Special considerations for leukemic patients during the COVID-19 pandemic: meta-analysis study

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Abstract

Patients with acute leukemia have an increased risk for severe COVID-19 disease and mortality. Treating patients with acute leukemia (ALL and AML) during a COVID-19 pandemic can be particularly challenging. The coronavirus disease 2019 (COVID-19) pandemic poses several challenges to the management of patients with leukemia. An important distinction is the prevalence of exposure versus clinical infectivity, which determine the risk versus benefit of modifying potentially highly curative therapies in leukemia. At present, the rate of mortality in cancer patients >30%, that needs careful consideration given to the risk of COVID-19 in leukemia. The goal of this study was to determine offer recommendations on the optimization of leukemia management during high-risk COVID-19 periods.

Key Words: Acute leukemia, COVID-19, Meta-analysis

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Introduction

Infection with SARS-CoV-2, the cause of coronavirus infectious disease–19 (COVID-19), has caused a pandemic after first being reported in Wuhan, China in December 2019 [1-2]. An over-representation of patients with cancer has been seen in the COVID-19 cohort in the Chinese National Database Repository [3-5]. Patients with cancer have been reported to have COVID-19-related case fatality rates of approximately 5-6% [6-8], and a 3 to 5-fold higher risk of severe COVID-19, compared to the general population [9]. Moreover, patients with hematological malignancies and COVID-19 have been reported to have case fatality rates of up to 37% [10-13]. Another study delineated higher mortality in hospitalized patients with hematological cancers who developed COVID-19 than in hospitalized health-care providers with COVID-19 [14-17]. Severe and prolonged immunosuppression is a corollary of treatment for acute leukemia, which heightens the risk of complications associated with COVID-19. Much remains to be known about incidence, management, and outcomes of COVID-19 in patients with cancer in general, and leukemias [18-21]. The mainstay of AML treatment is intensive induction and consolidation chemotherapy. Prompt initiation of therapy and achievement of complete remission are imperative for the potential of cure [22]. Consistent with the ALL-treatment approach discussed previously, all patients should be screened for SARS-CoV-2 regardless of symptoms, including baseline CT of the chest prior to induction as well as consolidation therapy if indicated [23-26]. The overall treatment of patients with newly diagnosed AML should not change during the COVID-19 pandemic, with a few caveats [27]. In two studies of patients with COVID-19 in China, only 10 of 1,099 patients and 18 of 1,590 patients, respectively, had a cancer diagnosis [28, 29]. nfected patients with cancer had higher rates of severe illness (intensive care unit admissions, invasive ventilation, or death) compared with others (39 vs. 8%; $p = 0.0003$). They were also significantly older (mean 63.1 ± 12.1 vs. 48.7 ± 16.7 years; $p < 0.001$) and more likely to have a history of smoking (22 vs. 7%; $p = 0.032$).

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Logistic regression identified cancer as the highest individual risk factor for severe events (OR: 5.4; 95% CI: 1.8-16.2; p = 0.003) [30]. Patients with cancer also developed severe disease symptoms more rapidly compared with others (median 13 vs. 43 days; p < 0.001). Similarly, a report of 28 infected patients with cancer found an increased risk of severe clinical events for patients who received anticancer therapy (including chemotherapy, radiotherapy, targeted therapy, or immunotherapy) within 14 days of COVID-19 diagnosis (HR: 4.079; 95% CI: 1.086-15.322; p = 0.037) [31-33]. This highlights the potentially severe impact of COVID-19 in patients with cancer [34].

Methods

Study design and literature search

We followed Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for the study design, analysis, and meta-analysis. An online literature search was conducted from 01 December 2019 to 01 March 2022, in PubMed, Cochrane, Embase, US National Library of Medicine (NLM) medical subject heading (MeSH) thesaurus using Medline MeSH browser. Based on the search results words COVID-19 and acute leukemia in abstracts, and full text. Papers with the following characteristics were selected for the meta-analysis:

- Original research papers,
- Clinical trial studies,
- Full-text availability,
- English language,

Excluded the duplicates articles

Duplicates were divided into type I (duplicates among databases) and II (duplicate publications). According to the origin of index and redundant papers, duplicates were classified as:

PubMed-PubMed,
PubMed-EMBASE,
PubMed-Cochrane,
EMBASE-EMBASE,
EMBASE-Cochrane,
Cochrane-Cochrane, and
PubMed-EMBASE-Cochrane

Results

Among the included patients, 58.1% had a diagnosis of Philadelphia-negative ALL, 25.7% had a diagnosis of AML, 9% had a diagnosis of APL, and 7.2% had Philadelphia-positive ALL. A total of 50.4% of patients included were male, and median age was 35 years (range: 14-90 years). Although patients presented across all ages, only 10.1% of the study population were > 60 years of age. Patients diagnosed with AML were significantly older (median 41 years) compared with those diagnosed with ALL (median 31 years) (P > .01). In terms of risk categories, most patients were considered high-risk patients (58.8%) and 68.3% were in complete remission, undergoing consolidative or maintenance therapy, whereas 14.5% of the sample represented newly diagnosed patients and 17.2% were patients with relapsed or refractory disease, table (1).

Table 1: Leukemia-specific risk factors for COVID-19

Leukemia type	Possible risk factors			
ALL	Myelosuppression Impaired B-cell function due to CD20-targeted monoclonal antibodies Prolonged steroid treated Pulmonary, renal impairment, cardiac dysfunction, and thrombosis due to the chemotherapy			
AML	Myelosuppression, cardiac dysfunction, and pulmonary injury			
Leukemia type	Events			Protocols
ALL	Induction/consolidation	Ph-negative	<60 years ≥60 years ≥70	HCVAD × 4 cycles followed by blinatumomab × 4 cycles or mini-HCVD + inotuzumab × 4 cycles followed by blinatumomab × 4 cycles Mini-HCVD + inotuzumab × 4 cycles

Leukemia type	Possible risk factors			
			years MRD-positive	followed by blinatumomab × 4 cycles Mini-HCVD + inotuzumab × 2 cycles followed by blinatumomab × 8 cycles Move to blinatumomab early after 2 cycles of HCVAD or mini-HCVD + inotuzumab or clinical trial for MRD positivity Allogenic SCT can be considered if benefit outweighs risks
		Ph-positive		Blinatumomab + TKI or inotuzumab + TKI *Blinatumomab + ponatinib preferred
	Maintenance			Important to still give maintenance May omit vincristine to reduce clinic visits and/or dose reduce 6-MP, MTX, or prednisone to minimize myelosuppression, if needed May transition to maintenance early if MRD negativity achieved and administering HCVAD or mini-HCVD is logistically difficult Incorporate blinatumomab or low-dose inotuzumab in late intensification
AML	Induction	<60 years		Intensive induction chemotherapy per institutional standard Consider low-intensity therapy: HMA + venetoclax or LDAC + venetoclax or cladribine + LDAC ± venetoclax if unable to deliver intensive induction due to limited resources from high local rate of COVID-19
		≥60 years		Low-intensity therapy: venetoclax + HMA or LDAC + venetoclax or cladribine + LDAC ± venetoclax
	Consolidation			Administer consolidation therapy as outpatient utilizing ambulatory intravenous pumps Administer cytarabine 1.5 g/m2/dose rather than 3 g/m2/dose on days 1–3 followed by peg filgrastim Transition to HMA-based therapy if patients unable to complete intensive consolidation courses as planned
	Maintenance			Utilize HMA ± venetoclax after completion of consolidation in patients awaiting allogeneic SCT

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/m2 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

Discussion

Few cases of concomitant occurrence of ALL with COVID-19 have been reported so far and the course of the infection has been generally mild.5 However, even in the midst of a deadly pandemic, ALL itself remains a huge threat to those that it afflicts, even when they are in remission, as was seen in our case [35]. Other recently reported recommendations from a panel of international experts about the management of hematological malignancies in adults in the COVID-19 pandemic [36]. It was suggested to consider delaying treatment for ALL, given the risk of severe COVID-19 with chemotherapy [37]. Antitumor treatment <14 days previously has been reported as a risk factor for severe COVID-19. All patients should be tested for SARS-CoV-2 before starting therapy and, in case of a positive test, treatment should be delayed by 10–14 days, except intrathecal therapies for central nervous system (CNS) symptoms. Similar recommendations were put forward by the French Society for the Fight against Cancers and Leukemias in Children and Adolescents (SFCE) [38]. In the situation that a patient is positive for SARS-CoV-2, but requires urgent initiation of induction treatment, it is recommended to treat while monitoring vigilantly for COVID-19 symptoms and disease course [39]. If symptoms develop, therapy should be discontinued, and early initiation of cytokine modulators should be considered [40]. For induction, it is recommended to consider minimizing steroid exposure and reducing the dose of daunorubicin and PEGylated asparaginase in older patients and to delay using anti-CD20 monoclonal antibodies [41]. Second-generation tyrosine kinase inhibitors with reduced dose steroids should be used in the Philadelphia chromosome-positive disease [6]. In addition, patients without COVID-19, should receive abundant growth factor support to hasten the recovery of the neutrophil count and to maintain an absolute neutrophil count of more than 1000 cells per μL across all phases of therapy. However, in moderate-to-severe COVID-19, the benefit of growth factor support should be weighed against the potential risk of exacerbating the pulmonary complications related to COVID-19. Use of G-CSF in our patient could be one of the factors that resulted in a faster recovery. At the time of the patient's COVID-19 diagnosis, the pandemic was in its initial stages and guidelines on chemotherapy with concomitant COVID-19 were evolving.

Conclusion

The management of patients with leukemia during the COVID-19 pandemic may be challenging. During high-risk COVID-19 periods, with optimal preventive measures and testing for COVID-19 (nasal swab, serology, chest CT), the risk of infection is still low although the mortality may be higher in patients with leukemia and COVID-19. The patient was able to survive COVID-19, but, unfortunately, had a relapse of ALL. Managing hematological malignancies effectively while trying to minimize the risk of severe COVID-19 due to immunosuppression secondary to chemotherapy is a challenging clinical situation, with evolving guidelines aiding clinical decision making.

Conflicts of interest

The authors declare no conflicts of interest.

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