Title: COVID-19 in pediatric cancer: where are the brain tumors?

Authors: Rebecca Ronsley, MD, FRCPC[1], Eric Bouffet, MD, FRCPC[2]

[1]Division of Hematology, Oncology & Bone Marrow Transplant, Department of Pediatrics, British Columbia Children's Hospital, Vancouver, Canada
[2]Division of Hematology and Oncology, Department of Pediatrics, Hospital for Sick Children, Toronto, Canada

Address for Correspondence:
Dr. Rebecca Ronsley
Division of Pediatric Hematology, Oncology & Bone Marrow Transplant
British Columbia Children's Hospital
4480 Oak Street, Vancouver, BC, Canada, V6H 3V4
Email: Rebecca.ronsley@cw.bc.ca
Fax: 604-875-2911

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Abbreviation	**Full word**
CNS	Central nervous system
COVID-19	novel coronavirus disease 2/SARS-CoV-2 2019

ABSTRACT

Treatment of pediatric oncology patients generally results in significant immunosuppression and when the COVID-19 pandemic arose, there was concern among pediatric oncologists about the implications of this virus. We reviewed the literature and describe all pediatric oncology patients with COVID-19 reported worldwide. Within this review, it is striking that CNS tumors are reported at low numbers (27/466 pediatric oncology patients with COVID-19). This may be related to decreased inpatient care when compared to other pediatric cancers. Additional work is needed to understand the risk of infection in this population and gain insight into the effect on delivery of oncology care.

INTRODUCTION

The novel coronavirus disease 2/SARS-CoV-2 2019 (COVID-19) virus is highly contagious and in 2020, resulted in a global pandemic declared by the World Health Organization that has been responsible of over 2.7 Million death to date [1]. Despite overall high mortality rates with COVID-19 worldwide, early data showed that children were less severely affected by the COVID-19 virus when compared to adults [2]. However, early report from China suggested that most children who required the intensive care unit had pre-existing conditions [3].

Pediatric oncology therapies often result in significantly compromised immune states in this patient population and high risk of infection-related mortality [4-7]. As such, there was significant concern at the onset of the pandemic that oncology patients would be particularly vulnerable.

CNS tumors are the largest group of solid tumors within pediatric oncology patients. Unlike other solid tumor groups, treatment of pediatric CNS tumors is more variable in its potential for immunosuppression from intensive inpatient therapy with high dose chemotherapy and stem cell rescue to outpatient oral chemotherapy to no chemotherapy at all, depending on the tumor type. The risk of COVID-19 to this tumor group is not clear from current publications and here we sought to review the literature and to identify pediatric CNS tumors patients reported to have COVID-19 and their outcomes.

The NCBI PubMed database was queried for reports and studies presenting cases of COVID-19 or SARS-CoV-2 2019 or the novel coronavirus in pediatric cancer patients. Search terms included “pediatric” or “children” AND “cancer” AND “COVID-19” or “SARS-CoV-2 2019” or

coronavirus. Only English language articles were reviewed. Single case reports were not included.

RESULTS

We identified 14 published studies describing COVID-19 cases in pediatric oncology patients world-wide (**Table 1**). This included publications from 11 countries. Of note, one study by André et al was a duplicate in that it included data also reported within the study by Rouger-Gaudichon et al and therefore those cases were only counted once. Within these reports, there are 466 cases of COVID-19 in pediatric oncology patients (6 cases in one study were within adult patients). Of these, there were 27 patients with CNS tumors. In fact, only 4 series reported patients with CNS tumors. Although generally reported in very low numbers, one French study included 7/33 patients with CNS tumors, a significantly higher proportion than in the other publications. Two studies did not report tumor type within the COVID-19 cases.

Within all cases of COVID-19 in pediatric oncology patients, reported rate of severe illness or hospitalization requirement ranged from 5-84%. Within these hospitalized cases, a 40-86% were already hospitalized for planned oncologic therapy. Within the 466 total cases, there were 19 deaths, of which 4 were attributed to COVID-19 and the remaining 15 the authors attributed to cancer or oncologic therapy related mortality. No deaths were reported within the patients with brain tumors in these publications.

DISCUSSION

On this review of the literature, we identified several cases of COVID-19 in pediatric oncology patients from many countries around the world. Based on these publications, children with

cancer do not seem to have a higher rate of mortality from COVID-19 than immunocompetent children; although difficult to understand fully in this population who have such significant comorbidities, which may independently result in death. The mortality rate from COVID-19 for these combined reports was 3.8%. Dr. Vijenthira and colleagues summarized 34 reports that included patients with hematologic malignancies and concurrent COVID-19 infections. While that report predominantly included adult patients, where the rate of mortality from COVID-19 was much higher, a small proportion of children were identified within their review and the rate of mortality from COVID-19 was 4% [8], in keeping with the current review. It should be noted that the COVID-19 related mortality may be lower than published numbers as within these reports, many authors identified COVID-19 positive patients who eventually died, but their deaths were thought to be related to cancer or therapy complications rather from the viral infection.

Of interest, despite the relatively high proportion of pediatric oncology patients with brain tumors, these patients were significantly under-represented within published cases of COVID-19. This may be related to treatment delivery location for pediatric brain tumors, which are commonly treated as outpatients. Furthermore, many of the therapies for pediatric brain tumors are not significantly myelosuppressive and the rates of admission for complications like fever and neutropenia is known to be lower than in other pediatric oncology patients [10]. This hypothesis is supported by the finding within our review that medulloblastoma, most commonly treated with inpatient, myelosuppressive chemotherapy was the most common tumor within the patients with brain tumors who had comorbid COVID-19. Furthermore, there were no reported

cases of COVID-19 in children with low grade gliomas, generally treated completely as an outpatient, within this review.

In keeping with this hypothesis, within these reports, leukemia and HSCT patients predominate, coinciding with therapy that is typically intensive and myelosuppressive and thus delivered in the inpatient setting. Furthermore, within patients with acute leukemia, the most common reported timing of COVID-19 was at diagnosis or in early induction therapy, times when patients are typically inpatients. In their review of 34 reports, Dr. Vijenthira and colleagues found that although rates of COVID-19 were higher in inpatients, the rate of mortality secondary to the virus was not increased from the general adult population [9]. These findings within that paper and within this review may reflect hospital COVID-19 testing practices which may identify more mildly or asymptomatic patients with the virus who are admitted for scheduled oncology therapy or stem cell transplant.

Within CNS tumors in the studies included in this review, the rate of mortality secondary to COVID-19 was similar to rates within other pediatric oncology patients. This is finding is difficult to clearly elicit given the very small numbers of patients with CNS tumors. In our review of the literature, we identified case reports describing very severe forms of COVID-19 within children with CNS tumors [10]; however, the meaning of these isolated reports of individual patients is not known. Furthermore, it is not clear whether concurrent steroid therapy may have an impact on severity of COVID-19 illness in some patients. Within these studies, there were no reported cases of diffuse intrinsic pontine glioma, a tumor typically treated with prolonged steroid therapy.

One limitation of this review that should be acknowledged is that inpatient pediatric oncology patients are likely more likely to be tested for COVID-19 than outpatients or than immunocompetent children and potentially are over-represented in these reports. There may be more asymptomatic patients with COVID-19 infections within pediatric oncology patients receiving outpatient-based therapy. Testing practices have also changed during the pandemic and may detect a high proportion of asymptomatic patients. Another limitation to this data is that the reviewed studies did not include denominators with which to assess the portion of pediatric patients with CNS tumors within the authors' practices. The International Society for Pediatric Oncology (SIOP) in collaboration with St. Jude Children's Research Hospital has developed a global registry of cases of laboratory-confirmed COVID-19 in children with cancer and analysis of this data is currently underway [11]. Early observations from this registry suggest a higher proportion of asymptomatic patients in the CNS tumor population compared to other malignancies (St Jude registry, accessed: March 27 2021). This registry may provide more comprehensive, large-scale data describing COVID-19 in oncology patients, which is needed to understand the rates and risk of infection in this population and gain insight into the effect on delivery of oncology care.

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Table 1: Reported COVID-19 infections in Pediatric Oncology Patients

Country	Total patients	CNS Tumors (N)	Severity of Illness	Citation Number
Algeria	**7**	**0**	3 asymptomatic, 4 hospitalized, 2 died from COVID-19 complications	12
Egypt	**7**	**0**	All hospitalized for fever (study criteria), 3 required ICU, 3 deaths (1 related to COVID-19)	13
France	**33***	**7**	5 admitted to ICU (1 CNS tumor), 1 death (HSCT patient, authors comment heavily pretreated)	14
France	**33****	**0**	28 mild/no symptoms, 5 required ICU	15
India	**15**	**0**	10 asymptomatic, 0 ICU, 0 deaths	16
Italy	**29**	**1**	12 with symptoms, 15 hospitalized (13 for cancer therapy), none in intensive care.	17
Pakistan	**2**	**0**	1 relapsed B-ALL, 1 thalassemia major post HSCT	18
Peru	**69**	**5**	37 asymptomatic, 13 hospitalized, 3 ICU, 7 died (3 COVID-19 related deaths)	19
Spain	**47**	**Not reported**	32 required hospitalization (12 were already admitted for cancer therapy). 11 severe disease, 4 ICU, 2 died of COVID−19−related complications (both post HSCT)	20
Spain (Madrid)	**15**	**0**	7 (47%) hospitalized due to COVID−19 infection, 4 (27%) hospitalized for cancer therapy, 4 (27%) managed as outpatient.	21
Turkey	**51**	**0**	25 asymptomatic/mild, 17 moderate/severe, and 9 critical disease. 38 hospitalized (6 were already hospitalized cancer therapy), 9 in ICU and 3 intubated	22
United Kingdom	**54**	**5**	15 (28%) asymptomatic, 34 (63%) mild infection, 5 (10%) moderate, severe or critical infections	23
United States (New York)	**19**	**0**	11 were hospitalized, four (21%) required supplemental oxygen, and two (11%) required ventilation.	24
United States (New York, New Jersey)	**98**	**9**	73 symptomatic, 28 inpatient, 7 ventilated, 4 deaths (none related to COVID-19)	25
United States (New York)	**20**	**Not reported**	16 none or mild symptoms, 3 mild symptoms and hospitalized for chemotherapy or fever and neutropenia, 1 required hospitalization for COVID-19	26

*6 adult patients included in this cohort. Authors do not specify whether these patients had brain tumors

**Duplicate cases within