Pediatric Cancer Research: Surviving COVID-19

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Abstract

A diverse panel of pediatric cancer advocates and experts, whose collective experience spans the continuum of international academic medicine, industry, federal research, and cancer advocacy, recently discussed challenges for pediatric cancer research in the context of Coronavirus Disease 2019 (COVID-19). Specifically, this special report addresses the following focus areas: (1) the critical role that translational research has played in transforming pediatric cancer outcomes; (2) the current and potential future impact of COVID-19 on pediatric cancer research; (3) target areas of COVID-19 research that may have application in immunity, oncogenesis and therapeutic discovery; and (4) future considerations and directions in maintaining pediatric cancer research during and after COVID-19.

Introduction

Stakeholders in pediatric cancer care and research, including academic physicians, basic science researchers, and leaders in pediatric cancer drug development, consortia, and advocacy groups recently participated in a webinar on April 28, 2020 entitled "The Pandemic's Impact on the Pediatric Cancer Research Landscape."[1] The purpose of the webinar was to discuss the impact of Coronavirus Disease 2019 (COVID-19) on pediatric cancer care and research. Topics pertinent to current and future directions for pediatric cancer care and research are summarized in this special report.

Improving patient outcomes in pediatric cancer: the critical role for translational research

Since the introduction of chemotherapy for the treatment of childhood leukemia more than 60 years ago, the prognosis for children with cancer has improved dramatically.[2] The 5-year survival rate for childhood cancers, many of which were uniformly fatal in the pre-chemotherapy era, is now approaching 80%[3]Significant improvements in outcomes for pediatric cancers are the result of enhanced understanding of disease biology, successful application of disease risk stratification, and improved therapeutic approaches including use of multiagent chemotherapy or multi-modality therapies. Despite these advances, several childhood cancers still have unacceptably low cure rates; and even when treatment is successful, the acute and long-term morbidity and mortality of current therapy can be substantial.[4]

Central to the continuous improvement in outcome for children with cancer have been collaborative clinical-translational research efforts throughout the world. In fact, pediatric oncology as a clinical and academic subspecialty evolved in tandem with improvements in cancer outcomes for children. As cancer continues to be the leading cause of death from disease in children, it is imperative that these research efforts continue and the infrastructure supporting such research be maintained in both the near and long term.

COVID-19: Current impact on pediatric oncology care and research

As of May 6, 2020, the COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has reached over 3.5 million cases and over 245,000 deaths globally.[5] The pandemic has caused healthcare capacities to be exceeded in many countries, most notably in China, Italy, Spain, the United Kingdom and the United States. As a result, healthcare workers and associated hospital staff have been challenged with depleting basic care necessities for themselves and their patients. In addition, routine patient care, including preventative care like vaccination administration and well-childcare, has been disrupted.

Beyond the devastating toll on human life and the healthcare systems, COVID-19 has caused severe economic disruption, negatively impacting the way of life for millions through necessary social isolation and work-from-home policies as well as indefinite job furloughs or even permanent job loss. Millions of people have been confronted with difficulties in providing for themselves, their families, or their employees. Healthcare systems have not been immune to negative budget effects, especially pediatric hospitals that have seen a shift to focus on COVID-19 and lower patient volumes for routine and elective care resulting in revenue loss and need for mandated worker furloughs.

Yet most pediatric hematology/oncology and transplant care continues, albeit with some modifications, including deferrals of off-therapy visits and imaging, long-term/survivorship follow-up visits, non-essential transplants as well as the use of telemedicine to replace non-urgent follow-up appointments. In contrast, patients with new hematologic or malignant diagnoses and those on-therapy patients appear to be receiving necessary therapies, including hematopoietic cell transplants. This experience differs from adult cancer care, which has been modified substantially given the burden of severe COVID-19 in adult patients.[6]

In contrast to maintaining continuity in clinical pediatric cancer care, pediatric cancer research has been significantly interrupted by the COVID-19 pandemic. Interruptions in research include disruptions in both clinical and basic science research, performance of only essential laboratory research, limited or deferred opening of new intervention and non-intervention clinical trials, delayed or deferred data collection and reporting, and reduced revenue to support research (**Table 1**).

Support from patient advocacy groups and charitable organizations are critical to pediatric cancer research, given the comparatively low levels of government funding earmarked for pediatric cancer research. Examples of support from advocacy groups include financial support for new research via grant funding, resources for patients and families to engage in clinical trials such as providing financial support for housing and transportation, patient and family education, and government advocacy at the local and national levels. Challenges during COVID-19 for patient advocacy groups and the charity sector include: limited resources for patients and families mainly due to dramatically reduced philanthropic support, but also due to social restrictions affecting patient movement and lodging; reduced community engagement given direct effects of the pandemic on donor finances and health; and less government advocacy impact given its focus on the pandemic and its reallocating resources to address the pandemic (**Table 2**).

Importantly, industry has a vital role in supporting pediatric cancer research through drug discovery, laboratory research, and co-development of and support for clinical trials. Current challenges faced by industry include reduced available workforce, reallocation of resources to focus on assessment of pipelines for agents with potential value for COVID-19 patients, and contracted budgets for drug discovery (**Table 3**).

Taken together, COVID-19-related challenges among academic institutions, advocacy groups and pharmaceutical industries are significant. How profound the impact these challenges will have on pediatric oncology research will be determined by several factors: sustained prevalence of COVID-19 determined by availability

of point-of-care viral screening and serologic testing as well as vaccine development; favorable risk-benefits for loosening social restrictions that currently limit research as well as impact patients and families; availability of laboratory reagents and clinical therapies as determined by supply line disruptions; and availability of funding and resources at the institutional, government[7] and philanthropic[8] levels based upon recovery of global and local economies.

COVID-19: focus on pediatrics and the immune response to SARS-CoV-2

Significant morbidity and mortality secondary to COVID-19 infection have largely spared the pediatric population, including pediatric hematology, oncology and hematopoietic cell transplant patients.[9]In general, immunocompetent pediatric patients with COVID-19 experience less severe disease than adult patients,[10,11]particularly adults with co-morbidities like cardiovascular disease, chronic lung disease, and diabetes.[12,13] Children identified at higher risk for severe COVID-19, as defined by the need for hospitalization or intensive care, include those with chronic cardiovascular or lung diseases, infants under one year of age, and immunocompromised patients receiving immunosuppression.[14]

SARS-CoV-2 viral loads correlate with disease severity, as patients with severe disease have higher viral loads and longer decay times than those with mild or moderate symptoms.[15] In contrast to viral dynamics, the immune response to SARS-CoV-2 remains undefined, though decreases in $CD8^+$ T-cells and B cells in adults have been correlated with severe COVID-19 and poor response to therapy[16] while $CD8^+$ T-cells and B cell recovery have been associated with moderate disease.[17] Decreases in regulatory T cells have also been linked with a hyperinflammatory response in adults,[18] requiring the use of monoclonal blocking antibodies like tocilizumab, an anti-interleukin 6 (IL-6) agent.[19] Interestingly, immune dysregulation and hyperinflammation as measured by whole blood transcription profiles have also been shown to correlate with severe respiratory syncytial virus (RSV) disease in infants,[20] who also have higher viral loads and more protracted viral decay than infants with mild RSV.[21] Similarly, reports are emerging that some children with COVID-19 are experiencing clinical symptoms and signs consistent with Kawasaki Disease,[22,23] a multisystem inflammatory disease of unclear etiology but often associated with respiratory viral infections.[24]

Despite their generally experiencing milder COVID-19, immunocompetent pediatric patients have high viral loads[25] and may shed SARS-CoV-2 for weeks from the upper respiratory and lower gastrointestinal tracts after primary infection.[26]This discrepancy between having milder COVID-19 despite having high viral loads and prolonged viral shedding suggests that children may differ from adults in their immune response to SARS-CoV-2. To this end, children and adults have defined differences in both innate[27] and adaptive immune responses[28]. As adults have a more pro-inflammatory background, they may be predisposed to more severe COVID-19 via a hyperinflammatory response to SARS-CoV-2.

Adults and children also differ in their immune response to viral challenge[29]. Type I interferons (IFN) are key cytokines that have direct viral cytotoxic effects[30]as well as immunomodulatory effects on both innate and adaptive immune cells.[31] Deficits in type I IFN have been correlated with persistent viral load and exacerbated inflammatory response in adult patients with severe COVID-19.[32,33]Interestingly, children with mild RSV disease (outpatient care) have recently been shown to have higher viral loads, greater induction of IFN genes and decreased gene expression of inflammation and neutrophils versus children with severe RSV (inpatient care).[34]

Taken together, epidemiologic and immunologic data on SARS-CoV-2 infection are emerging that may be helpful to explore why pediatric patients experience less severe COVID-19 and to implement potential therapies that would either augment helpful or inhibit harmful immune responses to SARS-CoV-2.[35]

COVID-19 and pediatric cancer research: potential avenues for common investigation

Our knowledge about anti-microbial and anti-cancer responses continues to evolve, as we gain understanding for their common inflammatory cellular and molecular pathways.[36,37] For example, type I interferons have direct anti-viral effects, but also have key roles in anti-tumor immunity.[38] Furthermore, both cancer and infectious pathogens use similar strategies to avoid immune recognition.[39] Finally, chronic inflammation[40]

and certain viral pathogens themselves promote oncogenesis. Therefore, immune profiling of SARS-CoV-2 infection may elucidate pathways involved in oncogenesis or inflammation that could be targeted with novel or repurposed cancer or supportive therapies.[41]

Commonalities between anti-viral and anti-tumor responses provide "silver linings" during the COVID-19 pandemic, given they could potentially foster and provide new directions for discovering therapies for cancer and COVID-19 (**Table 4**). For example, the BCR-ABL tyrosine kinase inhibitor (TKI), imatinib, revolutionized the treatment of Philadelphia-chromosome positive (Ph^+) ALL, such that allogeneic hematopoietic cell transplant in patients achieving molecular remission is no longer needed.[42] Given its development as an ABL kinase inhibitor, imatinib has been shown to block coronavirus membrane fusion, inhibiting viral entry into cells.[43] Similarly, the janus kinase (JAK) 1/2 inhibitor, ruxolitinib, and the blocking monoclonal IL-6 antibody, tocilizumab, may inhibit SARS-CoV-2-induced hyperinflammation[19] in addition to their use in steroid-refractory graft-versus-host disease (GvHD) following allogeneic hematopoietic cell transplant[44] and cytokine storm following chimeric antigen receptor (CAR) T cell therapy,[45] respectively. Lastly, type I IFN, a key cytokine against viral infection and cancer,[46] is being explored as a potential therapy against COVID-19.[47]

Community respiratory viral infections are the most common type of infection in children. Given its high prevalence, high transmissibility, and lack of established therapeutic and preventative agents, SARS-CoV-2 will likely infect the majority of adults and children. Therefore, defining potential associations of SARS-CoV-2 with future cancer risk, especially in minority populations,[48,49] seems warranted. As an example, *in utero* cytomegalovirus (CMV) infection has been associated with subsequent ALL risk (OR=3.71, p=0.0016) most pronounced in Hispanics (OR=5.90, p=0.0006) and hypothesized to occur given the supportive role of CMV in oncogenesis through induction of chromosomal instability and immune dysregulation.[50] To be clear, no specific endemic coronaviruses have been linked to cancer risk and there is no *a priori* biologic reason to hypothesize an association with COVID-19. But observations seem prudent, especially as the immune response to SARS-CoV-2 remains undefined at this time.

In summary, mechanistic investigation into how SARS-CoV-2 induces different immune responses in various patient populations could provide invaluable insights for the fields of infectious disease and oncology research. Likewise, clinical and epidemiology exploration defining the role of SARS-CoV-2 and the influence of COVID-19 in other disease processes might also reveal roles for the virus not previously appreciated.

COVID-19 and pediatric oncology: Where do we go from here?

COVID-19 has impacted the entire world. Beyond its staggering toll on the health and survival of multitudes of people, COVID-19 will continue to impact many more millions of people given the need to restructure life in response to an evolving pandemic. Adaptation to change requires flexibility in approaches for continuing pediatric oncology care and research, some of which may be carried forward given their potential longer-term value as measured by improved efficiency, decreased burden to families, cost reduction, and ultimately new growth opportunities (**Table 5**).

The health crisis caused by COVID-19 warrants both scientific collaboration and reallocation of resources to contain its spread and to eradicate the disease entirely. However, other significant health care crises remain and potentially may be exacerbated by COVID-19, both directly by the virus itself or indirectly by the changes in life that the virus has caused. To this end, pediatric cancer remains the primary disease-related cause for mortality in children. Therefore, we must not lose focus on the need to continue to support, both scientifically and financially, research that is vital to discovering potential cures for pediatric cancer both to minimize the negative impact of COVID-19 and to leverage the lessons learned to make us better than before. Not fulfilling these missions jeopardizes the future of children with cancer, their families, and their communities.

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Table 1. COVID-19-related challenges to pediatric cancer research performed at academic institutions

Challenges	Potential reason(s)	Potential consequence(s)
Workforce-related		
Reduced clinical research workforce	Contract COVID-19 Reduced staff (furloughs, job loss) Work from home mandates	Delay in patient recruitment Delays data collection and submission Potential compromise in data quality
Reduced laboratory research workforce	Contract COVID-19 Reduced staff (furloughs, job loss) Work from home mandates Exclusion of trainees due to social distancing	Little to no laboratory research being performed beyond "essential" Delays in publications, grant submissions, report deadlines due to incomplete data Delayed or compromised training of future workforce
Reduced capacity of institutional review board (IRB)	Reduced staff (furloughs, job loss) Work from home mandates More protocol amendments Influx of COVID-19-related protocols	Deferred or prolonged new protocol review Prolonged review of protocol amendments
On-site monitoring suspended	Sponsor (furloughs, job loss, work from home mandates)	Reduced interaction with sponsor Less sponsor oversight, increased data errors
Consent process by phone	Phone consent	Compromised patient understanding especially low socio-economic status patients
Research		
Observational research (natural history)	Deemed nonessential	Gaps in registry patient data
Biorepository databases	Deemed nonessential	Less patient biospecimens
Phase I and II trials	Suspended	Less treatment options for patients with relapsed, refractory disease
Reduced clinical revenue from hospital	Decreased patient volumes	Furloughed or permanent loss of clinical research workforce
Funding		
Institutional	Reduced patient care volumes, budget	Slower discovery and delayed impact on patients
Government	Limited or reallocated resources	Slower discovery and delayed impact on patients
Philanthropic	Reduced funding due to lower donations	Slower discovery and delayed impact on patients

Table 2. Challenges for pediatric cancer advocacy and funding groups during the COVID-19 pandemic

Challenge	Potential reason(s)	Potential consequence(s)
Reduced financial support / philanthropy	Limited donations given personal budget constraints or loss of revenues from in person event cancellations and economic uncertainties	Less resources to offer patients and families, less funding for treatment and non-treatment related expenses New programs delayed or cancelled Grant opportunities reduced, delayed or cancelled
New patients not recruited to sponsored clinical trials	Resources diverted to COVID-19 Perceived risk to patients	Increased anxiety and fear among patients and families Reduced options for treatment of relapsed/refractory disease, potential reduction in overall survival
Sponsored programs delayed or cancelled	Research and development resources diverted Research labs closed Workers furloughed	Pressure from donors and supporters to move programs forward Unanticipated additional costs
Reduced community engagement	Community focus on COVID-19	Reduced philanthropy
Limitations in available housing and transportation	Restrictions in place from COVID-19	Impact on clinical care
Reduced lobbying for pediatric cancer	Government focus on COVID-19	Less government awareness and earmarked funding
National and international pediatric oncology meetings cancelled or postponed	Missed opportunities for engagement with other stakeholders	Collaborative partnerships not developed

Table 3. Industry challenges due to COVID-19

Challenge	Potential reason(s)	Potential consequence(s)
Reduced financial support	Limited budgets	Less discovery of novel molecules
Reduced clinical research workforce	Contract COVID-19 Reduced staff (furloughs, job loss) Work from home mandates	Delay in recruitment Delays in data collection and submission Potential compromise in data quality
Reduced laboratory workforce	Contract COVID-19 Reduced staff (furloughs, job loss) Work from home mandates Exclusion of trainees due to social distancing	Little to no laboratory research being performed beyond "essential" Delays in publications, report deadlines due to incomplete data Delayed or compromised training of future workforce
Reallocation of resources	Shifting portfolios to COVID-19	Less discovery, less clinical trials in oncology

Challenge	Potential reason(s)	Potential consequence(s)
Implementation of novel therapeutics	Deferring trials involving agents that suppress immune system, increase susceptibly to COVID-19 Minimizing therapy-related risk to the patient	Less discovery, less clinical trials in oncology, less enrollment of eligible patients

Table 4. Potential new directions for cancer research related to COVID-19

	Focus	Potential benefit(s)
Basic science		
Immune response to SARS-CoV-2	Define immune pathways Define immune therapeutic targets Define antibody induction and duration	Redirection of new knowledge toward understanding and implementing immunotherapies for pediatric cancer
ACE2 receptor	Explore role in lung metastases	Increased understanding for tumor immunology
Endothelial cell activation	COVID-19-related microangiopathy and thrombosis	Increased understanding for vascular metastasis and thrombosis
Clinical research		
Biorepository	Collect samples prospectively, analyze retrospectively	Define mechanism of action and biologic effects as new diagnostics and therapies advance
Repurposing cancer therapeutics		
Data collection on cancer patients with and without COVID-19	Define influence of COVID-19 on cancer outcomes	
Epidemiology studies	SARS-CoV-2 and risk for childhood malignancies	

Table 5. New approaches and directions for pediatric oncology following COVID-19

	Previous approach	New approach / direction
Clinical		
Clinic visits	In-person visits	Telehealth visits for non-urgent follow-ups
Workforce	In-person work week	Work from home, staggered work schedule
Research		
Site monitoring	In-person sponsor visits	Video-link sponsor visits
Prioritization of new diagnostics and therapeutics	Conventional FDA review	Fast track FDA review
Database	Separate data collection and storage	Database sharing
Protocol accommodations	Administration of drug in hospital setting	Shipping investigational agent to patient's home

	Previous approach	New approach / direction
Government agencies	Visit to FDA and EMA	Work from home makes more flexible schedules, easier access
Other		
Rechanneling efforts	Investigators physically met at institution or national/international meetings to share data	Video conferencing facilitates data sharing and idea generation as well as environmental impact (reduction in carbon footprint and pollution resulting from loss of industrial activity and reduced travel)
Collaborations	Competition among research groups	Aligning resources and talents across borders and institutions Accessing and leveraging non-pediatric oncology disease research to interrogate potential oncolytic efficacy

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