisted of hydroxychloroquine, azitromycine, antivirals either as a single agent or in combination (Table 1). Convalescent plasma was used in three patients, one of whom additionally received mesenchymal stem cell, tocizulumab, and granulocyte transfusions and was intubated. At the time of COVID-19 diagnosis, 26 patients had neutropenia and among them 15 had fever. In all patients with febrile neutropenia, broad-spectrum empirical antibiotics were initiated. In addition, 12 patients received antimicrobial therapy due to clinically and/or microbiologically documented infections.

All patients, but one, fully recovered and the PCR tests became negative at a median of 7 (2-17) days. The patient who had received allogeneic SCT for relapsed leukemia/lymphoma and had progressive disease and fungal infection died due to COVID-19 infection.

The incidence of critical care disease and need for ICU care were found to be higher in patients with hematologic malignancies ($P = .012$), patients post SCT ($P = .001$), patients with other infections ($P = .005$), and patients with abnormal findings on chest CT scan ($P = .004$). Age, gender, elevated CRP, elevated D-dimer, being neutropenic, and having relapsed/refractory disease were not significant for critical disease.

It has been reported that children constitute about 2% of all patients with COVID-19.[15] In Turkey, children comprise 7.2% of all cases with COVID-19. The death rate for COVID-19 is 2.57% in Turkey and 0.19% of all deaths were in childhood.[17]

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TABLE 1 Demographic and clinical characteristics of patients with COVID-19, treatment and outcome

	n	%
Median age (range) (years)	6 (0.3-17.8)	
Sex		
Male	33	65
Female	18	35
Type of cancer (total number of cancer patients with cancer)	51	
Leukemia[a]	26	51
Lymphomas and reticuloendotehelial tumors (HL, NHL, LCH, HLH)[b]	5	9.8
Brain tumors[c]	5	9.8
Neuroblastoma	4	7.8
Bone tumors[d]	3	5.9
Soft tissue sarcomas[e]	3	5.9
Other solid tumors[f]	5	9.8
Disease status		
During primary treatment	28	55
Relapse/refractory disease	7	14
Stem cell transplantation	6	12
At diagnosis	6	12
End of treatment	4	7.8
Diagnosis		
PCR, clinic and radiologic positivity	23	45
PCR positivity only (contact with positive person)	13	26
PCR positivity at screening before surgery, radiotherapy, or SCT	6	12
PCR negative, clinical and radiological positivity	9	18
Definite case	40	78
Probable case	11	22
Contact history	24	47
Most frequent symptoms and findings		
Asymptomatic	19	37
Fever	29	59
Cough	21	41
Other respiratory system findings (tachypnea, dyspnea, hypoxemia)	16	31
Organs and systems involvement		
Respiratory system (upper respiratory tract infection + pneumonia)	33 (7 + 26)	65
Gastrointestinal system[g]	9	18
Central nervous system	4	7.8
Musculoskeletal system	3	5.9
Skin	2	3.9
Radiological findings		
Normal	25	49
Bilateral diffuse or patchy ground glass opacity	7	14
Diffuse or patchy pneumonic infiltration or consolidation	11	22
Pneumonic infiltration and ground glass opacity	9	18
Pleural effusion	3	5.9
ARDS	1	2.0
Laboratory findings		
Neutropenia	26	51
Lymphopenia	23/45	51
Anemia	33/47	70
Thrombocytopenia	25/47	53
CRP (mg/dL) median (range)	11.4 (0-270)	
Increased CRP (number of patients with increased CRP/no. tested)	28/48	58
D-dimer median (range)	400 (33-6530)	
Increased D-dimer(number of patients with increased D-dimer/no. tested)	13/31	42

(Continues)

TABLE 1 (Continued)

	n	%
Severity of disease		
Asymptomatic/mild	25	49
Moderate	15	29
Severe	2	3.9
Critical	9	18
Number hospitalized[h]	38	75
Length of hospitalization (median, range) (day)	11 (2-45)	(2-45)
Necessity of ICU	9	18
Necessity of intubation	3	5.9
Treatment		
No treatment	10	20
Azitromycine	10	20
Hydroxychloroquine	4	7.8
Hydroxychloroquine + azitromycine	14	27
Azitromycine + antivirals[i]	1	2.0
Hydroxychloroquine + azitromycine + antivirals[i]	3	5.9
Convalescent plasma (in addition to other medication)	1	2.0
Mesenchymal stem cell + tocizulumab (in addition to other medication)		
Interruption/delay of chemotherapy	32	63
Treatment delay (median, range) (days)	15 (3-45)	
Length of PCR positivity (median, range) (days)	7 (2-17)	
Outcome of disease		
Recovery	50	98
Death	1	2.0

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ARDS, acute respiratory distress syndrome; BMT, bone marrow transplantation; GIS, gastrointestinal system; HL, Hodgkin lymphoma; HLH, hemophagocytic lymphohistiocytosis; ICU, intensive care unit; LCH, Langerhans cell hystiocytosis; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma.

[a]ALL, n = 18; AML, n = 7; MDS, n = 1.

[b]HL, n = 2; NHL, n = 1; HLH, n = 1; LCH, n = 1.

[c]Medulloblastoma, n = 4; atypical teratoid rhabdoid tumor, n = 1.

[d]Ewing Sarcoma, n = 2; osteosarcoma, n = 1.

[e]Rhabdomyosarcoma, n = 2; desmoid fibromatosis, n = 1.

[f]Germ cell tumors, n = 2; hepatoblastoma, n = 1; Wilms tumor, n = 1; metastatic carcinoma, n = 1.

[g]Presented with diarrhea, colitis, and gastrointestinal bleeding.

[h]Six were already hospitalized for other reasons (such as diagnostic workup and surgery) and they received COVID-19 diagnosis during this time.

[i]Antivirals (favipiravir, lopinavir).

The COVID-19 infection prevalence among adult cancer patients has been reported to be higher than in the general population (1% vs 0.29%).[1] For pediatric cancer patients, prevalence was estimated as 1.3%, which is higher than that of the general pediatric population (0.8%).[7]

The median age of our patients was younger than most reports in the literature (6 vs 11 years).[7–9,12] There was a male preponderance (64.7%) similar to the gender distribution in the general adult and pediatric population.[4,17,18] Most of our cases (60.8%) had hematological malignancies, similar to some other series.[9,12]

COVID-19 causes multiple organ involvement due to widespread distribution of angiotensin-converting enzyme-2, the functional receptor for SARS-CoV-2 in multiple organs.[11,19] Shekerdemian et al[20] reported that 73% of the pediatric cases were admitted with respiratory findings, while 25% of cases presented with other system findings such as gastrointestinal and neurological systems. Involvement of other systems was documented in 35% of our cases.

In many pediatric cancer series, as in our study, 30-50% of the cases had febrile neutropenia.[6,7,9] Since differential diagnosis between COVID-19 and other infections is difficult during neutropenia, we suggest that children with cancer and febrile neutropenia should be tested for COVID-19.

Twenty-one percent of our patients had severe/critical disease and 17.6% of cases needed ICU care. Mortality rate was found to be 1.9%. Having a hematological malignancy, SCT, a mixed infection and abnormal CT findings were found to significantly increase the severity of the disease and the need of ICU in our study. In addition, delay in specific-cancer treatment may pose a problem.

It is hard to speculate which drugs are best for the disease as the search for the "standard of care" drugs are still under debate globally, national and international guides for management are frequently being revised.[6,7,10–12,20,21]

The evaluation and sharing of national data, as in our study that includes all children with cancer/SCT and COVID-19 within a time

frame, without any selection bias, and accumulation of international data shall lead to a better understanding of the disease, treatment and risk factors to guide health care professionals.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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