



The Care of the Leukemic Patients in Times of SARS-CoV-2

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Abstract

Purpose of Review The spread of the novel coronavirus SARS-CoV-2 and its associated disease, coronavirus disease of 2019 (COVID-19), has significantly derailed cancer care. Patients with leukemia are more likely to have severe infection and increased rates of mortality. There is paucity of information on how to modify care of leukemia patients in view of the COVID-19 risks and imposed restrictions. We review the available literature on the impact of COVID-19 on different types of leukemia patients and suggest general as well as disease-specific recommendations on care based on available evidence.

Recent Findings The COVID-19 infection impacts leukemia subtypes in variable ways and the standard treatments for leukemia have similarly, varying effects on the course of COVID-19 infection. Useful treatment strategies include deferring treatment when possible, use of less intensive regimens, outpatient targeted oral agents requiring minimal monitoring, and prioritization of curative or life-prolonging strategies. Reducing health care encounters, rational transfusion standards, just resource allocation, and pre-emptive advance care planning will serve the interests of leukemia patients.

Summary Ad hoc modifications based on expert opinions and extrapolations of previous well-designed studies are the way forward to navigate the crisis. This should be supplanted with more rigorous prospective evidence.

Keywords Coronavirus · COVID-19 · Pandemic · Leukemia

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first detected in Wuhan, China, in December 2019. It is spread by droplet, contact, and airborne routes. About 20% of patients are asymptomatic [1]. Coronavirus disease of 2019 (COVID-19) is caused by SARS-CoV-2 and is characterized by a syndrome of fever, coryza, dysgeusia, cough, dyspnea, diarrhea, lymphopenia, ground-glass opacities, hypoxemia, and cytokine storm [2]. The spectrum of disease is heterogeneous ranging from mild symptoms akin to a common cold, to an acute respiratory distress syndrome requiring invasive ventilation. COVID-19 has evolved into a worldwide pandemic affecting more than 105 million people,

with the USA contributing more than 26 million cases and over 450,000 deaths [3]. In the general population, the infection rates are reported to be <1–2% and the mortality rate approximately 1–5%. High-risk groups with higher probability of death if infected include the older patients with comorbidities such as diabetes, the overweight, African Americans, and the immunocompromised population including those with cancers. For patients with cancer, the case fatality rate is two times that of the general population (5.6% versus 2.3%) [4, 5]. People living with cancers are viewed as high-risk groups due to the immunosuppression relating to their diagnoses and their treatment. In China, 1% of COVID-19 cases had a history of cancer whereas the incidence of cancer in the overall Chinese population is 0.29%. More importantly, patients with cancer are more likely to have adverse outcomes defined by being admitted to intensive care unit for invasive ventilation or death [5]. The case rate of COVID-19 among hospitalized patients with hematological malignancies was 10% compared to <1% for other cancers [6, 7]. These patients also have more severe diseases and a higher fatality rate of up to 37% [8, 9, 10•]. Consensus-based guidance and expert recommendations are being expeditiously developed and updated to help navigate this landscape for patients with all cancers, including those with leukemia [11•, 12•, 13•, 14, 15, 16•, 17]. However,

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prospective evidence is still very limited. Here, we present a review of the available evidence relevant to the care of leukemia patients in the context of COVID-19.

The markers of severe disease are non-specific and include elevated d-dimer, CRP, LDH, troponin, ferritin, and CPK and lymphopenia. Abnormalities in these parameters can be seen in leukemic patients in different contexts, making interpretation of these values a challenge. Temporal trends should be reviewed and may provide more information regarding the possible etiology. Respiratory support and monitoring for cytokine storm is paramount. Patients with COVID-19 also have an increased risk of thromboses, with one study showing 31% of patients with thrombotic complications in the intensive care unit [18, 19, 20].

Several drugs have been approved for the treatment of COVID-19 and SARS-CoV-2 infections (Table 1). Vaccines have also been approved in the USA and other countries and are currently being administered to selected populations. Asymptomatic patients can be monitored for recovery in their homes. The commonly employed drugs in the management of severe COVID-19 are summarized as follows.

General Recommendations

From the early stages of the pandemic, missed or delayed diagnosis, delays or deferral in chemotherapy, decreased frequency of follow-up visits and patient assessments, postponement of allogenic hematopoietic stem cell transplantation (allo-SCT), and shortage of blood products became apparent [30]. Shortage of acute care beds in intensive care units and respiratory support devices like ventilators has occurred throughout the country during the recurrent peaks of the crisis. This is compounded by the stress exerted in the healthcare workers who themselves are frequently exposed, requiring quarantine or falling victims of COVID-19. Many new leukemia patients are acutely ill needing supportive care (e.g., transfusions), management of infections, and hospitalization, and some, particularly those with acute leukemias, requiring early initiation of chemotherapy, frequently intensive, to control their disease. Induction chemotherapy and high-dose consolidation chemotherapy cause severe and prolonged neutropenia with an increased risk of bacterial, fungal, and viral infections. Testing for SARS-CoV-2 and CT imaging of the chest in all leukemia patients regardless of symptoms is recommended for all-new diagnosis and before any high-dose chemotherapy [31]. If patients with acute leukemia test positive for SARS-CoV-2, a delay in the start of treatment by 10–14 days should be considered whenever possible, with the possible use of transient cyto-reductive agents to control rapid proliferation of the disease and in an attempt to minimize rapid progression (e.g., hydroxyurea, dexamethasone for acute lymphoblastic and other lymphoid leukemias, cytarabine single agent for acute myeloid leukemia). Such delays would not be expected

Table 1 Agents currently employed to prevent/treat COVID-19

Agent	Evidence	Indication	Benefit	Caveats
Remdesivir (antiviral)	Randomized controlled trial (ACTT-1) [19]	Requiring low-flow supplemental oxygen	Shorter time to recovery by 4 days	Can cause anemia and lymphopenia
Baricitinib (immunomodulatory)	Randomized controlled trial (ACTT-2) [20]	Requiring supplemental oxygen or ventilator support, use in combination with remdesivir	Shorter time to recovery by 1 day	No increased risk of anemia or venous thrombosis
Bamlanivimab± etesevimab, casirivimab-imevimbab (neutralizing monoclonal antibody)	Randomized controlled trial (BLAZE-1, NCT0425629) [21–23]	Mild-moderate infection, outpatient use	Viral load reduction, lower hospitalization rates	Rare thrombocytosis with bamlanivimab
Dexamethasone (anti-inflammatory)	Randomized control trial (RECOVERY) [24]	Requiring any level of supplemental oxygen	Lower 28-day mortality	Part of many leukemia regimens, minimize steroid use in mild COVID-19 cases
Convalescent plasma (neutralizing polyclonal antibody)	Limited randomized control trials	Hospitalized patients, early in disease course	Faster clinical recovery, inconclusive evidence	May be of more benefit in lymphodepleted patients (e.g. Receiving anti CD20 therapy), CLL patients [25]
IL-6 pathway inhibitors (anti-inflammatory)	Case series and observational studies [26]	Elevated inflammatory markers and pro-inflammatory cytokines	Decreased risk of invasive ventilation or death	May increase risk of infections [27]
BNT162b2 and mRNA-1273 (mRNA vaccines)	Randomized control trials [28, 29]	All adults	95% efficacy at preventing infection	Rollout limited by supply constraints and uptake, concern for limited efficacy in leukemia patients

ACTT, adaptive COVID-19 treatment trial; BLAZE, neutralizing antibody LY-CoV555 in outpatients with COVID-19; RECOVERY, randomized evaluation of COVID-19 therapy; CLL, chronic lymphocytic leukemia; IL, interleukin; mRNA, messenger ribonucleic acid

to negatively affect the outcome in most instances. Several analyses have shown that a delay in the start of chemotherapy in acute myeloid leukemia (in these reports for obtaining cytogenetic and molecular analysis) does not adversely affect the outcome in most instances [32, 33]. In some instances, treatment interruption or discontinuation may be considered if the patient develops COVID-19 infection during active treatment. This decision should be weighed against the possible adverse impact this may have on the overall outcome of the patient, particularly for patients receiving potentially curative therapy. Early initiation of cytokine modulators could be considered for patients symptomatic from COVID-19 infection [34]. Specific and clear criteria should be established to guide the timing for the start of chemotherapy; these algorithms should be regularly reviewed and updated according to the regional COVID-19 situation, the institutional resources and outcomes, and the results from recent patients in similar circumstances. Although no universal criteria exist and different institutions use variations of the general recommendations, some suggested criteria include confirmation of two consecutive negative SARS-CoV-2 tests and absence of symptoms (e.g., fever, respiratory symptoms). If the test is negative once, it is recommended to repeat testing after 24 h if high clinical suspicion as RT-PCR has <90% sensitivity [35, 36].

Use of negative pressure room during hospital admission, limited visitation, rigorous use of personal protective equipment (PPE), hand washing before entering the room and upon exit (and during the visit as needed), and adequate postings in the room door to advise of the SARS-CoV-2 status are important general measures to minimize contagion. All disposable equipment and PPE should be discarded inside the room before exiting. Prophylactic anticoagulation (e.g., low molecular weight heparin if platelets >50,000/ μ L) for all inpatients might be appropriate [37]. Any new fever while on treatment requires re-testing for SARS-CoV-2 if previously negative. Slots for outpatient appointments, transportation options, clinician availability, availability of blood products and new and even standard drugs, and enrollment into trials may all be

limited during the pandemic as resources are being diverted to areas of greatest need. Multidisciplinary coordination between hematologist/oncologist, infectious disease expert, pulmonologist/intensivist, and nursing managers is crucial at multiple levels. Importantly, infectious disease specialists should be involved early in the management of patients with active COVID-19 to co-manage whenever possible. General recommendations pertaining to care of patients with leukemia are presented in Table 2.

Whenever possible, ambulatory patients should be managed through telemedicine. Many patients with myeloproliferative neoplasm, chronic myeloid leukemia, low-risk myelodysplastic syndrome, chronic lymphocytic leukemia, and some patients with acute leukemia in remission might be good candidates for these approaches. An adequate supply of their ongoing treatment should be secured when possible to minimize interruptions unless treatment pauses are indicated.

The role of granulocyte colony-stimulating factor (G-CSF) injections and subsequent neutrophil recovery to minimize COVID-19 complications is not clear. The rare but potential risk of worsening pulmonary injury in COVID-19 infection requires careful assessment when considering the use of growth factors for patients with moderate to severe COVID-19 infection [39].

Geriatric assessment prior to starting new regimens is recommended for older patients [40]. Home premedication prior to administering outpatient infusions, when appropriate, and the use of prophylactic growth factors should be considered. Prophylactic antimicrobials for patients with prolonged neutropenia should include antibacterial, antifungal, and antiviral agents. Reduction in donor availability due to voluntary withdrawal, travel restriction, increased donor deferrals, interruptions in stem cell product supply chain, blood product shortage, and limited inpatient beds may make intensive chemotherapy and allo-SCT difficult or of higher risk for many patients.

Strategies to delay or defer allo-SCT may be pursued in select patients. Back-up donors, matched related donors or haplo-identical allo-SCT, and cryopreservation of the stem

Table 2 Considerations while caring for leukemic patients during the COVID-19 pandemic

Preventive measures	Supportive measures	Treatment modifications
<ul style="list-style-type: none"> • Wearing masks and gloves, social distancing, and frequent hand washing • Limited inpatient visitation • Adequate signage • Minimize labs • More telehealth/telephone visits 	<ul style="list-style-type: none"> • Prophylactic antimicrobials when neutropenic • Growth factors for highly myelosuppressive regimens and during infections, when indicated • Anticoagulation: when inpatient, when on asparaginase • Low threshold for blood transfusions (e.g., hemoglobin <7.5 gm/dL) [38], anti-fibrinolytic agents for platelet refractory patients 	<ul style="list-style-type: none"> • Await results of cytogenetics and mutation analysis before therapy • Use less intensive therapies • Oral targeted agents and outpatient regimens whenever possible • Factor-in transfusion and labs requirements in addition to monitoring for toxicities with each regimen • Omit maintenance if in molecular remission • Avoid growth factors in severe COVID-19 infection

cell product before conditioning can help navigate some barriers [41•]. Controversial allo-SCT indications like patients with active refractory acute leukemia or those with a high risk of non-relapse mortality should avoid transplantation.

Acute Myeloid Leukemia (AML)

Patients with acute myeloid leukemia are at very high risk for mortality from COVID-19, particularly during induction [42•]. Considerations for the management of AML patients with COVID-19 are presented in Table 3.

Induction

Patients with AML should be screened for SARS-CoV-2 with a nasopharyngeal swab and undergo imaging, ideally CT of the chest prior to the start of induction chemotherapy. Patients who test positive for SARS-CoV-2, particularly if symptomatic, should have initiation of therapy delayed whenever possible. This time can be also used to obtain the results of the cytogenetic and molecular assessments. Management of COVID-19 can be done according to recommended guidelines. In some patients with proliferative disease, hydroxyurea or a single dose of cytarabine may help control symptoms and proliferation. Patients who test negative for COVID-19 may start induction therapy once workup is completed. Those who tested positive may initiate therapy after 10–14 days from positive testing. For patients who are symptomatic, treatment should ideally be delayed until symptoms resolve (no respiratory symptoms, no fever for at least 24 h unless fever is confirmed to be from other reasons). AML treatment can be done

per standard approaches. Induction chemotherapy with cytarabine and anthracycline (e.g., 3+7 or other similar regimens per institutional guidelines) may be used for fit and younger (e.g., 18–65 years) patients [13•]. Fit adults ≥ 50 years old, receiving induction chemotherapy, should preferably remain hospitalized until counts recovery (absolute neutrophil count $> 1000/\mu\text{L}$). Unfit or older patients (e.g., > 65 years) should receive lower intensity regimens based on hypomethylating agents (HMA) or low-dose cytarabine. Venetoclax improves overall survival rates when combined with HMA or low-dose cytarabine but adds risk of prolonged myelosuppression. A bone marrow aspiration on days 14–21 is recommended to assess response and if blasts $< 5\%$, venetoclax should be interrupted. After the first cycle with venetoclax-based combination, if bone marrow contains $< 5\%$ blasts, then growth factors may be used to shorten the duration of neutropenia. Glasdegib and low-dose cytarabine are also approved for such patients and cause less myelosuppression so it can be considered if myelosuppression is a concern.

Consolidation/Maintenance

The timing of consolidation should be individualized for every patient. For patients without high-risk features, the start of consolidation may be delayed, the dose reduced, and/or the number of cycles reduced. These decisions could be informed by assessment of measurable residual disease (MRD) whenever possible. Consolidation with cytarabine on days 1–3 (instead of on days 1, 3, and 5) has been found to be equally effective and to reduce myelosuppression and should be used when consolidation is to be administered [43, 44]. Outpatient

Table 3 Risk factors, treatment considerations, and challenges during COVID-19 for treatment of acute leukemia

Disease	Risk factors for increased mortality	Treatment considerations	Challenges
AML	<ul style="list-style-type: none"> • Older age at diagnosis • Myelosuppression due to underlying disease and treatment • Transfusion needs • Drug toxicities: cardiac dysfunction from anthracycline exposure, pulmonary toxicity due to midostaurin 	<ul style="list-style-type: none"> • Intensive induction chemotherapy per usual guidelines • Use lower dose cytarabine followed by pegfilgrastim • Home labs till transfusions required • HMA based regimens for induction or maintenance favored 	<ul style="list-style-type: none"> • Delaying consolidation or maintenance • Delaying allo-SCT • Differentiate COVID-19 from other infections
ALL	<ul style="list-style-type: none"> • Myelosuppression due to underlying disease and treatment • Hypogammaglobinemia • Transfusion needs • Frequent clinic visits • Drug toxicities: Cardiac dysfunction due to anthracycline exposure, pulmonary impairment due to methotrexate, additive prothrombotic risk with asparaginase 	<ul style="list-style-type: none"> • Intensive induction chemotherapy per usual guidelines • Mini-HCVAD and blinatumomab preferable • Home labs till transfusions required • May omit vincristine 	<ul style="list-style-type: none"> • Delaying consolidation or maintenance • Delaying allogenic SCT • Differentiate COVID-19 from other infections

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; *allo-SCT*, allogenic stem cell transplantation; *HCVAD*, hyper fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone

administration should be favored whenever possible. Subsequent cycles of consolidation may be delayed (e.g., to 42–56-day cycles, instead of 28-day cycles) to allow a more robust recovery of counts between cycles and space out the periods of myelosuppression, particularly if access to regular monitoring, transfusions, and hospitalization is restricted. The number of consolidation cycles can be reduced to 2 or 3 particularly for patients with negative MRD after 2 cycles of consolidation chemotherapy. For patients where a stem cell transplant is indicated but not possible immediately, additional cycles of consolidation may be administered until SCT is considered feasible and safe. Allo-SCT should be deferred for patients without adverse risk disease especially when they are MRD negative. Maintenance with azacitidine ± venetoclax can also be considered as a bridging therapy until allo-SCT or as an alternative to intensive post-remission therapy after careful consideration [45]. A lower dose of venetoclax may be used to reduce risk of prolonged cytopenias, and for patients at higher risk of myelosuppression or when access to clinics, laboratory, and transfusions is limited, HMA can be used alone after complete remission.

Relapsed/Refractory Disease

These patients pose a particular challenge. For patients with a reasonable curative potential and with an option for a stem cell transplant, similar considerations as for initial therapy can be followed. Clinical trials should be considered when feasible. Re-assessment of cytogenetic and molecular characteristics of the disease are important as they may identify features that allow consideration of target-specific agents that may offer reasonable response probabilities with less myelosuppression such as FLT3 inhibitors, and IDH inhibitors. The timing of initiation of therapy should be tailored to the status of COVID-19 infection and the availability of adequate support in a similar way as has been described for frontline therapy.

Acute Promyelocytic Leukemia (APL)

APL is a highly curable disease, and delays in treatment can have serious adverse consequences. Thus, patients with APL should receive all-trans retinoic acid (ATRA) upon confirmation of diagnosis. The addition of arsenic trioxide and for patients with high-risk disease, gemtuzumab ozogomicin, or idarubicin should also be considered, following standard guidelines [46]. These treatments are not highly myelosuppressive, but patients require hospitalization for at least the first 14–21 days. All necessary precautions discussed earlier in this manuscript should be adopted to minimize the risk. Delaying the addition of arsenic trioxide may be considered in some low-risk patients if the patient has active COVID-19 and/or if the hospital resources are seriously limited.

Acute Lymphoblastic Leukemia (ALL)

General Considerations

ALL patients have been reported to have prolonged PCR positivity for weeks after COVID infection (possibly due to detection of viral fragments that have not cleared) but limited patient experience seems to support that it is safe to resume treatment once symptoms have resolved completely [47]. Table 3 highlights common issues relevant to care of ALL during COVID-19 times. All patients with newly diagnosed ALL should be screened for COVID-19 with the nasopharyngeal swab and CT chest. If positive, systemic intensive chemotherapy should be delayed whenever possible (e.g., in the absence of major hyperleukocytosis) although intrathecal treatment may be given for central nervous system symptoms [47]. Corticosteroids are an important component of treatment and may be used to manage ALL when temporizing measures are needed. In addition, dexamethasone can reduce mortality of patients hospitalized for COVID-19 [24]. Use of asparaginase is probably best avoided in most instances due to additive risk of thromboses with COVID-19. Growth factors are routinely used to hasten neutrophil recovery in ALL regimens and should be used if chemotherapy is being administered to minimize prolonged myelosuppression.

Induction

For Philadelphia (Ph) chromosome–negative disease, multi-drug chemotherapy regimens such as hyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, methotrexate, cytarabine, dexamethasone, and intrathecal chemotherapy) comprises the backbone of ALL treatment in young adults (e.g., <65 years) [48]. Older patients may receive reduced-intensity regimens (e.g., mini-hyper-CVAD; 50% dose–reduced cyclophosphamide, vincristine, dexamethasone, 75% dose–reduced methotrexate, 83% dose–reduced cytarabine, and omission of doxorubicin), possibly in combination with inotuzumab and alternating with blinatumomab [49]. A recent report suggests reduced myelosuppression with this approach [50]. For young adults (up to 40 years) treated with pediatric-inspired regimens, some recommendations include dose-reducing daunorubicin (50%) or using a reduced-dose Peg-asparaginase (e.g., 1000 IU/m²) in patients with high risk for complications [47]. However, the additive thrombotic potential when using asparaginase in the context of the risk of COVID-19-associated coagulopathy makes this regimen a less desirable option [51]. Rituximab is frequently used for CD20-positive ALL, but the associated B-cell depletion and the limited efficacy as a single agent make its use also less desirable in the setting of active COVID-19. Some recommend immunoglobulin G (IgG) level monitoring when it is used [47]. When available, outpatient administration of

chemotherapy is preferred, but this requires existing outpatient protocols, robust support infrastructure, and close monitoring.

For Ph-positive ALL, a second or third-generation tyrosine kinase inhibitor (TKI) alone or in combination with dexamethasone and blinatumomab can result in a high response rate and minimal myelosuppression [52, 53]. These combinations should be considered in patients with active COVID-19 in lieu of TKI + intensive chemotherapy. Patients may require hospitalization for the first few days of the first cycle of blinatumomab infusion to monitor for cytokine release syndrome, and the logistics of the continuous infusion may make administration of blinatumomab difficult when hospital and clinic resources are stretched. This regimen however starts with dasatinib and dexamethasone only which is less daunting and may be administered in the outpatient setting once the patient is stable. Other options are TKI plus mini-hyper-CVAD or TKI plus vincristine and steroids [54].

For patients with T-cell ALL, regimens such as hyper-CVAD with the addition of asparaginase and nelarabine are frequently recommended [55, 56]. However, in the context of active COVID-19, such approaches might not be optimal because of the myelosuppression induced by the combination chemotherapy and the coagulopathy associated with asparaginase. Reduced-intensity approaches can be considered, such as dexamethasone alone or in combination with nelarabine if therapy has to be initiated in a patient with active COVID-19 in an attempt to minimize prolonged and profound myelosuppression. A full combination regimen can be started once the patient recovers from the viral infection.

Consolidation/Maintenance

Consolidation is an integral part of ALL regimens. MRD status is checked during treatment and patients achieving negative MRD may be switched to early maintenance. Persistent MRD-positive patients after 2–3 cycles of intensive chemotherapy would benefit from switching to blinatumomab if not included in the initial regimen [57]. In patients where consolidation with intensive chemotherapy is not desirable because of an active COVID-19, temporizing measures such as dexamethasone with or without rituximab (if CD20 positive) may be considered, resuming consolidation once the patient is fully recovered from COVID-19. A dose-reduced consolidation (such as mini-hyper-CVAD) can also be considered.

Dose reductions for 6-mercaptopurine and/or methotrexate to minimize myelosuppression can be considered while on maintenance when using POMP (6-mercaptopurine, vincristine, methotrexate, and prednisone). Blinatumomab or inotuzumab can be used as later intensification strategy. High-risk ALL and relapsed ALL in second complete remission will require an allo-SCT, but the timing of the SCT should be delayed if the patient has active COVID-19, and adjusted to local conditions and hospital resources.

Relapsed/Refractory Disease

In a salvage setting, blinatumomab and inotuzumab offer survival benefit compared to intensive chemotherapy. Both are also less myelosuppressive than intensive chemotherapy, and, in randomized trials, infections were less common among patients treated with these agents compared to those treated with standard chemotherapy. Thus, these agents should be preferred for patients with COVID-19. Depending on the severity of the SARS-CoV-2 infection, the initiation may need to be delayed in some instances and patients temporized with dexamethasone.

Myelodysplastic Syndromes (MDS)

Epidemiology

MDS, particularly in patients with high-risk disease, may pose an increased risk to severe COVID-19 and a risk of mortality similar to AML [8]. One report suggested a lethality rate of 73% among male MDS patients with COVID-19 [58]. Mortality was particularly high among patients in the higher risk categories. Patients also had multiple comorbidities, in accordance with their reported median age of 78 years. This was higher than the median age (73 years) of the overall MDS population. Table 4 lists common issues with care of MDS patients during these times.

Treatment

Older age at diagnosis, qualitative and quantitative defects in neutrophils, and higher comorbidity index put these patients at higher risk regardless of MDS. Patients with higher risk MDS (IPSS-R score of ≥ 3.5) may be in need of treatment more immediately, although in most instances, this can be delayed by a few weeks, a time that is also valuable in obtaining full cytogenetic and molecular characterization. A delay in the start of therapy is not associated with worsened survival or increased risk of transformation [59]. Thus, patients with active COVID-19 should in most instances delay the start of therapy and be managed with supportive measures (transfusion support, prophylactic, or therapeutic antibiotics). Once the patient has recovered, therapy with HMA can be initiated. The standard is single-agent HMA and this approach should be used unless the patient is eligible for an available high-priority clinical trial, provided trials are feasible based on local conditions. HMA may alter type 1 interferon response, but its effect in the clinical course of COVID 19 infection is not clear [60]. Available therapies for patients with low-risk MDS such as erythroid stimulating agents, lenalidomide, and luspatercept reduce transfusion requirements and may be considered for such patients. Lenalidomide may cause

Table 4 Risk factors, treatment considerations, and challenges during COVID-19 for treatment of MDS and MPN

Disease	Risk factors for increased mortality	Treatment considerations	Challenges
MDS	<ul style="list-style-type: none"> • Older age at diagnosis • Myelosuppression due to underlying disease and treatment • Transfusion needs • Impaired neutrophil and T-cell function • Lymphopenia in high-risk patients • Comorbid renal, cardiovascular, or pulmonary dysfunction • Baseline inflammatory cytokine milieu 	<ul style="list-style-type: none"> • Risk stratification per usual guidelines • Growth factors to prevent neutropenia • Lenalidomide and HMA are myelosuppressive • Delay definite therapy if indicated 	<ul style="list-style-type: none"> • Delaying allo-SCT • Differentiate COVID-19 from other infections • Leukemoid reaction and fatal cytokine storm in CMML patients
MPN	<ul style="list-style-type: none"> • Prothrombotic state additive with COVID-19 infection • Impaired neutrophil and T-cell function • Baseline inflammatory cytokine milieu 	<ul style="list-style-type: none"> • Follow usual cytoreduction goals • Avoid abrupt discontinuation of JAK2 inhibitors • Avoid G-CSF in patients with splenomegaly 	<ul style="list-style-type: none"> • Need to reduce clinic visits • Increased risk of both thromboses and hemorrhage

MDS, myelodysplastic syndrome; *HMA*, hypomethylating agent; *allo-SCT*, allogeneic stem cell transplantation; *CMML*, chronic myelomonocytic leukemia; *MPN*, myeloproliferative neoplasms; *JAK2*, janus kinase 2; *G-CSF*, granulocyte colony-stimulating factor

myelosuppression in some patients with del (5q) MDS, so blood counts should be monitored closely upon starting therapy with lenalidomide. MDS/MPN (myelodysplastic syndrome and myeloproliferative neoplasm) overlap entities such as chronic myelomonocytic leukemias have baseline inflammatory cytokine profile and higher expression of ACE2 (angiotensin-converting enzyme 2) expression in monocytes and macrophages [61, 62]. Few cases of severe COVID-19 have been reported in patients with CMML and prophylactic cytoreduction is suggested as a strategy to reduce the risk of cytokine storm in the event of COVID-19 infection later [63–65]. The same principles discussed earlier for MDS can be used for managing patients with these entities.

Myeloproliferative Neoplasms

Epidemiology

In a survey from the GIMEMA group, 33.6% of tested patients with MPN were positive for SARS-CoV-2 (0.002% of all MPN patients included in the survey) [66]. Although 36% were asymptomatic, 27.8% had pneumonia. Mortality among patients who tested positive was 22%. A separate report, also from Italy, reported a mortality rate of 48% among patients with myelofibrosis, while no increased risk of mortality was identified for patients with essential thrombocythemia, polycythemia vera, and prefibrotic myelofibrosis [67]. Although these results were collected from a survey not reflecting the whole universe of patients and do not have full information about comorbidities and other risk factors, it highlights the seriousness of COVID-19 among patients with MPN.

Treatment

Patients in need of low-risk interventions such as phlebotomies or aspirin for prophylaxis of thrombosis should be managed as needed. Increased risk of thrombosis with MPN is a concern and this might be increased in the setting of COVID-19. Patients should be carefully assessed and managed according to standard guidelines. MPN patients with COVID-19 infection when hospitalized should be administered low molecular weight or unfractionated heparin in prophylactic or intermediate doses during inpatient or intensive care unit settings. For patients with myelofibrosis who are very symptomatic and/or with a very enlarged spleen, ruxolitinib can be initiated. Because of the effect ruxolitinib has on reducing pro-inflammatory cytokines, several studies are exploring the role of ruxolitinib in reducing the inflammatory consequences of COVID-19 [68]. However, it is not yet known whether it has a role in this indication. A recent phase 2 randomized study of patients with severe COVID-19 randomized to standard of care alone or with ruxolitinib failed to show statistically significant clinical improvement with ruxolitinib, but there was a trend in radiologic improvement and survival in favor of patients receiving ruxolitinib [69]. Still, patients with MPN in need of therapy with ruxolitinib can be treated and monitored closely. Patients already on therapy with ruxolitinib should not discontinue therapy if they develop COVID-19 [70]. Discontinuation of ruxolitinib has been associated with a “cytokine storm” that can have serious consequences [71]. In a recent report, among patients with MPN, treatment with ruxolitinib was not associated with an increased risk of death in a multivariate analysis, but treatment discontinuation led to death in 11 of 45 patients [67]. It is therefore important to ensure patients have adequate supplies of ruxolitinib. The theoretical immunosuppressive effects of ruxolitinib do not appear to have significant clinical

consequences in general or among patients with COVID-19 [72]. Common considerations for MPN management are outlined in Table 4.

Chronic Myeloid Leukemia (CML)

Epidemiology

Prevalence of COVID-19 in CML patients was 0.9% (0.1% in the general population) in a Chinese study, but preliminary results from a Dutch study did not show significantly increased prevalence compared to the general population [73•, 74•]. No signal for increased mortality was observed for patients receiving tyrosine kinase inhibitors (TKIs) in one report [75]. The International CML Foundation recently reported on 110 CML patients with COVID-19 from 20 countries around the world [76]. Seventy percent of them were on treatment with TKIs while others were not receiving treatment either because of elective treatment discontinuation (n=8) or other reasons, or treatment information was not available (n=14). COVID-19 was asymptomatic in 8 (7%) patients, mild in 49 (45%), moderate in 19 (17%), and severe in 19 (17%) (unknown in 15). At the time of the report, 12 patients (14%) had died due to COVID-19.

Treatment

Evaluation and choice of therapy for newly diagnosed CML is generally unaffected by COVID-19 [77]. TKIs can cause myelosuppression during the initial weeks of therapy and laboratory workup every 1–2 weeks is recommended [52]. This is less of a concern for stable patients on TKIs and hence therapy can be continued in the absence of neutropenia. TKIs do not seem to increase the risk of acquiring SARS-CoV-2 or of causing severe disease in COVID-19 patients. However, the side effect profile of some TKI may overlap with COVID-19-induced organ damage or predispose to complications. Dasatinib for example can cause pleural effusions and pulmonary arterial hypertension; nilotinib, dasatinib, and ponatinib can cause arterio-occlusive adverse events; bosutinib can frequently cause diarrhea. COVID-19 can cause similar symptoms in some patients and testing for active and recent infection with nasopharyngeal swab and antibody serology is recommended when there is increased symptom burden. For CML patients with mild infections, TKIs can be continued. However, in case of severe COVID-19 infection or patients with cardiopulmonary symptoms, consideration can be given to a treatment hiatus, particularly for patients with stable disease. For accelerated phase and, particularly, for blast phase CML, TKIs are frequently combined with intensive or lower intensity chemotherapy. Considerations for initiation of chemotherapy parallel what was discussed earlier for AML and ALL. In patients with active

disease, single-agent TKI can be used until the patient recovers from COVID-19 and then add the chemotherapy if this is being considered as part of the treatment plan (e.g., blast phase CML).

For patients in remission, routine BCR-ABL1 PCR monitoring (typically every 3 months) may be spaced out further and remote testing can be utilized along with telemedicine. Follow-up bone marrow biopsies and attempts at treatment-free remission should be delayed unless absolutely necessary and adequate resources and monitoring are available.

Chronic Lymphocytic Leukemia (CLL)

Epidemiology

CLL is a disease mostly affecting older patients which is frequently accompanied clinically by both humoral and cell-mediated immune dysfunctions. In Italy and Spain, 79% of CLL patients hospitalized with COVID-19 had severe disease (need of supplemental oxygen and/or intensive care admission) compared to 13.4% among the general population in the same countries; 36.4% of the CLL patients included in this analysis died, underscoring the high risk for these patients [78]. Interestingly, 60% of patients with severe COVID-19 were off therapy within the last 12 months or had never received therapy for CLL, compared to less severe cases (38.5%). The effect of various treatments however may be different. Hospitalization rates for severe COVID-19 were lower for patients on ibrutinib compared to those on other regimens or off treatment. Interestingly, BTK (Bruton tyrosine kinase) inhibitors appear to exert some protective effect against severe disease, consistent with studies showing an anti-inflammatory effect in CLL [79]. Contemporary issues in CLL management are enlisted in Table 5.

Treatment

For patients with CLL who are on surveillance, telemedicine visits with home labs or no labs are suggested for follow-up. Initiation of treatment according to the International Workshop on CLL indications (anemia and/or thrombocytopenia, splenomegaly, lymphadenopathy, lymphocyte doubling time <6 months, extranodal involvement, B symptoms) are usually not urgent and in most instances can be delayed with close follow-up, until symptoms of COVID-19 resolve and resources are available and circumstances are appropriate for proper monitoring.

Chemoimmunotherapy regimens like FCR (fludarabine, cyclophosphamide, rituximab) and BR (bendamustine, rituximab) should be avoided in most instances in favor of highly effective oral targeted agents. BTK inhibitors like ibrutinib and acalabrutinib require fewer clinic visits. Interestingly, *in vitro* studies have suggested that these agents might be protective in

Table 5 Risk factors, treatment considerations, and challenges during COVID-19 for treatment of chronic leukemia

Disease	Risk factors for increased mortality	Treatment considerations	Challenges
CML	<ul style="list-style-type: none"> • Older age at diagnosis • Drug toxicities: cardiac injury due to dasatinib, nilotinib, ponatinib; pulmonary injury due to dasatinib; thrombotic risk with ponatinib and nilotinib 	<ul style="list-style-type: none"> • Continue TKI and BCR-ABL monitoring • Space out follow-up visits and telemedicine • Do not attempt trial of TKI discontinuation • Single-agent TKI when possible for BP patients until COVID-19 resolved 	<ul style="list-style-type: none"> • Differentiating drug toxicities from COVID-19 symptoms
CLL	<ul style="list-style-type: none"> • Older age at diagnosis • Hypogammaglobinemia • Impaired innate immune responses • Drug toxicities: impaired B-cell function due to anti-CD20 monoclonal antibodies, pneumonitis with PI3Ki 	<ul style="list-style-type: none"> • Initiate treatment per usual guidelines • Chemoimmunotherapy not preferred • Anti-CD20 therapies and venetoclax avoided • Space out follow-up visits and telemedicine 	<ul style="list-style-type: none"> • PI3Ki pneumonitis and opportunistic infections, e.g., PJP, CMV can mimic COVID-19

CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitor; BCR-ABL, breakpoint cluster region-tyrosine protein kinase ABL1; BP, blast phase; CLL, chronic lymphocytic leukemia; PI3Ki, phosphoinositide 3-kinase inhibitor; PJP, *Pneumocystis jirovecii* pneumonia; CMV, cytomegalovirus

COVID-19 infection [80, 81]. Patients still should be monitored for efficacy and safety, with telehealth whenever possible. Anti-CD20-targeted agents like rituximab and obinutuzumab carry the risk of B-cell lymphodepletion and may worsen the severity of COVID-19 infection. These should therefore be avoided or deferred [82–84]. Venetoclax and obinutuzumab are the only fixed duration frontline therapy but carry risk of tumor lysis syndrome and neutropenia in addition to the lymphopenia associated with obinutuzumab. It is ideal to delay the start of therapy for patients with COVID-19 or at high risk of infection. Patients treated with venetoclax or with neutropenia from other therapies can be supported with filgrastim. Patients with indications for intravenous immunoglobulins (IVIG) may continue these infusions, but the frequency should be evaluated according to patient and healthcare facility's needs. IVIG increases the risk of thrombosis, which should be considered. There are reports of successful treatment of severely ill COVID-19 patients with high-dose IVIG [85, 86]. A syndrome of CLL flare and cytokine release akin to COVID-19 is seen on discontinuation of BCR signaling inhibitors (ibrutinib, acalabrutinib, idelalisib, duvelisib) which resolves on resumption of the drug [87, 88]. Patients with CLL who contract COVID-19 should consider stopping or dose adjusting immunosuppressive therapy until they are free of symptoms and at least 14 days from onset of symptoms with preferably negative nasopharyngeal swab [14].

Conclusion

COVID-19 is an unprecedented healthcare crisis, and this has percolated to affect patients' care and prognosis. Patients with leukemia and hematological malignancies and the health care infrastructure are forced to cope up with this situation. Patients with leukemia are in many instances at increased risk of severe disease and mortality. Sound ethical rationing of the existing resources and using evidence-based adjustments to the

treatment paradigms will be our path forward as the COVID-19 outbreak is likely to last months and might recur in the future in a cyclical pattern [89].

Author Contribution JC and NRK conceived the review. JC searched the literature and provided relevant references. NRK reviewed and analyzed the literature. NRK drafted the report. JC edited the manuscripts and TL performed revisions. TL verified the accuracy of references.

Availability of Data and Materials Not applicable.

Code Availability Not applicable.

Declarations

Conflict of Interest NRK and TL have no conflict of interest to declare. JC is a consultant for Pfizer, Novartis, Takeda, Jazz, Biopath Holdings, and Sun Pharma; he has received research support (to his institution) from Pfizer, Novartis, Takeda, Jazz, Biopath Holdings, Sun Pharma, Actuate, and Telios.

Ethics Approval Not applicable.

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