





How the COVID-19 Pandemic Reshaped the Management of Leukemia and Affected Patient Outcomes

Noha Sharafeldin, MD, MSc, PhD^{1,*} 
Benjamin Bates, MD²
Pankit Vachhani, MD¹ 

Address

^{*1}Division of Hematology and Oncology and O'Neal Comprehensive Cancer Center, Heersink School of Medicine, University of Alabama at Birmingham (UAB), 1600 7th Avenue South, Lowder 500, Birmingham, AL, 35233, USA
Email: nsharaf@uab.edu

²The Institute for Health, Health Care Policy, and Aging Research, Rutgers University, New Brunswick, NJ, USA

Published online: 25 March 2022

© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2022

This article is part of the Topical Collection on *Leukemia*

Keywords Leukemia · COVID-19 · Cancer care · COVID-19 vaccination · Adult malignancy pediatric malignancy

Opinion statement

The coronavirus disease-19 (COVID-19) pandemic has posed numerous challenges to the global healthcare system. Of particular gravity is adult and pediatric patients with hematologic malignancies who are among the most vulnerable groups of patients at risk of severe COVID-19 outcomes. In the early phases of the pandemic, several treatment modifications were proposed for patients with leukemia. Largely speaking, these were adopting less-intense therapies and more utilization of the outpatient setting. Over time, our understanding and management have become more nuanced. Furthermore, equipped with vaccinations to prevent COVID-19 infection and availability of treatments in the presence of COVID-19 infection, the recommendations on management of patients with leukemia have evolved. Patient's leukemia characteristics, possibility of targeted therapy, vaccination status, symptomatology, comorbidities, goal of anti-leukemic therapy, the intensity of therapy, the setting of treatment, as well as loco regional factors like dynamic incidence of COVID-19 in the community and hospital/ICU bed status are among many factors that influence the decisions. Furthermore, the oncology community has adopted delaying the anti-leukemia therapy for a limited time frame, if clinically possible, so as to still deliver most appropriate therapy while minimizing risks. Early adoption of growth factor support and conservative blood transfusion practices have helped as well. In this

review, we discuss the impact of COVID-19 on outcomes and share considerations for treatments of leukemias. We describe the impact on both clinical care (from diagnosis to treatment) and research, and cover the literature on vaccines and treatments for COVID-19 in relation to leukemia.

Introduction

The coronavirus disease-19 (COVID-19) pandemic has affected virtually every aspect of cancer care in the United States (US) and globally, extending from the initial diagnosis of cancer to enrollment in clinical trials [1–4]. In part due to the nature of hematologic malignancies and the associated interventions, patients with acute and chronic leukemias are considered among the highest risk for contracting COVID-19, presenting with symptoms, and developing severe outcomes [5, 6–10]. There have been significant breakthroughs in the repurposing of

available therapies and in the development of new therapies to reduce the risk of infection and severe outcomes among patients who are infected with COVID-19 [11]. Despite therapeutic successes, the mutagenicity of COVID-19, resultant successive waves of COVID-19, and poor serologic response among immunocompromised persons, further clinical and epidemiologic studies are needed regarding benefits and risks of COVID-19 interventions [12].

Epidemiology of COVID-19 outcomes in acute and chronic leukemia

Multiple retrospective studies of real-world data have supported an increased risk of developing severe outcomes-related to COVID-19 among patients with hematologic malignancies [5, 7, 9, 10, 13]. Most studies, however, have reported on hematologic malignancies collectively without differentiating between subtypes [5, 10]. Mileham et al., using the American Society of Clinical Oncology (ASCO) Registry, focused on risk factors associated with outcomes in patients with hematologic malignancies and identified a higher risk of mortality among older patients with B-cell malignancies. Compared to patients ≤ 60 years, 61–70 years were at twice the risk of death (95%CI 1.3–3.3) while >70 years were at 4.5 times the risk (95%CI 1.8–11.1). A similar association with older age was not observed in patients with metastatic solid tumors [9]. Leveraging two different European sources to aggregate 941 patients with chronic lymphocytic leukemia (CLL), Chatzikonstantinou et al. described a mortality of 27% among patients with CLL who contracted COVID-19; among patients who developed severe COVID-19 (defined in this study as hospitalization plus oxygen requirement or admission to an intensive care unit (ICU)), the mortality was 38% [7]. Roeker et al. demonstrated a similarly elevated mortality among patients with CLL who contracted PCR-diagnosed COVID-19 (28% mortality overall; 36% among the hospitalized) [8]. Using the NCATS National Covid Cohort Collaborative (N3C), a centralized dataset representing one of the largest repository of COVID-19 cases and controls in the US, Sharafeldin et al. found patients with electronic health record diagnosis of a hematologic cancer had approximately 15% greater mortality rate within 10

days of admission to the hospital with COVID-19 compared to a COVID-19 positive non-cancer control [5•]. Results from the COVID-19 and Cancer Consortium (CCC19), a registry formed in March 2020 to study COVID-19 outcomes in patients with current or past history of cancer, showed among cancer patients, hematologic malignancies were consistently associated with worse COVID-19 outcomes [10, 14], and was the highest among CLL compared to other hematologic malignancies [15]. A multicenter study of 66 hematology units from Italy, showed hematologic malignancy patients had a 4 times higher mortality risk compared to the general population; furthermore, mortality among hematologic malignancy patients infected with COVID-19 were 41 times higher than non-infected patients. Hazard ratio of death among acute myeloid leukemia was estimated at 3.49 (1.56–7.81) [16]. A case-series study of leukemia patients across 7 centers in Istanbul reported a significantly higher mortality rate among acute myeloid leukemia patients infected with COVID-19 compared to patients without COVID-19, underscoring the need for aggressive infection prevention among hospitalized acute leukemia patients [17].

Delays in diagnosis and disruptions to care

The pandemic caused delays and disruptions in health care worldwide including cancer care, affecting screening practices, diagnosis, treatment, palliative, and rehabilitation services [18]. An April 2020 analysis of 20 US healthcare institutions, using the COVID and Cancer Research Network, reported a 46.6% reduction in patients with new incidence of hematologic cancers and a 39% reduction in encounters in patients with cancer compared to the same time period in 2019 [19]. A systematic review of studies examining the impact of COVID-19 on essential health services identified 38 different categories of overall delays and disruptions of cancer care globally: 22 were treatment-related, 7 were diagnosis-related, and 9 were related to general health services [20]. Only 5% of the studies reviewed, however, had reported on patients with hematological cancers. For example, interruption of bone marrow biopsies was reported by 14% of oncologists surveyed at 63 different Italian Centers [21]. A follow-up review by the same group on the impact of strategies to mitigate delays and disruptions of cancer care found they were not carefully designed to specifically address an outcome of interest which hinders their ability to inform the decision-making process. Furthermore, consensus best practices continued to rely on expert committees' recommendations [22].

Optimal cancer care must balance the risks of potentially exposing cancer patients and/or their caregivers to COVID-19, while also ensuring early diagnosis and timely treatment. Cancer-related deaths were projected to increase as a result of the impact of the pandemic on health care systems. A study from the UK using real-world and modeled data on cancer care estimated an 8.3% increase in 1-year mortality risk among prevalent cases of leukemia and 19.6% among incident cases. Assuming a 10% COVID-19 infection rate, leukemia was among the top 10 cancers with excess cancer-related deaths over 1-year period; the rise in those estimates was proportional to an increase in the infection rate [23]. Those early projections were a clear indication that delays in

diagnosis and disruptions to treatment would exacerbate further the detrimental effects among the most vulnerable patients with hematologic malignancies.

Clinical trial participation

Disruptions to cancer care were not limited to clinical care but also extended to research activities including conduct of cancer clinical trials. Several academic and community-based clinical trial programs halted or prioritized screening and enrollment for certain clinical trials and ceased research-only visits, as shown by a survey launched by ASCO [24]. Enrollment on cancer trials and protocol adherence proved to be challenging early in the pandemic, compounded with challenges faced by investigators to modify trial procedures through lengthy discussions with sponsors, contract research organizations (CROs), and institutional review boards. Challenges were also observed on the patient side, with over half of survey respondents indicating a decrease in patient ability and willingness to come to study visits. Despite the initial implementation challenges, the pandemic also offered opportunities for improvement in the conduct of clinical trials that could be adapted long-term post-COVID-19. The vast majority of surveyed investigators were in favor of telehealth participant visits and remote patient review of symptoms, while sponsors and CROs positively viewed remote site initiation visits and trial monitoring [24]. A subsequent report published by ASCO evaluating adaptations in cancer care delivery, research operations, and regulatory oversight in response to the COVID-19 pandemic, recommended five goals each for clinical research and cancer care delivery as the pandemic recedes [25]. The goals centered on ensuring equitable, accessible, affordable research and care, minimizing regulatory burdens, retaining well-trained work-force, and promoting telemedicine.

Despite being one of the most vulnerable populations to severe COVID-19 outcomes, exclusion of patients with cancer from participating in COVID-19 treatment and/or vaccination clinical trials continued to persist [26]. One of the earliest efforts to address disparities in clinical trial participation included the trial (LLS Protocol Number: BAML-16-001-COV1) launched by the Leukemia & Lymphoma Society (LLS) to test the drug acalabrutinib (Calquence) in patients who had tested positive for COVID-19 and were diagnosed with acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndromes, and aplastic anemia, all of whom are often excluded from COVID-19 clinical trials based upon very low blood counts. However, early reports of the CALAVI phase II trials for acalabrutinib in patients hospitalized with respiratory symptoms of COVID-19 did not meet the primary efficacy endpoint and the trial was prematurely terminated [[ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04497948) identifier, NCT04497948]. Trial reports showed addition of acalabrutinib to best supportive care did not increase the proportion of patients who remained alive and free of respiratory failure. In February 2021, the VOICE (vaccination against COVID in cancer) [[ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04715438) identifier, NCT04715438] a multicenter, prospective, non-inferiority trial was launched in the Netherlands [26]. The trial, however, only enrolled patients with solid tumors, and showed patients on active chemotherapy, immunotherapy, or both mounted an adequate antibody response to vaccination with no serious safety concerns or vaccine-related deaths [27]. At

the time of this review, an ongoing, actively recruiting trial, sponsored by the US National Cancer Institute (NCI) was launched in April 2021 to study the safety and immunogenicity of the COVID-19 vaccine in patients with hematologic malignancies [[ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04847050) Identifier: NCT04847050]. Participants will receive 2 doses of the mRNA-1273 vaccine, with options for up to 2 booster injections on study and will be followed prospectively for 12 months. Results from this trial will provide critically needed information supporting safety and tolerability of vaccinations in this vulnerable group of patients.

Prevention and management of COVID-19 in leukemia patients

General care recommendations

An international panel of hematologists and oncologists specialized in leukemia, myeloid neoplasms, and transplant care provided sets of key recommendations for leukemia care during the pandemic [28••]. Summary of the main recommendations included shifting the patient care to the outpatient setting and /or telehealth as feasible and individualizing the need for an in-person follow-up and testing; advance care planning especially for patients with poor prognosis; maintaining a hemoglobin serum concentration ≥ 7 g/dL and avoid prophylactic transfusions during times of severe blood product shortages; consider liberal use of growth factor support in patients without COVID-19 to minimize neutropenia; avoid the use of growth factors in patients with moderate to severe COVID-19 infection to protect against rare but potential risk of exacerbating COVID-19-related inflammatory pulmonary injury; continue patient accrual in therapeutic and late salvage clinical trials offering the only viable treatment option for patients while enrollment on clinical trials of commercially available standard-of-care therapies should be re-evaluated during pandemic surges [28••].

Vaccination among non-hospitalized patients

The immunosuppressed state of people with leukemia has been a concern since the beginning of the COVID-19 pandemic. The development of COVID-19 vaccines was an important milestone to reduce the risk of contracting and developing severe COVID-19 symptoms [11]. Nevertheless, the immunocompromised state of patients with leukemia, a combination of disease and immunosuppressive therapies, has raised questions regarding the effectiveness of COVID-19 vaccines among people with leukemia [6, 29–31]. Some of the strongest evidence regarding reduced antibody formation from COVID-19 relate to B-cell-depleting therapies, such as anti-CD20 monoclonal antibodies (e.g., rituximab, ofatumumab, obinutuzumab) [29, 32, 33]. Specifically, Zeng et al., using a study population comprised of patients with cancer and non-cancer control health care workers (HCW), demonstrated CLL demonstrated a lower mean antibody response than solid tumors and HCW controls; in comparing patients with CLL who were not prescribed B-cell-depleting therapy, B-cell-depleting therapy use was associated with lower mean antibody levels [32].

Greenberger et al. conducted a prospective cohort study using The Leukemia & Lymphoma Society National Registry to assess the serologic response of patients with hematologic malignancies following mRNA vaccine [30]. Among the patients with B-cell malignancies, 78% were seronegative prior to the third

dose; and 65% demonstrated an increase in the antibody level after the third dose of vaccine. Following three vaccine doses, 35% were still non-responders. In subgroup analysis, among patients who had received anti-CD20 antibodies, 33% demonstrated seroconversion following only two doses, 9.5% seroconverted following the third-dose of vaccine, and 57% did not seroconvert even after the third-dose. BTK inhibitors (BTKi) appeared to be correlated with poor antibody development following vaccination. Overall, the study found many patients with hematologic malignancies were at risk of not producing antibodies after two doses of the mRNA vaccines. Despite failure to mount a full antibody response, the safety profiles of SARS-CoV-2 mRNA vaccines were similar to age-matched healthy individuals supporting the NCCN recommendations to vaccinate patients with hematologic malignancies [30]. Early evidence showed increased antibody titers in cancer patients who received an additional vaccine dose with similar side effects to prior doses [29]. However, in two participants with CLL treated with obinutuzumab in the prior year remained seronegative. In another prospective study of patients on active treatment for myeloproliferative malignancies (MPM), including chronic myeloid leukemia receiving the BNT162b2 vaccine, demonstrated a 5-week immunogenic response of 88% seroconversion rate which was significantly higher than multiple myeloma patients [34].

Further investigation is required to understand to what extent booster doses may be able to improve antibody response among patients recently or currently exposed active cancer treatments.

Patients with hematologic malignancies continue to be over-represented among vaccinated patients with cancer who develop breakthrough COVID-19 infections [35], and were the highest among lymphoid and myeloid leukemia compared to solid tumors [6]. Furthermore, the most recent evidence on vaccine effectiveness and infection-acquired immunity showed two doses of BNT162b2 vaccine were associated with initial short-term protection against SARS-CoV-2 infection that waned in the following 6 months while infection-acquired immunity boosted with vaccination remained high for more than 1 year after infection [36]. These findings collectively underscore the importance of maintaining COVID-19 precautions including vaccination of close contacts, masking, boosters, and social distancing. In August 2021, the FDA authorized a third vaccine dose (preferably an mRNA-based vaccine) for certain immunocompromised individuals, including patients with leukemia, signifying an immunocompromised person requires three doses of a COVID-19 vaccine to be considered “fully vaccinated” [37].

Monoclonal antibodies among non-hospitalized patients

Patients with leukemia who develop COVID-19 are designated as immunocompromised and are managed accordingly. If the patient is not hospitalized, then the standard recommendation is that the patient be provided a monoclonal antibody authorized by the FDA’s COVID-19 Emergency Use Authorization (EUA) [38]. The majority of the monoclonal antibodies available under the EUA were developed to target the SARS-CoV-2 spike protein, which is used by the virus to enter the cells of the infected host. Example monoclonal antibodies include bamlanivimab/etesevimab, casirivimab/imdevimab, sotrovimab, and bebtelovimab. At the time of the initial EUA, these monoclonal antibodies were

recommended for patients with diagnosed COVID-19 and an underlying immunocompromised state. Tixagevimab/cilgavimab was created as a pre-exposure prophylaxis against COVID-19 and recommended to be used for patients who are considered moderate or severely immunocompromised due to an underlying medical condition or treatment; have history of severe adverse reaction to COVID-19 vaccine or its components; or may not mount an adequate immune response to the vaccine.

While research on monoclonal antibodies is actively ongoing, mutations in the spike proteins of Omicron variant have raised concerns regarding the effectiveness of monoclonal antibodies. Specifically, the mutations are considered to most effect bamlanivimab/etesevimab and casirivimab/imdevimab. At this time for the Omicron variant, sotrovimab and bebtelovimab are considered most effective for non-hospitalized treatment purposes, while tixagevimab/cilgavimab can be used as a pre-exposure prophylaxis, respectively [39].

Interventions among hospitalized patients

Similar to outpatient management of COVID-19, patients with leukemia are categorized as being immunocompromised; furthermore, the changing nature of the pandemic and treatment options should be carefully followed. At the present time per the Infectious Disease Society of American IDSA guidelines, there is evidence to suggest the following therapies may demonstrate effectiveness among hospitalized patients with COVID-19: corticosteroids, tocilizumab, sorilumab, remdesivir, baricitinib, tofacitinib [40]. Table 1, adapted from the IDSA guidelines, categorizes use of hospitalized (severe vs. critical disease), strength of evidence (suggest vs. recommend), and certainty of evidence (high, moderate, low, and very low). Convalescent plasma therapy was also shown to have a potential survival benefit and an estimated 40% reduction in 30-day mortality in hospitalized patients with COVID-19 and hematologic cancer (HR, 0.60; 95% CI, 0.37–0.97). This association remained significant after

Table 1. COVID-19 treatment options for patients hospitalized with COVID-19 according to the Infectious Disease Society of America (IDSA)

Treatment	Hospitalized with severe disease		Hospitalized with critical disease	
	Strength of evidence	Certainty of evidence	Strength of evidence	Certainty of evidence
Baricitinib + remdesivir + corticosteroids	Suggest use	Moderate		
Corticosteroids	Suggest use	Moderate	Recommend use	Moderate
Remdesivir	Suggest use	Moderate		
Baricitinib + remdesivir	Suggest use	Low		
Tocilizumab	Suggest use	Low	Suggest use	Low
Tofacitinib	Suggest use	Low		
Sarilumab	Suggest use	Very low	Suggest use	Very low

These recommendations were adapted from guidelines v6.0.0—last updated January 12, 2022. Please see online version for IDSA most recent updates and recommendations [40]

Table 2. Cancer care consideration during COVID-19 pandemic by leukemia subtype

	Acute myeloid leukemia (AML)	Acute lymphoblastic leukemia (ALL)	Chronic myeloid leukemia (CML)	Chronic lymphocytic leukemia (CLL)
Risk for severe COVID-19	Greater than general population: Myelosuppression secondary to induction therapy	Greater than general population: Myelosuppression secondary to induction therapy	Similar to general population: Risk stratify by considering standard COVID-19-related factors, including age, underlying comorbidities, living conditions, and vaccination status	Greater than general population: Due to underlying immunodeficiency and inadequate immune response to infections, patients with CLL are at elevated risk for infections.
Minimization of	Interactions for COVID exposure	Minimize in-person healthcare interaction through promotion of telehealth, minimization of routine bloodwork, minimize aggressive treatment that may require prolonged inpatient care (promote outpatient cancer treatment as appropriate)		
Cancer treatment (COVID-19 negative)	COVID-19 community burden: For all types of leukemias, the incidence of COVID-19 and hospital capacity should be considered when considering treatments of choice. If incidence of COVID-19 is low, then abiding by disease-based guidelines should be adhered to. However, as the local incidence of COVID-19 rises, greater caution with regards to the use of high-risk therapies should be applied. Induction therapy: Continue to offer 7+3 (or similar regimen); may consider lower intensity therapy as may allow for less healthcare utilization needs (e.g., clinic visitations, transfusions) Consolidation therapy: If candidate for high-dose cytarabine, can continue to offer but may consider decreasing the number of cycles from four to three Salvage therapy: While re-induction may be considered, should also weigh against prolonged hospitalization with greater restriction on visitations.	Induction therapy for ALL Ph-: Continue with current care but may consider dose reducing daunorubicin (50%) or pegasparagase (e.g., 1,000 IU/m ²), if patient considered at high risk for complications from myelosuppression. Induction therapy for ALL PH+: Preference for less aggressive measures (e.g., TKI with steroids), rather than aggressive induction chemotherapy; goal to avoid prolonged hospitalization during the pandemic Consolidation therapy: In order to reduce hospitalization stay, may use inotuzumab outpatient or quickly transition to blinatumomab outpatient treatment	Tyrosine kinase inhibitors (TKI): Can continue standard TKI treatment as there is no evidence to suggest TKIs elevate or lower the risk of COVID19 Treatment-free remission: In order to minimize healthcare interaction, it can more readily consider initiation of treatment-free remission (but with continuation of PCR every 3 months).	B-cell receptor (BCR) signaling inhibitors: Continue with standard treatment as there is no evidence to suggest BCR signaling inhibitors elevate the risk of COVID-19. CD20 targeting monoclonal antibodies: Due to the specific immunosuppressive effects of CD20 monoclonal antibodies, some physicians may avoid or skip treatment with these therapies, especially if being used in combination with other targeted agents. Venetoclax: Initiation of venetoclax requires inpatient setting or multiple extended clinic visits with lab testing initially; if able, can consider deferring initiation until later period

Table 2. (Continued)

	Acute myeloid leukemia (AML)	Acute lymphoblastic leukemia (ALL)	Chronic myeloid leukemia (CML)	Chronic lymphocytic leukemia (CLL)
Cancer treatment (COVID-19 positive)	During periods of COVID-19 surge, test patients for COVID-19 prior to hospitalization; if COVID-19 positive, withhold cancer-directed therapy for 14 days following COVID-19 diagnosis. Then, even if PCR-positive, can start or restart cancer-directed therapy as viral fragments can be present for extended duration	During periods of COVID-19 surge, test patients for COVID-19 prior to hospitalization; if COVID-19 positive, withhold cancer-directed therapy for 14 days following COVID-19 diagnosis. Then, even if PCR-positive, can start or restart cancer-directed therapy as viral fragments can be present for extended duration	TKI: For non-severe COVID-19 infection, can continue TKI. However, if respiratory symptoms are worsening, TKI interruption should be considered due to the potential for overlapping cardiopulmonary complications.	BTK signaling inhibitors: There is no evidence to support stopping BTK signaling inhibitors. In fact, there are some studies to support potential benefit from BTKis; also potential for CLL flare and cytokine release following BTKi discontinuation, potentially mimicking symptoms of COVID-19 CD20 targeting monoclonal antibodies: Due to the specific immunosuppressive effects by CD20 targeting antibodies, it is recommended to stop therapy during COVID-19 infection
Vaccination	Vaccination is strongly recommended for all leukemia subtypes. Studies have demonstrated reduced antibody response to vaccination, notably for patients receiving B-cell depleting therapies. However, there is no current evidence to support concern regarding COVID-19 vaccination from reducing cancer treatment effectiveness or increasing risk of underlying treatment.			
Comments for each of the leukemia subtypes are adapted from the American Society of Hematology expert opinion: AML (https://www.hematology.org/covid-19/covid-19-and-acute-myeloid-leukemia), ALL (https://www.hematology.org/covid-19/covid-19-and-all), CML (https://www.hematology.org/covid-19/covid-19-and-cll), and CLL (https://www.hematology.org/covid-19/covid-19-and-cll).				

propensity score matching (HR, 0.52; 95% CI, 0.29–0.92) and the protective effects were sustained among patients admitted to the ICU and patients requiring mechanical ventilation when compared to patients not receiving convalescent plasma [41].

Impact on therapy

Since the start of the pandemic, the infrastructure of daily cancer care has dramatically changed: virtual visits with the cancer care team, more meticulous planning of lab tests, and lower bar to reduce intensity of therapy or substitute therapeutic options. Conversely, due to the lethal nature of acute leukemia or potential treatment resistance with undue treatment discontinuation, some treatment standards are immutable despite the pandemic. The general consensus of practicing oncologists appears to be pragmatic in relation to optimizing benefits, reducing risks, and considering the prevalence of local COVID-19 in treatment considerations, if appropriate. We adapted information from the American Society of Hematology (ASH) to create a simple comparison of treatments and considerations used for different types of acute and chronic leukemia [40] (Table 2).

Blood or marrow transplantation

The European Society for Blood and Marrow Transplantation (EBMT), a collaborative network of centers and individuals working in the field of BMT and cellular therapy, has been updating their recommendations since the start of the pandemic. The 17th version was published in January 2022 [42]. Immunosuppressed patients treated with BMT or CD19-directed chimeric antigen receptor T cell (CAR-T) cell therapy should continue to adhere to prevention practices limiting their exposure to COVID-19, isolate for 14 days prior to transplant conditioning and avoid unnecessary in-person clinic visits or opt to telemedicine as appropriate. To avoid harming patients by delaying transplant or other treatment procedures, availability of adequately trained staff, ICU beds, ventilators, as well as availability of the stem cell product should be ensured prior to starting the transplant procedure. One of the earlier studies during the pandemic retrospectively examined clinical variables associated with COVID-19 severity and assessed lymphocyte populations in patients diagnosed between March and May 2020 [43]. Among 77 COVID-19 patients treated with BMT, 30-day survival was 78%, worsening of graft-versus-host disease was not identified among allogeneic BMT recipients, and there was a rapid recovery in lymphocyte populations across lymphocyte subsets. Comorbidities, infiltrates, and neutropenia were associated with COVID-19 severe outcomes. Findings from a CCC19 study showed rates of severe COVID-19 (36% v. 38%) and 30-day mortality (23% v. 19%) were similar in patients treated with BMT or CAR-T within a year of COVID-19 diagnosis compared to patients who had not received such therapies within a year prior to COVID-19 diagnosis [15]. These findings supported the favorable clinical outcomes in patients with COVID-19 treated with BMT for hematological malignancy. A risk-benefit assessment on a case-by-case basis should be evaluated, however, if a BMT or CAR-T candidate is infected with COVID-19 to avoid delay

of treatment and potential progression of underlying disease. Use of monoclonal antibodies, antivirals (remdesivir, paxlovid, and in less-grade molnupiravir), convalescent plasma, and anti-inflammatory therapies in reducing the risk of progression to severe COVID-19 should be considered in such cases (Table 1). As for vaccination, the Centers for Disease Control recommends that fully vaccinated BMT or CAR-T cell therapy recipients should get revaccinated with a full schedule at least 3 months following their treatment procedure.

Long-COVID/PASC impact on cancer management

Post-acute sequelae of SARS-CoV-2 (PASC) or long-COVID is an increasingly recognized syndrome following COVID-19 infection. Multiple national and international initiatives have been initiated to characterize the impact of PASC. The RECOVER is a research initiative supported by the US National Institutes of Health (NIH) to understand, prevent, and treat PASC [<https://recovercovid.org/>]. However, the prevalence and impact of PASC on survival of patients with cancer remains unclear. Findings recently published from the OnCovid, an active European registry study enrolling consecutive adult patients with a history of solid or hematological malignancy and a PCR-confirmed diagnosis of COVID-19, reported a prevalence of PASC in up to 15% of patients with cancer, 13% of which were patients with hematological malignancy (2% of the total sample) [44•]. Most common symptoms included fatigue and respiratory symptoms. PASC was associated with a severe COVID-19 infection and adversely affected survival and cancer-related outcomes. Permanent discontinuation of cancer therapy, but not cancer treatment adjustments, increased risk of death underscoring the consensus that fear of COVID-19 infection or PASC does not justify drastic treatment changes or discontinuation [44•].

Management considerations in pediatric patients

Similar to adult cancer patients, centers treating pediatric cancers experienced a dramatic drop in diagnosis rates early on in the pandemic [45]. Preliminary evidence from six pediatric oncology centers in Italy, one of the earliest worst-hit areas of the world, suggested anti-cancer treatments for pediatric patients could continue safely without adjustment [45]. An early report from two US tertiary pediatric referral centers highlighted the critical need to maintain access to cancer care irrespective of COVID-19 infection. Notable long gaps in new leukemia diagnosis were observed and 75% of new pediatric leukemia/lymphoma diagnoses required pediatric intensive care unit care, compared with a historic monthly average of 12% (maximum 40%) during 2018–2019 [46]. Despite an overall lower COVID-19 infection rate among children during the first waves of the pandemic compared to adults, its indirect impact was shown to have unintended consequences on morbidity in a vulnerable pediatric population.

In an effort to provide pediatric oncologists with data on the clinical course and outcomes in children with cancer and COVID-19, the Pediatric Oncology COVID-19 Case (POCC) Report registry was created to capture clinical and

sociodemographic characteristics on children and young adults, 0–39 years of age, treated for cancer and infected with COVID-19 across a 100+ US institutions [47•]. In this US nationally representative sample of pediatric patients with cancer and COVID-19, there was an overrepresentation of children under the age of 21 years with hematologic malignancy and COVID-19 (65.8%) compared to the general US childhood cancer population (38.3%) [48]. Hematologic malignancy was associated with worse COVID-19 outcomes. Although cancer treatment was changed in 44.9% of children and changes were more common among hematologic malignancy (48.1%) than solid tumors (44.9%), risk of change to therapy was the lowest among BMT patients. Patients with hematologic malignancy were also more likely to receive COVID-19-directed treatments. These findings support a similar COVID-19 risk profile in pediatric hematologic malignancy patients to that of adults and are critical for guiding prevention and management considerations in pediatric patients.

Funding

Noha Sharafeldin is supported by the Leukemia and Lymphoma Society (LLS 3386-19) and the National Marrow Donor Program Be The Match Foundation. Benjamin Bates is supported by the New Jersey Commission on Cancer Research and Patterson Trust Mentored Clinical Research Award.

Declarations

Conflict of Interest

Noha Sharafeldin has stock ownership in Johnson & Johnson and Proctor & Gamble. Benjamin Bates has stock ownership in Pfizer. Pankit Vachhani received consulting fees or had advisory role at Blueprint Medicines, Incyte, AbbVie, Jazz Pharmaceuticals, CTI BioPharma Corp, Novartis, Amgen, Pfizer, Genentech, Stemline; and received honoraria for lectures from Incyte.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
 - Of major importance
1. Kutikov A, Weinberg DS, Edelman MJ, Horwitz EM, Uzzo RG, Fisher RI. A war on two fronts: cancer care in the time of COVID-19. *Ann Intern Med.* 2020;172(11):756–8.
 2. Bakouny Z, Hawley JE, Choueiri TK, Peters S, Rini BI, Warner JL, et al. COVID-19 and cancer: current challenges and perspectives. *Cancer Cell.* 2020;38(5):629–46.
 3. Urun Y, Hussain SA, Bakouny Z, Castellano D, Kilickap S, Morgan G, et al. Survey of the impact of COVID-19

- on oncologists' decision making in cancer. *JCO Glob Oncol.* 2020;6:1248–57.
4. Desai A, Mohammed TJ, Duma N, Garassino MC, Hicks LK, Kuderer NM, et al. COVID-19 and cancer: a review of the registry-based pandemic response. *JAMA Oncol.* 2021;7(12):1882–90.
 5. Sharafeldin N, Bates B, Song Q, Madhira V, Yan Y, Dong S, et al. Outcomes of COVID-19 in patients with cancer: report from the National COVID Cohort Collaborative (N3C). *J Clin Oncol.* 2021;39(20):2232–46.
- The study reports on COVID-19 outcomes of cancer patients using real-world data from a large US nationally representative cohort of cancer patients. It provided insights on risk factors of COVID-19 infection and risk of severe outcomes and mortality from COVID-19.
6. Song Q, Bates B, Shao YR, Hsu F, Liu F, Madhira V, et al. Risk and outcome of breakthrough COVID-19 infections in vaccinated patients with cancer: real-world evidence from the National COVID Cohort Collaborative (N3C). *J Clin Oncol.* 2022.
 7. Chatzikonstantinou T, Kapetanakis A, Scarfo L, Karakatsoulis G, Allsup D, Cabrero AA, et al. COVID-19 severity and mortality in patients with CLL: an update of the international ERIC and Campus CLL study. *Leukemia.* 2021;35(12):3444–54.
 8. Roeker LE, Eyre TA, Thompson MC, Lamanna N, Coltoff AR, Davids MS, et al. COVID-19 in patients with CLL: improved survival outcomes and update on management strategies. *Blood.* 2021;138(18):1768–73.
 9. Mileham KF, Bruinooge SS, Aggarwal C, Patrick AL, Davis C, Mesenhowski DJ, et al. Changes over time in COVID-19 severity and mortality in patients undergoing cancer treatment in the United States: initial report from the ASCO Registry. *JCO Oncol Pract.* 2021;OP2100394.
 10. Kuderer NM, Choueiri TK, Shah DP, Shyr Y, Rubinstein SM, Rivera DR, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet.* 2020;395(10241):1907–18.
 11. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med.* 2021;384(15):1412–23.
 12. Cele S, Jackson L, Khoury DS, Khan K, Moyo-Gwete T, Tegally H, et al. Omicron extensively but incompletely escapes Pfizer BNT162b2 neutralization. *Nature.* 2022;602(7898):654–6.
 13. Rivera DR, Peters S, Panagiotou OA, Shah DP, Kuderer NM, Hsu CY, et al. Utilization of COVID-19 treatments and clinical outcomes among patients with cancer: a COVID-19 and Cancer Consortium (CCC19) cohort study. *Cancer Discov.* 2020;10(10):1514–27.
 14. Grivas P, Khaki AR, Wise-Draper TM, French B, Hennessy C, Hsu CY, et al. Association of clinical factors and recent anti-cancer therapy with COVID-19 severity among patients with cancer: a report from the COVID-19 and Cancer Consortium. *Ann Oncol.* 2021.
 15. Rubinstein S, Lynch RC, Desai A, Stratton C, Jha A, Bakouny Z, et al. Severity of Sars-Cov-2 infection in patients with hematologic malignancies: a COVID-19 and Cancer Consortium (CCC19) registry analysis. *Blood.* 2020;136(Supplement 1):28–30.
 16. Passamonti F, Cattaneo C, Arcaini L, Bruna R, Cavo M, Merli F, et al. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. *Lancet Haematol.* 2020;7(10):e737–e45.
 17. Buyuktas D, Acar K, Sucak G, Toptas T, Kapucu I, Bekoz H, et al. COVID-19 infection in patients with acute leukemia; Istanbul experience. *Am J Blood Res.* 2021;11(4):427–37.
 18. Patt D, Gordan L, Diaz M, Okon T, Grady L, Harmison M, et al. Impact of COVID-19 on cancer care: how the pandemic is delaying cancer diagnosis and treatment for American seniors. *JCO Clin Cancer Inform.* 2020;4:1059–71.
 19. London JW, Fazio-Eynullayeva E, Palchuk MB, Sankey P, McNair C. Effects of the COVID-19 pandemic on cancer-related patient encounters. *JCO Clin Cancer Inform.* 2020;4:657–65.
 20. Riera R, Bagattini AM, Pacheco RL, Pachito DV, Roitberg F, Ilbawi A. Delays and disruptions in cancer health care due to COVID-19 pandemic: systematic review. *JCO Glob Oncol.* 2021;7:311–23.
 21. Palandri F, Picciocchi A, De Stefano V, Breccia M, Finazzi G, Iurlo A, et al. How the coronavirus pandemic has affected the clinical management of Philadelphia-negative chronic myeloproliferative neoplasms in Italy—a GIMEMA MPN WP survey. *Leukemia.* 2020;34(10):2805–8.
 22. Pacheco RL, Martimbianco ALC, Roitberg F, Ilbawi A, Riera R. Impact of strategies for mitigating delays and disruptions in cancer care due to COVID-19: systematic review. *JCO Glob Oncol.* 2021;7:342–52.
 23. Lai AG, Pasea L, Banerjee A, Hall G, Denaxas S, Chang WH, et al. Estimated impact of the COVID-19 pandemic on cancer services and excess 1-year mortality in people with cancer and multimorbidity: near real-time data on cancer care, cancer deaths and a population-based cohort study. *BMJ Open.* 2020;10(11):e043828.
 24. Waterhouse DM, Harvey RD, Hurley P, Levit LA, Kim ES, Klepin HD, et al. Early impact of COVID-19 on the conduct of oncology clinical trials and long-term opportunities for transformation: findings from an American Society of Clinical Oncology Survey. *JCO Oncol Pract.* 2020;16(7):417–21.
 25. Pennell NA, Dillmon M, Levit LA, Moushey EA, Alva AS, Blau S, et al. American Society of Clinical Oncology road to recovery report: learning from the COVID-19

- experience to improve clinical research and cancer care. *J Clin Oncol.* 2021;39(2):155–69.
26. van der Veldt AAM, Oosting SF, Dingemans AC, Fehrmann RSN, GeurtsvanKessel C, Jalving M, et al. COVID-19 vaccination: the VOICE for patients with cancer. *Nat Med.* 2021;27(4):568–9.
 27. Oosting SF, van der Veldt AAM, GeurtsvanKessel CH, Fehrmann RSN, van Binnendijk RS, Dingemans AC, et al. mRNA-1273 COVID-19 vaccination in patients receiving chemotherapy, immunotherapy, or chemo-immunotherapy for solid tumours: a prospective, multicentre, non-inferiority trial. *Lancet Oncol.* 2021;22(12):1681–91.
 - 28.●● Zeidan AM, Boddu PC, Patnaik MM, Bewersdorf JP, Stahl M, Rampal RK, et al. Special considerations in the management of adult patients with acute leukaemias and myeloid neoplasms in the COVID-19 era: recommendations from a panel of international experts. *Lancet Haematol.* 2020;7(8):e601–e12
- This viewpoint provided consensus on clinical practice guidance for leukemia care by a convened international panel of hematologists and oncologists specialized in leukemia care. The panel provided detailed general care recommendations as well as treatment guidelines for the management of the different leukemias.
29. Naranbhai V, Pernat CA, Gavralidis A, St Denis KJ, Lam EC, Spring LM, et al. Immunogenicity and reactogenicity of SARS-CoV-2 vaccines in patients with cancer: the CANVAX cohort study. *J Clin Oncol.* 2022;40(1):12–23.
 30. Greenberger LM, Saltzman LA, Senefeld JW, Johnson PW, DeGennaro LJ, Nichols GL. Antibody response to SARS-CoV-2 vaccines in patients with hematologic malignancies. *Cancer Cell.* 2021;39(8):1031–3.
 31. Gong IY, Vijenthira A, Betschel SD, Hicks LK, Cheung MC. COVID-19 vaccine response in patients with hematologic malignancy: a systematic review and meta-analysis. *Am J Hematol.* 2022.
 32. Zeng C, Evans JP, Reisinger S, Woyach J, Liscynsky C, Boghdady ZE, et al. Impaired neutralizing antibody response to COVID-19 mRNA vaccines in cancer patients. *Cell Biosci.* 2021;11(1):197.
 33. Houot R, Levy R, Cartron G, Armand P. Could anti-CD20 therapy jeopardise the efficacy of a SARS-CoV-2 vaccine? *Eur J Cancer.* 2020;136:4–6.
 34. Pimpinelli F, Marchesi F, Piaggio G, Giannarelli D, Papa E, Falcucci P, et al. Fifth-week immunogenicity and safety of anti-SARS-CoV-2 BNT162b2 vaccine in patients with multiple myeloma and myeloproliferative malignancies on active treatment: preliminary data from a single institution. *J Hematol Oncol.* 2021;14(1):81.
 35. Schmidt AL, Labaki C, Hsu CY, Bakouny Z, Balanchivadze N, Berg SA, et al. COVID-19 vaccination and breakthrough infections in patients with cancer. *Ann Oncol.* 2022;33(3):340–6.
 36. Hall V, Foulkes S, Insalata F, Kirwan P, Saei A, Atti A, et al. Protection against SARS-CoV-2 after Covid-19 vaccination and previous infection. *N Engl J Med.* 2022.
 37. Release FN. Coronavirus (COVID-19) Update: FDA authorizes additional vaccine dose for certain immunocompromised individuals, August 12 2021 2021 [Available from: <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-vaccine-dose-certain-immunocompromised>].
 38. IDSA. The Infectious Diseases Society of America - anti-SARS-CoV-2 monoclonal antibodies 2022 [updated January 28, 2022. Available from: <https://www.idsociety.org/covid-19-real-time-learning-network/therapeutics-and-interventions/monoclonal-antibodies/#Bebtelovimab>].
 39. CDC. Centers for Disease Control and Prevention - Science Brief: Omicron (B.1.1.529) Variant 2021 [updated December 2, 2021. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-omicron-variant.html>].
 40. IDSA. The Infectious Diseases Society of America (IDSA) Guidelines on the Treatment and management of patients with COVID-19 2022 [updated February 22, 2022. Available from: <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/>].
 41. Thompson MA, Henderson JP, Shah PK, Rubinstein SM, Joyner MJ, Choueiri TK, et al. Association of convalescent plasma therapy with survival in patients with hematologic cancers and COVID-19. *JAMA Oncol.* 2021.
 42. EBMT. European Society for Blood and Marrow Transplantation (EBMT) COVID recommendations update - 26 January 2022 2022 [Available from: <https://www.ebmt.org/sites/default/files/2022-02/EBMT%20COVID-19%20guidelines%20v.17.2.pdf>].
 43. Shah GL, DeWolf S, Lee YJ, Tamari R, Dahi PB, Lavery JA, et al. Favorable outcomes of COVID-19 in recipients of hematopoietic cell transplantation. *J Clin Invest.* 2020;130(12):6656–67.
 - 44.● Pinato DJ, Tabernero J, Bower M, Scotti L, Patel M, Colomba E, et al. Prevalence and impact of COVID-19 sequelae on treatment and survival of patients with cancer who recovered from SARS-CoV-2 infection: evidence from the OnCovid retrospective, multicentre registry study. *Lancet Oncol.* 2021;22(12):1669–80
- Study provides findings from an active European registry on the prevalence of post-COVID-19 sequelae and their association with post-COVID-19 survival.
45. Ferrari A, Zecca M, Rizzari C, Porta F, Provenzi M, Marinoni M, et al. Children with cancer in the time of COVID-19: an 8-week report from the six pediatric onco-hematology centers in Lombardia, Italy. *Pediatr Blood Cancer.* 2020;67(8):e28410.

46. Ding YY, Ramakrishna S, Long AH, Phillips CA, Montiel-Esparza R, Diorio CJ, et al. Delayed cancer diagnoses and high mortality in children during the COVID-19 pandemic. *Pediatr Blood Cancer*. 2020;67(9):e28427.
47. • Johnston EE, Martinez I, Davis ES, Araya B, Richman J, Brackett J, et al. The pediatric oncology COVID-19 Case (POCC) Report 2022 [Available from: <https://www.uab.edu/medicine/icos/icos-research/the-pocc-report>].
48. Johnston EE, Martinez I, Davis ES, Caudill C, Richman J, Brackett J, et al. SARS-CoV-2 in childhood cancer in 2020: a disease of disparities. *J Clin Oncol*. 2021;39(34):3778–88.

The POCC report represents a US national registry to provide pediatric oncologists with real-time information on the clinical course of children, adolescents, and young adults diagnosed with cancer and infected with SARS-COV-2 and/or received a COVID-19 vaccine.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.