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Treatment of Acute Leukemia During COVID-19: Focused Review of Evidence

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Abstract

The Coronavirus disease-2019 (COVID-19) pandemic is an unprecedented health care crisis and has led to over 1.5 million deaths worldwide. The risk of severe COVID-19 and mortality is markedly raised in patients with cancer, prompting several collaborative groups to issue guidelines to mitigate the risk of infection by delaying or de-escalating immunosuppressive therapy. However, delayed therapy is often not feasible for patients requiring treatment for acute leukemia or stem cell transplantation. We provide a focused review of the recommendations and evidence for managing this high-risk group of patients while minimizing the risk of COVID-19 infection, and provide a small snapshot of treatment data from our center.

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Introduction

The severe acute respiratory syndrome-coronavirus 2 (SARS-CoV2) is an RNA virus which has led to an ongoing global pandemic.[1] Since its first description in December 2019, it has caused over 68 million infections and 1.5 million deaths over a 1-year period. Illness caused by this virus (named Coronavirus disease-2019, or COVID-19 for short), can present as a spectrum from an asymptomatic carrier state to respiratory failure and multi-organ dysfunction.[2] The COVID-19 pandemic is an unprecedented crisis, and demonstrates a case fatality rate of approximately 5% to 7%.[3] The case fatality rate underestimates the burden of infection, as patients with mild or asymptomatic disease are excluded, which may constitute over 50% of all cases. A better measure is provided by the infection fatality rate, which is estimated to range from 0% to 1.6%.[4] Meta-analysis of clinical data has shown that approximately 30% of patients require intensive care unit admission, and the mortality rate in this subset approaches 39%.[5] The risk of severe disease and mortality is higher is certain subgroups, including those with comorbidities, active malignancy, or advanced age (> 60 years).[6]

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Owing to disease and treatment-related factors, patients with cancer are at an especially high risk of severe disease and have been noted to have a mortality rate exceeding 25%.[7,8] This initial surge in mortality in patients with cancer prompted several groups to recommend delay or deferral of curative chemotherapy to minimize the risk of mortality owing to severe COVID-19.[9] However, delays in treatment of patients with hematologic malignancies, especially those with acute leukemia planned for chemotherapy or transplantation, are associated with a risk of disease progression and inferior outcomes. For these patients, added efforts must be made to minimize infection risk while ensuring continuation of treatment. A judicious modification of protocols at each stage of treatment to minimize the risk of infection must be attempted, depending on disease status and local factors.[10] We provide a focused review on the current evidence and recommendations for management of patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) during the COVID-19 pandemic.

Patients With Hematologic Malignancies are Predisposed to COVID-19 and Have Distinctly Poorer Outcomes

Dysregulation of several components of innate and acquired immunity is noted in most malignancies.[11] Patients with AML have higher expression of negative regulatory receptors and proliferation of regulatory T cells.[12] This is potentiated by disruption of normal NK cell development and defective metabolism, further attenuating the host response.[13] Patients with AML have an added risk owing to myelosuppression and myeloid dysfunction, and patients with ALL have an added risk owing to hypogammaglobulinemia and

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Table 1 Salient Features of the Largest Datasets on Outcomes of Patients With COVID-19 Infection and Hematologic Malignancies

Reference	Study and Total Patients Included	Patients With COVID-19 and Hematologic Cancers	Fatality Rate, %	Others
18	National Turkish Database of COVID-19 patients: 188,897 patients with COVID-19 from database	740	13.8	Higher rates of severe disease, hospital stay, and ventilator requirement in this group compared with COVID-19 without hematologic cancers (mortality, 13.8% vs. 6.8 %)
15	Electronic Health Record Screening: 73 million EHRs screened, 17,130 with COVID-19	420	14.8	Death rate for COVID-19 alone was 5.1% and hematologic malignancies without COVID was 4.1%
19	Meta-analysis, 3377 patients across 39 studies	3377	34	Mortality in patients < 60 y: 25% Mortality in patients > 60 y: 47% Mortality in pediatric age group: 4%

Abbreviations: COVID-19 = coronavirus disease-2019; EHR = electronic health record.

prolonged use of steroids.[10] All these factors work in tandem to increase the risk of various viral and fungal infections, including uncommon pathogens in patients with acute leukemia.[14] The highest risk of COVID-19 infection has been noted with ALL, followed by essential thrombocytosis and AML. This surprising finding indicates the undefined role of many factors beyond myelosuppression in mediating the risk of infection and disease.[15]

From the beginning of 2020, several reports indicated a higher risk of mortality with COVID-19 in patients with cancer.[16,17] However, as treatment of acute leukemia can often not be delayed, COVID-19 infections were documented in several patients with hematologic cancers, providing valuable insights into infection risk and outcomes. The largest body of data is available from 3 studies, summarized in Table 1. The first study is a database review from Turkey, which included all patients with COVID-19 infection from a national database.[18] Of a total of 188,897 patients, 740 were noted to have concurrent COVID-19 and hematologic malignancy. This subset of patients was compared with another 740 patients with COVID without hematologic malignancies and found to have a 2-fold higher mortality (13.8% vs. 6.8%). The second study is a large retrospective database analysis of United States health records, which compared outcomes with hematologic malignancies in patients who were diagnosed recently versus historic cohorts. This study included 73 million records and identified 17,000 patients with COVID-19, of whom 420 had co-existent blood cancer. A significantly higher risk of death was noted in patients with COVID-19 compared with those without COVID.[15] The third is a meta-analysis that included 34 adult and 5 pediatric studies comprising 3377 patients and demonstrated an initial mortality of 34% for all patients with hematologic cancers, which was much higher for patients > 60 years of age.[19] Similar data has also become available from low- and middle-income settings, indicating the importance of low-cost infection control measures in resource-constrained settings. In a large tertiary care center from India, 7043 patients with cancer were screened, out of which 230 patients (hematologic malignancies, 37%) had concurrent COVID-19 while receiving active treatment. This subgroup was noted to have a relatively high 30-day mortality of 10%, much higher than the case fatality rate with COVID-19 in general.[20] A majority of patients in this subgroup had mild COVID-19, and outcomes with severe disease are expected to be worse. Further data is expected from the COVID Hematologic Cancer Registry of India (The CHCRI Study), which has accrued 277 patients as of December 2020.

Infection Control Measures Should be Instituted Universally in Health Care Settings

Several professional organizations have published guidelines recommending measures for prevention and early detection of COVID-19 before initiation of therapy. The Infectious Disease Society of America (IDSA) has published detailed guidelines and strongly recommends testing for SARS-CoV2 before initiating

Table 2 Summary of Recommendations to Further Reduce the Risk of COVID-19 Infection or Severe Disease in Patients with Leukemia

Acute Myeloid Leukemia	Acute Lymphoblastic Leukemia
COVID-19 testing before starting treatment	COVID-19 testing before starting treatment
Continue environmental precautions	Continue environmental precautions
Young patients: full dose induction chemotherapy	Full dose induction (with steroids)
Reduce HiDAC to 1.5 g/m^2 per dose	Reduce anthracycline dose for those at high risk of infection
Higher transfusion cutoff	Outpatient management of post-induction cycles
Minimize hospital stay by discharging early	Use TKIs as much as possible for Ph-positive ALL

Abbreviations: ALL = acute lymphoblastic lymphoma; COVID-19 = Coronavirus disease-2019; HiDAC = high-dose cytarabine; Ph = Philadelphia chromosome; TKI = tyrosine kinase inhibitor.

chemotherapy, stem cell transplantation, immunotherapy, or steroids (https://www.idsociety.org/practice-guideline/covid-19-guideline-infection-prevention/). It is recommended that the testing be performed as close to treatment initiation as possible, ideally no more than 2 to 3 days in advance. As patients often have repeated visits or re-admissions for treatment, frequent testing at every visit is not recommended, but regular screening for symptoms should be performed. Similarly, the American Society for Clinical Oncology (ASCO) provides a framework for cancer care delivery during the COVID-19 pandemic (https://www.asco.org/asco-coronavirus-resources/care-individuals-cancer-during-covid-19/general-information-about-covid-19). Before patients are admitted or enter a cancer care facility, screening for symptoms must be conducted, along with compulsory mask use. Patients who have symptoms of cough, fever, myalgias, headache, or dyspnea should be triaged for assessment so that testing for COVID-19 and appropriate site of management can be decided. Physical measures such as social distancing, patient isolation, and visitor restriction must be followed. Simple measures such as screening, masking,[21] and social distancing[22] are highly effective in halting the spread of COVID-19.

In high-risk clinical situations, such as leukemia wards and stem cell transplant units, the importance of environmental control in infection prevention is accentuated.[23] For hospital staff, it is essential to take universal precautions with extended mask use, hand hygiene, and limiting nonclinical interactions. Universal screening of all patients and visitors to identify potentially infected patients is recommended. Environmental surfaces such as medical pagers, elevator buttons, computer mice, and telephones have been noted to have high rates of infective contamination.[24] Although the virus is most stable on steel and plastic, it is still found active on cotton clothes for up to 1 hour, indicating the utility of distancing and hand hygiene.[25] Use of approved disinfectants containing chlorine, alcohol, or H2O2 has been found to be effective in eliminating COVID-19 after 60 seconds of exposure from most surfaces.[26] Visitor restriction and availability of positive pressure rooms are additional measures that must be implemented if feasible. Simple measures of social distancing, patient segregation, screening, and appropriate disinfection can be performed effectively in resource-constrained settings.[20]

Specific Recommendations for AML

Patients diagnosed to have AML need to be initiated on treatment depending on patient age, fitness, and comorbidities. Younger, fit patients should receive induction therapy with an anthracycline-cytarabine combination to achieve rapid disease control.[27] Typically, this treatment protocol is followed by neutropenia lasting for 2 to 3 weeks, during which a patient is at risk of infections, bleeding, and treatment-related mortality. The mortality rate during AML induction in Western countries has been brought down to approximately 3% to 4%, but continues to be above 15% in India, necessitating added precautions to reduce the risk of COVID-19 infection.[28] The American Society of Hematology (ASH) and National Cancer Research Institute (NCRI) AML Working Party have published recommendations in this regard, with the primary focus of adopting measures to reduce hospital stay and infection exposure. The guidelines recommend shifting certain aspects of care to outpatient basis with close monitoring. Outpatient management of patients following intensive chemotherapy for AML has been found to be safe and feasible if close follow-up after discharge is maintained.[29,30] Patients on outpatient follow-up with neutropenia must be educated about risks of neutropenia and the need for re-admission in case of fever or development of new symptoms.[31] In-hospital stay constitutes the largest proportion of the initial cost of AML induction independent of blood product usage, and the above measures should also help in reducing costs.[32] Patients who develop febrile neutropenia should be re-tested for COVID-19 if no other focus of infection is found, as COVID-19 reverse transcription polymerase chain reaction (RT-PCR) can be falsely negative in the initial stages of infection.[33]

Patients classified as low-risk AML continue with consolidation chemotherapy with high-dose cytarabine, and those as intermediate or high risk are candidates for stem cell transplantation.[27] For patients who are elderly, unfit, or otherwise not candidates for intensive chemotherapy, treatment with hypomethylating agents, preferably with the addition of venetoclax, is recommended.[34] For consolidation with high-dose cytarabine, the AML 15 trial provides evidence for reducing the dose of high-dose cytarabine from 3 g/m^2 to 1.5 g/m^2, which reduces the duration of neutropenia while achieving similar outcomes.[35]

COVID-19 lends significant challenges to transfusion services, leading to a blood component shortage and the potential for donor or staff infection.[36] Even in developed countries, a shortage of blood components and reduction in voluntary donations has been documented.[37] To reduce the burden on supportive care, a higher threshold for transfusion support is recommended. A threshold of 7 g/dL before blood transfusion in AML is associated with comparable length of hospital stay, mortality, and treatment response rates while reducing resource utilization.[38] Likewise, a lower platelet cut off of 10,000/ul rather than 20,000/ul before prophylactic transfusion is safe and cost-effective without increasing the risk of bleeding.[39]

Specific Recommendations for ALL

The ASH also provides expert recommendations on management of ALL during the COVID-19 pandemic. For patients with Ph-negative ALL, the usual induction doses of steroids are advised. The initial concerns about worsening COVID-19 disease with steroids have been alleviated with demonstration of safety and efficacy of steroids in treating severe COVID-19.[40] Many experts recommend lowering anthracycline doses by 50% and using granulocyte colony stimulating factor to hasten count recovery to reduce the duration of myelosuppression. As anthracyclines contribute vitally to the efficacy of the induction regimen, this decision should be taken after thorough consideration.[41] While continuing subsequent cycles post induction, attempts should be made to administer treatment on an ambulatory basis if feasible. Outpatient treatment following induction has been found to be safe for adult patients with ALL.[42] In extreme situations and with close monitoring, administration of high-dose methotrexate on an outpatient basis has also been found safe.[43] An individualized decision to continue subsequent cyclophosphamide, cytarabine, or etoposide on an outpatient basis can be made if patients are expected to comply with instructions on neutropenic care and regular follow-up.[44] As ALL is a curable disease in many age groups, it is recommended that priority be given to minimizing treatment delays. These principles are even

more pertinent in the pediatric age group, where excellent long-term outcomes are noted with strict compliance to treatment protocols.[45] For patients with ALL on treatment who developed COVID-19, therapy may have to be temporarily halted. The ASH guidelines recommend that treatment delays, if any, must not exceed 2 weeks. A decision to restart or withhold treatment must be made on a patient-by-patient basis, considering the phase of treatment, presence of neutropenia, additional infections, and remission status.

For induction therapy of Ph-positive ALL, anthracyclines can be safely omitted by using a less myelosuppressive combination of vincristine, steroids, and tyrosine kinase inhibitor.[46] For subsequent cycles, tyrosine kinase inhibitors should be continued as far as possible to avail maximal benefit.[47]

For patients with relapsed ALL, newer non-myelosuppressive options include blinatumomab for B-cell ALL and nelarabine for T-cell ALL, which avoid prolonged cytopenia and the attendant risk of infections.[48,49] However, availability and cost play a major role before using these drugs, and for most patients in the Indian setting, combination salvage chemotherapy with appropriate precautions may be the only option.[50] Table 2 summarizes recommendations for management of AML and ALL during COVID-19.

Stem Cell Transplantation

Indications for stem cell transplantation in acute leukemia include high-risk disease (based on cytogenetic and mutation data or inadequate response to therapy) or refractory disease.[51]

Patients with AML who need a transplant should be referred as soon as possible, as a delay leading to even minimal residual disease positivity is associated with disease progression and inferior survival.[52] It must be emphasized that the risk of donor to patient transmission of COVID-19 is low, and blood-borne transmission has not yet been documented despite the presence of low-level viremia.[53] However, if a donor tests positive for COVID-19, temporary deferral is universally advised. The European Bone Marrow Transplantation (EBMT) guidelines recommend a 3-month deferral if a donor tests positive for COVID-19, and a 28-day deferral in case of a potential exposure to an infected individual.[54] It is vital to adapt these guidelines to local practice, as a delay of 1 to 3 months may not be feasible for certain high-risk patients. This principle is mirrored in the American Society for Transplantation and Cellular Therapy (ASTCT) guidelines, which recommend consideration of a donor with recent infection after 28 days on a case-by-case basis.[23]

Our Center's Data on COVID-19 and Hematologic Malignancies

We recently submitted data on in-patient management of hematologic cancers from our center, a 99-bed cancer unit of a 1600-bed teaching hospital (National Medical Journal of India, Manuscript 620_20, under issue preparation). The data has been updated since then, and the following is a short summary highlighting the steps taken to mitigate the risk of COVID-19 in this patient subset.

Owing to necessity and urgency of treatment, hematology-oncology services continued as usual after the onset of the pandemic, and stem cell transplantation services restarted in June 2020 after a 3-month interval.

Preventive measures for infection control included the following:

(1) Health care staff
   a. Provision of personal protective equipment for all health care staff (plastic fronted gowns, masks, and face shields) provided by the hospital.
   b. Screening before entering the premises with an infrared thermometer. Those with fever, upper respiratory symptoms, or a history of potential contact were triaged according to risk of exposure. High-risk contacts were quarantined for 14 days and retested before joining duty.

(2) Outpatient clinics
   a. To reduce person-to-person spread, patient numbers in the clinic were capped, and patients were shifted to telemedicine at the discretion of the primary physician.
   b. For patients, mandatory testing with nasal swab for COVID-19 RT-PCR was done before admission, and

Table 3 Our Institutional Data on Patients With Hematologic Malignancies Managed In-patient During the COVID-19 Pandemic

	N	Median Age (Range), y	Patients With COVID-19 Infections and Details	Patient Deaths Owing to COVID-19
AML	17	35 (20-73)	3 Pt 1: APML at presentation with type 1 respiratory failure Pt 2: AML in peak cytopenia with respiratory failure Pt 3: AML post induction with normal counts prior to starting HiDAC	Pt 1 died owing to progressive respiratory failure before treatment could be started Pt 2 died of worsening respiratory failure in peak cytopenia
ALL	15	35 (14-75),	1 Pt 4: B-ALL at diagnosis, skipped daunorubicin, uneventful recovery	
Stem cell transplantation	12	39.5 (10-60)	0	
Lymphoma (all subtypes)	22	46 (23-66)	0	
Myeloma with complications	2	70 (68-72)	0	
Total	68			2

Abbreviations: ALL = acute lymphoblastic lymphoma; AML = acute myeloid leukemia; APML = acute promyelocytic leukemia; B-ALL = B-cell acute lymphoblastic leukemia; COVID-19 = Coronavirus disease-2019; HiDAC = high-dose cytarabine; Pt = patient.

patients were admitted in a temporary pre-COVID area before shifting to wards.

c. If found positive, patients were shifted to isolation wards or home quarantine as decided by the infectious diseases team.

d. Those who developed respiratory symptoms or hypoxia in-hospital were re-tested with high-resolution computed tomography of the chest and nasal swab and shifted temporarily to a pre-COVID holding area until reports were ready.

e. Strict visitor restriction was placed, and only 1 visitor was allowed in the hospital.

(3) High-risk areas (leukemia wards and stem cell transplantation)

a. In bone marrow transplantation, mandatory testing of stem cell donors and family members was performed. No visitors were allowed inside with the exception of pediatric patients, and visitation was done by iPad or mobile phones.

b. Surface cleaning of high-traffic surfaces was performed every 6 hours according to protocol.

All necessary measures as listed above were broadly followed, and no dose reduction was done for any patient unless otherwise indicated. Since April 2020, a total of 68 adult patients were admitted in the hospital for treatment of hematologic malignancies, including 56 for chemotherapy and 12 for stem cell transplantation. The indication for admission was AML in 17 (25%) patients, ALL in 15 (22%), lymphoma in 22 (32%), complicated myeloma in 2 (3%), and stem cell transplantation in 12 (17.6%). Overall, short-term mortality was noted in 10 (14.7%) patients. Two patients died of severe COVID-19 with respiratory failure The first patient was a 27-year-old woman with acute promyelocytic leukemia who had severe hypoxia and required mechanical ventilation at presentation. The second patient was a 35-year-old woman with AML who received 7/3 induction, and developed severe COVID-19 with respiratory failure while cytopenic. Both patients died within 48 hours of onset of symptoms. The above experience emphasizes the utility of basic infection control measures in controlling the risk of COVID-19 infection without a significant increase in treatment cost, and their applicability in resource constrained settings. Details of the aforementioned patients are summarized in Table 3.

Conclusions

The COVID-19 pandemic is an unprecedented event and has adversely affected health care services globally. Management of high-risk cancers and stem cell transplants must continue as before while mitigating the risk of acquiring infection. Several amendments to routine management approach to acute leukemia are recommended by expert groups. These changes, along with basic measures like hand hygiene, surface cleaning, mandatory mask use, social distancing, and reducing hospital stay are effective steps that can permit continuation of treatment while minimizing the risk of COVID-19.

Disclosure

The authors have stated that they have no conflicts of interest.

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