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Original Research

Flash survey on severe acute respiratory syndrome coronavirus-2 infections in paediatric patients on anticancer treatment

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Abstract ***Introduction:*** Since the beginning of COVID-19 pandemic, it is known that the severe course of the disease occurs mostly among the elderly, whereas it is rare among children and young adults. Comorbidities, in particular, diabetes and hypertension, clearly associated with age, besides obesity and smoke, are strongly associated with the need for intensive treatment and a dismal outcome. A weaker immunity of the elderly has been proposed as a possible explanation of this uneven age distribution. Thus, there is concern that children treated for cancer may allso be at risk for an unfavourable course of infection. Along the same line, anecdotal information from Wuhan, China, mentioned a severe course of COVID-19 in a child treated for leukaemia.

Aim and methods: We made a flash survey on COVID-19 incidence and severity among children on anticancer treatment. Respondents were asked by email to fill in a short Web-based survey.

Results: We received reports from 25 countries, where approximately 10,000 patients at risk are followed up. At the time of the survey, more than 200 of these children were tested, nine of whom were positive for COVID-19. Eight of the nine cases had asymptomatic to mild disease, and one was just diagnosed with COVID-19. We also discuss preventive measures that are in place or should be taken and treatment options in immunocompromised children with COVID-19.

Conclusion: Thus, even children receiving anticancer chemotherapy may have a mild or asymptomatic course of COVID-19. While we should not underestimate the risk of developing a more severe course of COVID-19 than that observed here, the intensity of preventive measures should not cause delays or obstructions in oncological treatment.
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1. Introduction

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing the coronavirus disease (COVID-19) pandemic in 2020 was identified in December 2019. By 17th March 2020, it has affected 200,000 cases in 163 countries, and in several foci, the numbers rise exponentially [World Health Organization, 'Rolling updates on coronavirus disease (COVID-19)' https://www.who.int/emergencies/diseases/novel-

coronavirus-2019/events-as-they-happen]. Despite a high mortality rate, the spectrum of COVID-19 includes asymptomatic infection, upper respiratory tract infection, lower respiratory tract infection through severe respiratory failure and other problems such as myocarditis, sepsis [1] and diarrhoea (Pan *et al.*, Am. J. Gastroenterol., In Press). The age distribution of the more severe course of the disease is strikingly skewed towards older patients, especially those older than 65 years [1,2]. In contrast, paediatric patients rarely develop critical illness [3–7]. In one study, only 5% and 0.6% of 2141 evaluable children with confirmed COVID-19 had severe or critical illness, respectively [7]. The biology underlying this disparity in severity is unknown.

The possibility that more severe disease associated with immunosenescence, along with an increased risk of severe disease in adults with cancer, and a single case report of a critically ill child who developed COVID-19 during myelosuppressive chemotherapy have raised the concern that COVID-19 among immunosuppressed children might be a much more severe illness than that seen in otherwise healthy children [2,8–10]. This is consistent with data for other coronaviruses, which do cause more severe infections in immunocompromised children [11]. To evaluate this, we used a flash survey to determine whether there was current evidence that paediatric patients with cancer in SARS-CoV-2–affected areas had been tested for this virus or had developed severe COVID-19 disease.

2. Results

On 16th March 2020, we circulated a simple survey on COVID-19 incidence and diagnostic and preventative measures. A Web-based form was sent by email to 89 addressees, who work in paediatric haematology/oncology (PH/O) departments in many countries. Data were collected one day later. In total, 32 centres or countries provided data on COVID-19 incidence in children treated with chemotherapy or intensive immunosuppression in their institutions or countrywide (Table 1). The results are shown together with COVID-19 incidence in the general population.

In brief, of more than 200 patients who were tested for SARS-CoV-2 in these PH/O departments, which care for close to 10,000 at-risk patients, only eight cases of proven infection were identified. Given that there is no general recommendation regarding testing of asymptomatic individuals, many centres only tested symptomatic patients, so the true rate of infection is not known. None of the reported cases required intensive care because of COVID-19. Case 1 was a febrile adolescent after mediastinal radiotherapy for osteosarcoma; no information was available regarding prior chemotherapy. Case 2 was a 16-year-old girl with febrile neutropenia after adjuvant chemotherapy for hepatoblastoma. She received azithromycin and granulocyte colony-stimulating factor (G-CSF), no pulmonary involvement was present on routine testing, although CT scan performed for other indication showed parenchymal nodular micro-thickenings, and after 5 days, she was free of both neutropenia and fever. In addition, case 3 had febrile neutropenia, after chemotherapy for a cervical rhabdoid tumour. There were no radiologic signs of pulmonary involvement, but she required oxygen for nightly desaturations. She received G-CSF and azithromycin, and after 10 days, she was dismissed from the hospital. Case 4 was a 6-year-old boy admitted in a hospital for a cisplatin cycle for hepatoblastoma, with a COVID-19–positive swab after the end of therapy; he was discharged without therapy and remained in good condition. Cases 1–4 were also mentioned in another study (Balduzzi *et al.*, submitted). Case 5 was a child with metastatic Ewing sarcoma who developed febrile neutropenia after the 5th cycle of chemotherapy. Case 6 was a child with Wilms' tumour who presented with fever and diarrhoea after 6 weeks of chemotherapy; this child did have lymphopenia but not neutropenia. None of these two patients had respiratory symptoms, and both became afebrile within 12–24 h. Both received hydroxychloroquine, and case 5 also received lopinavir-ritonavir. Three more cases were reported two days after the survey responses were collected. One of them (case 7) had febrile neutropenia treated for acute lymphoblastic leukaemia (ALL), and no data on outcomes are available yet. Case 8 was a 2-year old child in febrile neutropenia treated for a solid tumour; except for fever she stayed in a very good clinical condition. The other one (case 9) was on maintenance treatment for ALL without typical symptoms, tested because his parents were positive for COVID-19; the antileukaemic maintenance treatment was interrupted until two negative results are obtained.

3. Discussion

To our knowledge, this is the first survey of paediatric oncology centres in SARS-CoV-2–affected areas. We found that the number of infected patients appears to be low and that the few who were identified had mild and possibly self-limited infection.

The low rate of identified infection is somewhat surprising as it is reasonable to assume that the paediatric patients with cancer would be at least as susceptible to SARS-CoV-2 infection as their healthy peers. SARS-CoV-2 does infect children in general, although lower severity of the infection makes children prone to be under-reported [3,6]. Thus, at least in the countries with high COVID-19 incidence, either the transmission of SARS-CoV-2 was prevented by standard infection prevention measures or cases remained undiagnosed as the

Table 1
Flash survey results.

Investigator	Name of the institution	Countrywide incidence of COVID-19 per million	Number of patients on chemotherapy	Tested for COVID-19	Proven COVID-19, total
C.R., B.B., A.Bal.	PH/O unit, University of Milano-Bicocca, MBBM Foundation, ASST Monza, Italy	463	100	2	0
	PH/O, Università degli Studi di Padova, Italy		150	88	0
	Italy (entire country)		1500–2000	Not known	4 (cases 1–4)
J-P.B.	Kinderspital Zürich, Switzerland	317	100	1–10	0[a]
S.R.	Hospital Sant Joan de Déu de Barcelona, Spain	244	250	0	0
N.D.P.	Hospital Virgen de la Salud, Spain		35	3	1 (case 5)
M.d.P.C., M.E.V.A.	Hospital General Universitario de Albacete, Spain		4	1	1 (case 6)
K.S.	Copenhagen University Hospital, Rigshospitalet, Denmark	160	90–100	1–10	0
	Denmark (entire country)		180	1–10	0
A.A.	St Anna Kinderspital, Vienna, Austria	148	100	1–9	0
	Austria (entire country)		250	Not known	0
P.G.	PH/O, Karolinska University Hospital, Stockholm, Sweden	116	100	0[a]	0[a]
K.M.	Sahlgrenska University Hospital, Gothenburg, Sweden		100	5	0
J.T.B.v.d.W.	UZ Brussel, Belgium	107	10	0	0
A.Bar.	PH/O, University Hospital Robert Debré, Paris, France	102	150	5	0
R.P.	Princess Maxima Center, the Netherlands	99.5	900	5–10[b]	0
M.Sch.	Childrens Hospital Medical Center Schleswig-Holstein, Kiel, Germany	95.2	50	5	0
T.B., A.Bo.	PH/O and Clinical Immunology, Heinrich Heine University Düsseldorf, Germany		125	50	0
G.E.	PH/O, Universtitätsklinikum Eppendorf, Germany		100	5	0
M.L.	University Hospital Schleswig-Holstein, Campus Lübeck, Germany		24	2	0
M.St.	Medizinische Hochschule Hannover, Germany		100	5	0[a]
O.S.	National Children's Cancer Service, Children's Health Ireland at Crumlin, Dublin, Ireland	59.1	224	10	0
A.E.J.Y.	Singapore (entire country)	45.5	200	10	0
S.E.	Schneider Children's Medical Center of Israel	37.4	220	3	0
O.H.	Czechia (entire country)	37	250	2–10	0
A.V.	Great Ormond Street Hospital, UK	22.7	500	5	0
C.-K.L.	Hong Kong Children's Hospital	22.4	210	3	0
H.A.	University of Malaya, Kuala Lumpur, Malaysia	20.8	100	1	0
	Malaysia (entire country)		500	1–10	0
A.K.	Slovakia (entire country)	17.8	180	3	0
L.D.	The Children's Hospital at Westmead, Australia	17.7	300	0	0
	Australia (entire country)		1740	Not known[c]	0
R.F.	LAU MC-Rizk Hospital, Beirut, Lebanon	17.6	20	1	0
J.L.	University Children's Hospital, Belgrade, Serbia	8.2	30	0	0

A.M.	Hokkaido University in Sapporo, Japan	6.9	30	0	0
	Japan (entire country)		2500–4000	Not known	0
J.Sty.	Poland (entire country)	5.8	1048	13	0
G.O.	PH/O, University of Pécs, Hungary	5.2	7	0	0
G.K.	Hungary (entire country)		250	4	0
M.F.	Hospital de Pediatría, "Prof. Garrahan", Argentina	1.5	90–100	1–10	0

PH/O = (Department of) Paediatric Haematology/Oncology.
Data reflect a situation as of 17th March 2020.
[a] Three positive cases were diagnosed by 21st March 2020—in Switzerland (case 7) in Stockholm, Sweden (case 8), and in Hannover, Germany (case 9)—all are also mentioned in the Results section.
[b] Additional 80 cases screened by 19th March 2020—all were negative.
[c] As of 26th March, 47 to 60 cases were tested in 7 Australian hospitals within ANZCHOG group—all were negative.

course of the infection did not raise a suspicion of COVID-19. In some areas, the devastating overall situation made the diagnostics of mild cases a low priority.

The mild disease experienced by the three children in this study is in direct contrast to the only previously published case of which we are aware. An 8-year-old child undergoing myelosuppressive chemotherapy for T-cell ALL in Wuhan hospital developed respiratory failure over the course of 3 weeks, eventually requiring mechanical ventilation; the patient had not recovered at the time of the report [8] (and included in the studies by Lu et al [3] and Sun et al [9]). During the course of that patient's disease, C-reactive protein and interleukin-6 levels were only mildly elevated, but ferritin levels were high (6417––15,758 μg/L). This is reminiscent of features of hemophagocytic lymphohistiocytosis, which has been previously described to co-occur with infections [12]. Possible correlation between the severity of infection and the composition and intensity of chemotherapy should be studied in larger cohorts.

The participating countries are gradually strengthening general preventative measures, usually aiming at social distancing, quarantine for the infected and contacts, clean hands and surfaces and cautious checking for possible symptoms—similar to measures successfully applied in Hong Kong during the SARS epidemic in 2003 [13].

In PH/O departments, precautions are always taken to protect patients from any infections. The degree of these precautions typically depends on the severity of immunosuppression and differs among hospitals [14]. Although our study portrays symptomatic COVID-19 as a rare finding among heavily immunocompromised children, at least in the first weeks of pandemics, other viruses do occasionally infect these patients in hospital wards despite these precautions [15]. The responders to this survey recommend taking additional measures during the COVID-19 epidemic to protect patients and staff from being either infected or in quarantine. As the epidemiological situation develops, only scientifically supported measures should remain in place, not to cause unwanted delays in the treatment of the underlying malignancies.

The overall experience with daily life in hospitals during the peak COVID-19 epidemics has been thoroughly described by Italian physicians (Balduzzi *et al.*, submitted).

There are large differences among countries regarding the specific measures recommended. Most commonly, social contact is being minimised in the general population during high epidemic risk. Whole hospitals or hospital areas in Italy and Spain are designated as 'dirty' (suspected or proven SARS-CoV-2 infection) and 'clean' (no suspicious symptoms or the SARS-CoV-2 test is negative) areas. Facial masks are recommended for all caregivers and, if possible, for patients any time during personal contact. Health professionals taking care of immunocompromised patients

are separated into teams without mutual physical contact, to avoid simultaneous infection or preventative quarantine in the entire staff. This can be done by working on alternate days (unless the workload forbids it) or weeks and not sharing offices and common areas. Fewer or no in-person conferences take place. Children with respiratory symptoms are screened for SARS-CoV-2 before entering PH/O units. Outpatient visits for patients needing long-term surveillance are postponed. Immunosuppressed children are recommended to be isolated from general paediatric patients, where possible. Although these infection prevention measures might reduce the risk of SARS-CoV-2 transmission, they can also directly or indirectly complicate patient care. It can cause a shortage of clinical doctors, nurses, diagnosticians and technical supportive staff, drug shortages, higher stress in accompanying parents, logistic problems with transfusion and transplant products and organisational inaccuracies in clinical decision-making process due to lack of meetings.

In conclusion, heavily immunocompromised patients in the PH/O wards remain at high potential risk of acquiring infectious diseases, including COVID-19. In a striking contrast, the current number of reported cases of COVID-19 among these patients is limited to a single previously reported case from China plus the four cases reported here. More research is needed to better understand the epidemiology of SARS-CoV-2 infection and COVID-19 in paediatric patients with cancer or other immunocompromised children. More cases are expected as the pandemic is only just unfolding in many countries. This flash survey, although providing a very early picture of COVID-19, shows that the disease may have a mild course even in children receiving anticancer chemotherapy. The risk of severe disease with COVID-19 in profoundly immunocompromised children is still unknown, and predictors of asymptomatic infection, mild disease or severe and life-threatening infection would help support the development of approaches to prevent and to optimise treatment of COVID-19 in this vulnerable patient population.

Conflict of interest statement

The authors have no conflict of interest with regard to this study.

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