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Treating Leukemia in the Time of COVID-19

Shilpa Paul[a] Caitlin R. Rausch[a] Nitin Jain[b] Tapan Kadia[b] Farhad Ravandi[b] Courtney D. DiNardo[b] Mary Alma Welch[b] Bouthaina S. Dabaja[c] Naval Daver[b] Guillermo Garcia-Manero[b] William Wierda[b] Naveen Pemmaraju[b] Guillermo Montalban Bravo[b] Philip Thompson[b] Srdan Verstovsek[b] Marina Konopleva[b] Hagop Kantarjian[b] Elias Jabbour[b]

[a]Division of Pharmacy, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [b]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [c]Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

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Abstract
The coronavirus disease 2019 (COVID-19) pandemic poses several challenges to the management of patients with leukemia. The biology of each leukemia and its corresponding treatment with conventional intensive chemotherapy, with or without targeted therapies (venetoclax, FLT3 inhibitors, IDH1/2 inhibitors, Bruton's tyrosine kinase inhibitors), introduce additional layers of complexity during COVID-19 high-risk periods. The knowledge about COVID-19 is accumulating rapidly. 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 clinical infection is <1–2% worldwide. With a mortality rate of 1–5% in COVID-19 patients in the general population and potentially of >30% in patients with cancer, careful consideration should be given to the risk of COVID-19 in leukemia. Instead of reducing patient access to specialized cancer centers and modifying therapies to ones with unproven curative benefit, there is more rationale for less intensive, yet effective therapies that may require fewer clinic visits or hospitalizations. Here, we offer recommendations on the optimization of leukemia management during high-risk COVID-19 periods.

Introduction

The novel betacoronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initially described in Wuhan, China, in December 2019. Since then, more than 2.5 million people worldwide have been infected with coronavirus disease 2019 (COVID-19), and more than 170,000 have died [1, 2]. About 25–50% of people exposed to COVID-19 are asymptomatic. Among symptomatic "clinically infected" people, the associated clinical findings can escalate from mild symptoms of dry cough, fever, and malaise to severe complications such as

S. Paul and C.R. Rausch contributed equally to this work.

karger@karger.com
www.karger.com/aha

Elias Jabbour
Department of Leukemia, University of Texas MD Anderson Cancer Center
1515 Holcombe Blvd., Box 428
Houston, TX 77030 (USA)
ejabbour@mdanderson.org

Table 1. Anticipated risk factors for COVID-19 in patients with leukemia

Risk factor	Cause		
	leukemia diagnosis	treatment	patient-specific
Neutropenia	X	X	
Leukopenia	X	X	
Hypogammaglobulinemia	X	X	
Depressed immune function	X	X	
Hypercoagulable state	X	X[a]	
Organ dysfunction (cardiac, renal, liver, pulmonary)	X	X	X
Comorbid conditions			X
Age			X

COVID-19, coronavirus disease 2019. [a] With asparaginase treatment.

life-threatening pneumonia, acute respiratory distress syndrome, neurologic dysfunction, disseminated intravascular coagulopathy and associated thrombotic events, and cardiomyopathy leading to cardiac arrest, multiorgan failure, and ultimately death [1]. In regions that became disease epicenters, the number of confirmed cases increased rapidly, overwhelming existing medical infrastructures (hospital beds, intensive care unit beds, ventilators, dialysis machines, personal protective equipment, healthcare workers). This may have contributed to the higher mortality rates (10–13% in Spain, Italy, and France) and infection rates among healthcare workers (10–20%) [3–5]. As this pandemic persists, healthcare workers are navigating the risk of COVID-19 exposure while providing optimal care to high-risk patient populations, including those with cancer.

Knowledge of the COVID-19 disease process in patients with cancer, particularly hematologic malignancies, is scarce but steadily increasing. The infection rate in patients with cancer may be higher than that of the general population [6]. 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 [1, 7]. Infected 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%; $p = 0.032$). Logistic regression identified cancer as the highest individual risk factor for severe events (OR: 5.4; 95% CI: 1.8–16.2; $p = 0.003$) [7]. 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; $p = 0.037$) [8]. This highlights the potentially severe impact of COVID-19 in patients with cancer. Unfortunately, there are limited studies with leukemia; thus, the ramifications in that specific population are not well known [9, 10]. However, patients with leukemia are often immunosuppressed, myelosuppressed, and may have low immunoglobulin levels, rendering them to be potentially more vulnerable to COVID-19 and its complications.

Patients with leukemia may be at a uniquely higher risk of developing COVID-19 for multiple reasons associated with both their underlying diagnosis and treatment as well as patient-specific factors (Table 1). Each leukemia subtype may also be associated with particular COVID-19-associated risks due to disease biology or associated therapy (Table 2). For example, patients with lymphoid malignancies are at higher risk of infection due to impaired humoral response caused by disease- or treatment-related hypogammaglobulinemia. Immunocompromised leukemia patients with COVID-19 can also be at higher risk of superimposed bacterial or fungal pneumonia. Given the above, guidelines concerning the management of leukemia in COVID-19 high-risk periods would be helpful. Factors to consider include reduction of inpatient stays, less intensive and less myelosup-

Table 2. Leukemia-specific risk factors for COVID-19

Leukemia type	Possible risk factors
ALL	Myelosuppression due to underlying disease and treatment Hypogammaglobulinemia Impaired B-cell function due to CD20-targeted monoclonal antibodies Prolonged steroid exposure Pulmonary and renal impairment due to methotrexate therapy Cardiac dysfunction due to anthracycline exposure Increased risk of COVID-19-associated thrombosis with asparaginase
AML	Myelosuppression due to underlying disease and treatment Cardiac dysfunction due to anthracycline exposure Pulmonary injury due to midostaurin
CML	Cardiac injury due to dasatinib, nilotinib, ponatinib Pulmonary injury due to dasatinib Increased risk of COVID-19-associated thrombosis with ponatinib and nilotinib
CLL	Hypogammaglobulinemia Impaired B-cell function due to CD20-targeted monoclonal antibodies Impaired innate immune response as well as B-cell and T-cell function with BTK inhibitors
MDS	Myelosuppression due to underlying disease and therapy Impaired neutrophil and T-cell function Potential increase risk of COVID-19 associated hyperinflammation due to baseline elevated IL-1, IL-6, TNF, and other cytokines Renal, cardiovascular, or other comorbidities due to underlying comorbidities
MPN	Risk of thrombosis in myeloproliferative disorders Rare but potential risk of cytokine reaction with abrupt discontinuation of JAK inhibitor Potential increased risk of COVID-19-associated hyperinflammation due to baseline elevated IL-1, IL-6, TNF, and other cytokines

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; COVID-19, coronavirus disease 2019; MDS, myelodysplastic syndromes; MPN, myeloproliferative neoplasms.

pressive regimens whenever possible, transition of therapy to the outpatient setting with virtual appointments when possible, optimization of dosing and administration times in outpatient infusion centers, simplification of laboratory monitoring, reduction of unnecessary regulatory burdens that do not improve quality of patient care or safety, and increased use of growth factors if applicable.

This review discusses management practices for patients with leukemia during the COVID-19 pandemic (Table 3). Some of the fundamental principles can be extrapolated to other patients if needed. The decision to continue, delay, reduce, or withhold treatment depends on the leukemia type as well as patient-specific factors including age, comorbidities, and COVID-19 disease severity, among others. This should be determined on an individual basis and will not be thoroughly discussed. Leukemia experts should carefully assess and discuss the benefits versus risks of alternative approaches with each patient in order to deliver optimal care.

Acute Leukemias

Treating patients with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) during a COVID-19 pandemic can be particularly challenging. One must weigh the treatment of a lethal, acute illness requiring aggressive therapy against the systemic limitations of inpatient stays, frequent clinic visits, and increasingly restricted blood product supply. The development of several targeted therapies to treat both ALL and AML may allow a reduction of dose-intensity while preserving efficacy and the potential of cure.

Table 3. Treatment alternatives for patients with leukemia during COVID-19 high-risk periods

Leukemia type	Scenario			Treatment recommendations
ALL	Induction/ consolidation	Ph-negative	<60 years	HCVAD × 4 cycles followed by blinatumomab × 4 cycles or mini-HCVD + inotuzumab × 4 cycles followed by blinatumomab × 4 cycles
			≥60 years	Mini-HCVD + inotuzumab × 4 cycles followed by blinatumomab × 4 cycles
			≥70 years	Mini-HCVD + inotuzumab × 2 cycles followed by blinatumomab × 8 cycles
			MRD-positive	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/m^2/dose rather than 3 g/m^2/dose on days 1–3 followed by pegfilgrastim 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
CML	Initiation			Consider imatinib or low-dose dasatinib Avoid bosutinib and nilotinib
	Continuation			Continue current therapy and BCR-ABL1 monitoring Delay initiation of treatment-free remission
CLL	Initiation	Not meeting IWCLL criteria		Watch and wait
		Meeting IWCLL criteria		Avoid FCR Consider ibrutinib or acalabrutinib weighing benefit versus risk Consider obinutuzumab + venetoclax, but may require additional clinic visits or hospitalization for tumor lysis syndrome monitoring and can cause neutropenia
	Continuation			If on FCR, consider switching or oral targeted therapy if feasible If on venetoclax, maintain therapy if tolerating If on ibrutinib or acalabrutinib, maintain therapy if tolerating; abrupt discontinuation may cause disease flare
MDS	Initiation			Newly diagnosed: consider risk-adapted assessment approach High-risk MDS: HMA-based therapy; consider delaying intensive induction therapy if possible
	Continuation			Continue standard of care therapies with best supportive care (e.g., epoetin alpha, luspatercept, etc.) or HMA If on HMA, consider adding G-CSF to prevent prolonged neutropenia

Table 3 (continued)

Leukemia type	Scenario	Treatment recommendations
MPN		May continue non-immunosuppressive medications (interferon, hydroxyurea, etc.) If on ruxolitinib: may continue therapy as abrupt discontinuation may cause disease flare, but benefit verses risk must be conisdered as it can cause immune dysregulation If stopping JAK inhibitor, taper dose instead of stopping abruptly If on anticoagulation, may continue therapy; consider switching to low-molecular weight heparin if patient has COVID-19 infection If receiving phlebotomy, consider reducing number of sessions and encourage increasing hydration to reduce clinic visits

AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; COVID-19, coronavirus disease 2019; FCR, fludarabine, cyclophosphamide, and rituximab; G-CSF, granulocyte colony-stimulating factor; HCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, methotrexate, cytarabine, dexamethasone, and intrathecal chemotherapy; HMA, hypomethylating agent; IWCLL, International Workshop on CLL; LDAC, low-dose cytarabine; MDS, myelodysplastic syndromes; mini-HCVD, 50% dose reduction of cyclophosphamide and dexamethasone, 75% dose reduction of methotrexate, 83% dose reduction of cytarabine, and omission of doxorubicin; MPN, myeloproliferative neoplasms; MRD, minimal residual disease; MTX, methotrexate; SCT, stem cell transplantation; TKI, tyrosine kinase inhibitor; 6-MP, 6-mercaptopurine.

Acute Lymphoblastic Leukemia

The treatment of ALL was historically based on pediatric-inspired intensive regimens that use multiagent chemotherapy, including steroids. The recent development of less myelosuppressive regimens incorporating the CD3-CD19 bispecific antibody, blinatumomab, and the anti-CD22 conjugated antibody, inotuzumab ozogamicin, have improved treatment options and demonstrated overall safety and efficacy, particularly in older patients.

All newly diagnosed patients with ALL and those receiving consolidation therapy should be screened for COVID-19, including a baseline computed tomography (CT) of the chest without contrast due to the potential for false-negative PCR from the nasopharyngeal swab, regardless of symptoms [11].

Ph-Negative ALL. Patients newly diagnosed with ALL during the COVID-19 pandemic should receive treatment with curative intent. One of the standard treatment regimens for ALL, known as HCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, methotrexate, cytarabine, dexamethasone, and intrathecal chemotherapy), has been significantly modified over the years to incorporate newer, more effective therapies [11–15] and to make it more adaptable to individuals or situations such as the COVID-19 pandemic. If a patient is COVID-19-negative and is younger than 60 years, a less intensive regimen using mini-HCVD (consisting of cyclophosphamide at a 50% reduced dose, vincristine, dexamethasone, methotrexate at a 75% reduced dose, cytarabine at an 83% reduced dose, and omission of doxorubicin) ± rituximab with inotuzumab (including urosodiol 300 mg three times daily as prophylaxis) and blinatumomab, given in a sequential fashion, can be used to minimize myelosuppression and risk of COVID-19 without compromising outcomes. Although this regimen can be applied to the younger patient population, it has established safety and efficacy in the frontline setting for older patients without causing significant myelosuppression [12, 13]. A second option is to treat younger patients with four courses of HCVAD ± rituximab followed by four courses of blinatumomab, then 1.5 years of maintenance [14, 15]. In an ongoing study, 34 patients who received this treatment had a 2-year overall survival (OS) of 90% [16]. The advantage of these two regimens is three-fold. First, blinatumomab is significantly less myelosuppressive. Although currently administered after four courses of HCVAD or mini-HCVD, patients can switch to blinatumomab earlier, after two courses, to avoid additional myelosuppression. Second, given that patients have no or low tumor burden after receiving intensive chemotherapy, the incidence of cytokine release syndrome (CRS) or need for hospitalization is significantly reduced. Thus, blinatumomab dose escalation can occur on day 5 instead of day 8. With the option for bag exchanges every 7 days, this treatment can be given mostly in an outpatient setting with reduced clinic visits. Third, using blinatumomab earlier in treatment helps deepen minimal residual disease (MRD) response and may safely shorten maintenance from 30 to 18 months. As part of either of these approaches, mini-HCVD plus inotuzumab and blinatumomab or HCVAD plus blinatumomab, either blinatu-

momab or low-dose inotuzumab (0.3 mg/m^2 on days 1 and 8 per cycle) can be incorporated as late intensification for three courses. There are concerns with the use of steroids during the COVID-19 outbreak because of their immunosuppressive effects. Notably, the World Health Organization has recommended against their use in treatment of viral pneumonia or acute respiratory distress syndrome when COVID-19 is suspected [17, 18]. However, steroids are an integral part of ALL treatment, and these recommendations should not apply to specific populations in which they represent an essential component of the curative therapeutic backbone. If needed, dexamethasone in HCVAD can be reduced from 40 to 20 mg on days 1–4 and days 11–14 in all odd cycles. Monoclonal antibodies, such as rituximab and ofatumumab, used in CD20-positive patients may increase the risk of infection through B-cell depletion, potentially reducing the humoral response to the virus. However, the benefit of these therapies in improving outcome in CD20-positive patients outweighs the risk at this time. The decision to withhold this therapy should be made only in individuals where the risk outweighs the benefit. If withheld, consider adding rituximab/ofatumumab to the treatment regimen at a later time or when the risk of COVID-19 is not as imminent. If a patient is COVID-19-negative and ≥60 years of age or unfit for more intensive therapy, treatment with four courses of mini-HCVD with inotuzumab and four courses of blinatumomab, given in a sequential fashion, is recommended. This therapy has demonstrated a 3-year OS of 54% compared with 32% with historical HCVAD in patients ≥60 years of age [13]. For patients aged ≥70 years, a further reduction to only two courses of mini-HCVD with inotuzumab is implemented, followed by eight cycles of blinatumomab, thereby reducing overall exposure to cytotoxic chemotherapy. All patients should receive triple antibiotic prophylaxis [15]. Growth factor support using pegfilgrastim or its equivalent biosimilar should be administered with each HCVAD and mini-HCVD course to hasten neutrophil count recovery. Treatment with HCVAD or mini-HCVD should be done based on institutional practice as some centers are more experienced to administer it in an outpatient setting than others. Intrathecal prophylaxis remains the same [11, 14]. If a patient has active COVID-19 or high suspicion of COVID-19 due to clinical, laboratory, and/or CT chest findings, the treatment decision should be individualized. Those with mild to moderate symptoms may need a delay in therapy, and a less intensive regimen with mini-HCVD plus inotuzumab and blinatumomab can be considered regardless of age. Those requiring hospitalization for COVID-19 would need stabilization of their status before treatment can be considered.

Ph-Positive ALL. Treatment of Ph-positive ALL relies on the incorporation of a tyrosine kinase inhibitor (TKI), preferably ponatinib, into the backbone of therapy. To minimize myelosuppression and reduce clinic visits, ponatinib plus blinatumomab or low-dose inotuzumab (with ursodiol 300 mg three times daily) can be used. If ponatinib is unattainable, a second-generation TKI may be utilized. The selection of TKI should be based on patient-related factors. Ponatinib plus blinatumomab is preferred as this combination has been shown to be highly effective in the relapsed setting [19–21]. Patients should be admitted for the first course to monitor for CRS. Those with leukocytosis may need cytoreduction with cyclophosphamide and/or dexamethasone prior to starting blinatumomab to decrease the incidence and severity of CRS. To limit the duration of hospitalization, blinatumomab can be dose escalated on day 5 instead of day 8 if the patient is tolerating therapy without complications. Blinatumomab bags can also be changed every 7 days instead of every 2 days to reduce clinic visits. For patients deemed unfit to receive blinatumomab, inotuzumab plus TKI is an option. Alternative options include TKI plus mini-HCVD or TKI plus vincristine and steroids as per the European Working Group on Adult ALL (EWALL) international study [22]. It is important to still administer a total of 12 intrathecal chemotherapies for central nervous system prophylaxis in patients with Ph-positive ALL. The lumbar punctures can be coordinated on the days of required clinic visits such as for blinatumomab bag changes.

T-Cell ALL. Patients with T-cell ALL can pose a challenge during this time because of limited treatment options. The HCVAD regimen with the addition of nelarabine and asparaginase is effective [23]. Although the combination of nelarabine and asparaginase is not significantly myelosuppressive and can be given in an outpatient setting, the latter can possibly increase the thrombotic risk known to be a complication of COVID-19. Therefore, careful evaluation of its benefit versus risk needs to be done on an individual basis. For patients <60 years of age and fit for intensive therapy, HCVAD with nelarabine ± asparaginase should be considered with modifications as mentioned above, including reducing the dose of dexamethasone. If asparaginase is deemed necessary, the pegylated version is recommended, as it allows for less frequent administration compared with shorter-acting versions such as *Erwinia* asparaginase. Patients aged ≥60 years can be treated with an age-adjusted

HCVAD combination with nelarabine ± asparaginase [15].

Consolidation and Maintenance. If a patient is COVID-19-negative, every effort should be made to deliver consolidation and maintenance therapies effectively without compromising outcomes. In consolidation with HCVAD, dose reduction may be warranted based on patient tolerance to induction (i.e., neuropathy with vincristine, delayed count recovery) [15]. If the patient is MRD-negative and administering HCVAD or mini-HCVD is logistically difficult, transitioning the patient to maintenance early can be considered. Among patients who remain MRD-positive after two to three courses of HCVAD or mini-HCVD, a poor prognostic marker for relapse and survival, strong consideration should be given to transition to blinatumomab or to a clinical trial addressing eradication of MRD with agents such as inotuzumab. Whether to transplant patients who are MRD-positive and subsequently become negative after blinatumomab is an unresolved question. In the BLAST trial, patients who achieved MRD negativity in first complete remission did not benefit from allogeneic stem cell transplantation (SCT) [24, 25]. Thus, during COVID-19 high-risk periods, SCT in these patients is not favored and they should be maintained with blinatumomab. The risks of SCT, including myelosuppression and transplant-related complications (graft versus host disease, venous occlusive disease, etc.) that can potentially increase morbidity and mortality, need to be considered. Maintenance with POMP (6-mercaptopurine [6-MP], vincristine, methotrexate, and prednisone) should continue when feasible. In order to decrease clinic visits the administration of vincristine can be eliminated. Dose reduction of 6-MP, methotrexate, and/or prednisone from 200 mg to 100 mg daily for 5 days can be considered for some patients where there is concern that myelosuppression could be life-threatening. Blinatumomab or low-dose inotuzumab (0.3 mg/m^2 on days 1 and 8) can be substituted for cytotoxic chemotherapy as late intensification and can be given in an outpatient setting with significantly less myelosuppression. Incorporating these agents can help shorten maintenance from 30 to 15–18 months if chemoimmunotherapy was given initially. Patients in remission who are routinely followed every 3–6 months can reschedule their visits to a later time or can be followed via telemedicine if appropriate. For Ph-positive ALL patients in remission, *BCR-ABL1* transcript monitoring can be done locally

Consolidation with Radiation Therapy. Radiation therapy given for extramedullary leukemia should be done with a short course using hypofractionation as per the recently published COVID guidelines from the International Lymphoma Radiation Oncology Group [26]. On the other hand, to avoid radiation long-term side effects, radiation therapy should be given at standard dose and fractionation for mediastinal (T-cell ALL/lymphoblastic lymphoma) and central nervous system locations (whole brain or craniospinal irradiation) [27, 28].

Salvage Therapies. Patient who are COVID-19-negative with relapsed or refractory ALL should receive salvage therapy with lower intensity regimens such as mini-HCVD and inotuzumab followed by blinatumomab [13, 29–32]. Patients in second complete remission can be considered for allogeneic SCT as the chances of relapse are high. Treatment with CAR T-cell therapies could be carefully considered in selected patients. COVID-19-positive ALL patients or those with high suspicion of COVID-19 based on clinical, laboratory, and CT chest findings may need their treatment delayed until after at least 14 days of quarantine and resolution of all symptoms. Thereafter, low-intensity treatments can be utilized.

Acute Myeloid Leukemia

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. 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 [11]. The overall treatment of patients with newly diagnosed AML should not change during the COVID-19 pandemic, with a few caveats.

Induction. Patients undergoing induction chemotherapy, especially those aged ≥50 years, should be treated in the inpatient setting. Patients should remain hospitalized until neutrophil count recovery (absolute neutrophil count >1,000 cells/mm^3). However, due to the expected high demand of inpatient beds during the COVID-19 pandemic, this may not be feasible, particularly in areas deemed to be epicenters of COVID-19. A number of effective lower-intensity regimens have been developed for the treatment of AML, primarily for patients aged >60 years or those deemed unfit for intensive chemotherapy. These regimens include venetoclax with hypomethylating agents or low-dose cytarabine [33–35]. While these regimens have not been compared with high-intensity therapy and are not typically recommended for patients aged <60 years who are otherwise fit for intensive therapy,

they may be considered in areas with high rates of COVID-19 where access to inpatient beds is limited. These regimens can be safely administered in the outpatient setting, but venetoclax-based therapies are associated with cytopenias and tumor lysis syndrome (TLS), requiring close follow-up with routine blood draws. To reduce the duration of myelosuppression with venetoclax combinations, particularly during the first cycle, a bone marrow evaluation can be done around day 14–21. If there is no morphologic evidence of leukemia, venetoclax may be held and the use of growth factor support can be considered to hasten neutrophil recovery.

Consolidation. Consolidation chemotherapy courses should continue according to the initial treatment plan. We recommend that patients receiving high-dose cytarabine consolidation receive a dose of 1.5 g/m^2 due to the lack of OS benefit with the higher 3 g/m^2 dose [36, 37]. This can be done in the outpatient setting with the utilization of ambulatory infusion pumps for cytarabine. A condensed cytarabine schedule on days 1–3 with the addition of pegfilgrastim or its equivalent biosimilar product has been shown to reduce the time to neutrophil count recovery, rate of infection, duration of hospitalization, and platelet transfusion requirement [38].

Maintenance. Maintenance therapy should be considered, particularly among patients who may be unable to complete their intended intensive consolidation courses. The results of the QUAZAR maintenance trial with oral azacitidine demonstrated an improved relapse-free survival and OS in patients aged ≥55 years who had previously achieved complete remission with intensive chemotherapy [39]. Azacitidine maintenance administered at a dose of 50 mg/m^2 daily for 5 days every 4–6 weeks has been shown to be a feasible maintenance strategy for patients aged >60 years [40]. Given the delays in both related and unrelated donor SCT during the COVID-19 pandemic, maintenance with azacitidine ± venetoclax (NCT0406266) should be considered after patients have completed consolidation therapy while awaiting SCT, or as an alternative post-consolidation approach (for 1–2 years) in order to maintain remission.

Relapsed Disease. Patients with relapsed or refractory AML should continue to pursue clinical trials whenever available at centers with extensive leukemia experience. Genomic testing should be performed at the time of relapse to identify the utility of approved targeted agents such as for IDH1, IDH2, or FLT3. The risk and benefit of treatment with standard therapies should also be discussed. Utilizing an outpatient, lower-intensity regimen alone or in combination with targeted therapies whenever possible should be considered. Allogeneic SCT should be pursued if clinically indicated and safe.

The strategies outlined above apply to newly diagnosed or relapsed patients after an individualized assessment of the risk, benefit, and prognosis: (1) lower-intensity therapy ± venetoclax, (2) lower-intensity therapy ± FLT3 inhibitors or IDH inhibitors (in appropriate subsets), and (3) longer-term maintenance therapy. The treatment of patients with AML who are positive for SARS-CoV-2 infection is even more challenging. There are no available data yet on the clinical course or outcomes among COVID-19-positive patients with AML. Our recommendation here would be to carefully evaluate such patients as one would for any newly diagnosed AML patient who presents with active infection, which is not uncommon, with a particular focus on the patient's respiratory status and pulmonary reserve. Patients' leukemia and bone marrow failure should be urgently stabilized with appropriate chemotherapy and blood product support. Subsequent definitive therapy can be designed based on baseline genomic data and the patient's medical condition. Effective, lower-intensity therapeutic options are now available and may be beneficial in these patients.

Acute Promyelocytic Leukemia

Patients with newly diagnosed acute promyelocytic leukemia with standard (WBC $<10 \times 10^9$/L) or high-risk disease (WBC $>10 \times 10^9$/L) should be treated with the combination of all-trans retinoic acid and arsenic trioxide with or without gemtuzumab ozogamicin depending on their risk status [41, 42]. This regimen is not myelosuppressive, has been proven to be superior in standard-risk patients, and is at least equivalent to chemotherapy regimens in all patients [42, 43].

Chronic Leukemias

Chronic Myeloid Leukemia

Chronic myeloid leukemia (CML) treatment relies on the use of continuous BCR-ABL1 TKIs. Patients with CML are not at a particularly high risk of infection as a result of their underlying malignancy or TKI therapy. Therefore, there is no indication to delay or hold treatment in patients with chronic-phase CML. For newly diagnosed patients, the side effect profile of each TKI should be considered in light of COVID-19-associated complications: pulmonary failure; cardiovascular compromise including cardiomyopathy in approximately 1/3 of patients and cardiac arrest [44]; diarrhea; and thrombotic

events [1]. These sequelae may be worsened with TKIs that can cause similar toxicities. For example, patients with COVID-19 may have reduced pulmonary reserve if they are on dasatinib therapy, worse cardiovascular or thrombotic complications if they are on nilotinib or ponatinib therapy, and worse diarrhea if they are on bosutinib therapy. Therefore, any symptomatic patients with CML on TKIs should be tested with nasopharyngeal swab and blood serology (COVID-19-neutralizing IgG) if available. If they have any active infection, TKIs should be held until recovery. If the IgG serology is positive, they may be immune, and TKIs should be continued. The management of accelerated-phase CML with TKIs should not change, and the risks and benefits of pursuing intensive chemotherapy in combination with TKI should be evaluated. In patients with CML in blast phase, TKIs should still be continued in combination with either intensive or lower-intensity chemotherapy.

Routine PCR testing should continue according to local recommended guidelines and the results discussed remotely (phone, telemedicine) to avoid outpatient visits. Attempting treatment-free remission may be delayed at this time due to the increased need for monitoring that may not be feasible. Patients in a stable treatment-free remission should continue the recommended monitoring.

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is generally a disease of the elderly and is associated with underlying immunodeficiency, both of which may place patients at a higher risk for COVID-19 and related complications. In patients not meeting International Workshop on CLL treatment indications, the wait and watch strategy should continue to be applied. The frequency of clinic visits can be decreased if the patient has no major change in symptoms. In patients meeting International Workshop on CLL treatment indications, the therapeutic decision should be based on individual factors such as symptom burden and comorbidities, along with molecular and cytogenetics abnormalities. If feasible, initiation of new therapies should be delayed during the COVID-19 high-risk period to prevent frequent clinic visits and potential hospitalization.

Treatment with fludarabine, cyclophosphamide, and rituximab (FCR) may be avoided due to myelosuppression and need for frequent clinic visits. If treatment must be initiated, consideration should be given for COVID-19 testing before starting myelosuppressive chemoimmunotherapy such as FCR or bendamustine plus rituximab. The use of monoclonal antibodies, such as rituximab and obinutuzumab, may need to be avoided if possible due to B-cell depletion potentially reducing the humoral response to the virus.

The landscape of CLL therapy has drastically changed over the past few years from chemoimmunotherapy to highly effective oral targeted therapies. Several novel oral targeted therapies are now available, including ibrutinib, acalabrutinib, and venetoclax. The choice of targeted therapy depends on several patient- and disease-related factors [45–50]. Ibrutinib and acalabrutinib generally require fewer clinic/laboratory visits at the time of treatment initiation compared with the venetoclax + obinutuzumab regimen. However, ibrutinib and acalabrutinib can cause atrial fibrillation and increased risk of bleeding. Bleeding risk associated with Bruton's tyrosine kinase (BTK) inhibition may be relevant in patients with severe lung inflammation, especially as patients with severe COVID-19 often develop severe thrombocytopenia [3]. Venetoclax plus obinutuzumab is a time-limited frontline therapy but requires TLS monitoring and leads to higher rates of neutropenia than treatment with BTK inhibitors.

If patients are currently on oral targeted therapy without complications, they should maintain the same therapy. If neutropenia occurs while on venetoclax, filgrastim or an equivalent biosimilar product can be utilized to increase the neutrophil count. Although BTK inhibition can compromise innate immune response as well as T- and B-cell function, which may lead to compromised cellular and humoral response to SARS-CoV-2, BTK inhibition has also been shown to inhibit cytokine production and potentially reduce the risk of hyperinflammation associated with infection [51]. Consequently, ibrutinib and acalabrutinib are now being studied for the treatment of CRS associated with COVID-19.

Hairy Cell Leukemia

The initial treatment of patients with hairy cell leukemia has been with a nucleoside analog, usually cladribine. At MD Anderson Cancer Center, the combination of cladribine plus rituximab is now the standard of care [52]. These agents are both immunosuppressive and may also cause myelosuppression, increasing the potential risks of COVID-19. Antibiotic prophylaxis and growth factor support are used to prevent infection and reduce the duration of neutropenia. Deferral of therapy may be discussed during COVID-19 high-risk periods unless the

patient has significant disease burden manifested by significant constitutional symptoms or cytopenias. Deferral of therapy should be weighed against a potential 10-year disease-free survival rate of 90% with one course of cladribine and eight weekly doses of rituximab. However, in patients requiring therapy, a non-myelosuppressive approach including the BRAF inhibitors vemurafenib or dabrafenib plus the MEK inhibitor trametinib may have a significant role [53, 54].

Myelodysplastic Syndromes and Myelodysplastic/Myeloproliferative Neoplasms

Myelodysplastic syndromes (MDS) and myelodysplastic/myeloproliferative neoplasms (MDS/MPN) generally affect older individuals with a median age at diagnosis of 68 years and increasing frequency in individuals aged >70–80 years [55]. Given the high risk of severe COVID-19 disease observed in older individuals, particularly with comorbidities, it should be factored in the treatment decisions on most patients with MDS [56–58]. Therefore, irrespective of the degree of neutropenia, all patients with MDS or MDS/MPN should be considered at high risk for complicated COVID-19, and medical comorbidities should be aggressively managed both in COVID-19-negative and -positive patients.

Although there are no data on the outcomes of COVID-19 in patients with MDS, those with lower-risk MDS or MDS/MPN, particularly chronic myelomonocytic leukemia (CMML), typically have high baseline inflammation with increased levels of multiple cytokines and chemokines (including IL-1, IL-6, or TNF) [59–63], and therefore they may be at particular risk of experiencing immune overactivation and hyperinflammation from SARS-CoV-2 infection. Consequently, close monitoring of patients with lower-risk MDS or CMML with SARS-CoV-2 infection is warranted even in case of mild disease. In patients with excess blasts or profound leukopenia, the predominant risks may be direct viral pathogenicity and superinfection or coinfections.

For patients with a new diagnosis of MDS during the COVID-19 pandemic, selection of therapy should be based on a risk-adapted approach using the International Prognostic Scoring System [64] or its revised version [65] and following standard guidelines. For patients with lower-risk MDS, therapy with erythroid-stimulating agents, luspatercept, lenalidomide, or low doses of azacitidine or decitabine should still be considered as clinically indicated. In patients with lower-risk disease who are transfusion-independent, initiation of therapy should be deferred to minimize the need for clinic visits and exposure.

Despite the potential risk of worsening cytopenias with decitabine and azacitidine during the first two cycles of therapy, the eventual improvement in cytopenias with response to treatment and impact on survival outweighs this risk in patients with higher-risk MDS and proliferative CMML [66]. Therefore, we do not believe that therapy should be delayed in these patients, particularly in those who are transfusion-dependent and those with high blast percentage, unless clinically indicated. Intensive therapy should be discouraged during the pandemic, even in younger patients, given the higher risk of prolonged myelosuppression, infections, and the potential increased mortality in the event of COVID-19. Prophylactic antimicrobials and other supportive measures (as described later) should be considered in all patients. Allogeneic SCT should be pursued if clinically indicated and safe, provided SARS-CoV-2 testing is performed and negative, even in asymptomatic patients.

In patients who experience progression of disease to higher risk or relapse after treatment with hypomethylating agents, the management will be challenging given the absence of approved therapies. However, treatment should still be considered given the short-expected survival without therapy [67, 68]. All patients who are candidates for SCT should still be considered for this treatment modality. Given the potential expected delays of SCT in the COVID-19 pandemic, bridging therapy may be needed. Therapy with low doses of cytotoxic agents such as cladribine or clofarabine with low-dose cytarabine [69] should only be considered in selected patients with higher-risk disease and normal karyotype, provided COVID-19 testing is negative. Other therapies, such as venetoclax, should only be considered within clinical trials and in centers with sufficient expertise, if deemed necessary, given close monitoring is needed for potential myelosuppression.

Supportive Care Considerations

The standard hygiene and social distancing measures should continue to be pursued. Visits to the inpatient setting should be limited or completely restricted. Patients should also be reminded to take extra precautions by practicing good hand hygiene, social distancing, and wearing a mask and gloves when leaving their homes. Patients' outpatient schedules need to be designed to minimize exposure and presence in the clinic (e.g., less fre-

quent blood tests, more frequent telemedicine or phone calls, lower thresholds for transfusions of blood or platelet products). If patients need to come for bloodwork or clinic visits, attempts should be made to minimize crowds by prolonging time between appointments and encouraging social distancing. Patients who typically travel a long distance for laboratory or clinic visits should have care coordinated with a local oncologist at a facility equipped to administer chemotherapy and blood products whenever possible. Patients with acute leukemia should receive appropriate antimicrobial prophylaxis, including antibacterial, antifungal, and antiviral agents, during periods of neutropenia. The empiric use of intravenous immunoglobulin (IVIG) to prevent secondary infections in patients is not routinely recommended given the unlikely acquired humoral immunity of donors against COVID-19 at this early time point in the pandemic and the potential prothrombotic risk associated with IVIG administration. In addition, IVIG is ineffective as a single agent against COVID-19 [70, 71]. Therefore, the use of IVIG should be limited to patients who have active or recurrent severe infections and IgG levels <400–500 mg/dL.

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. Therefore, the risk of COVID-19 complications should be weighed very carefully against restricting access of patients with leukemia to highly specialized centers and advocating for regimens without known equivalent curative potential. Efforts to reduce patient and staff exposure while maintaining optimal care should be prioritized. Utilizing less intensive therapies, reducing patient visits, and establishing collaborative care at local centers or through telemedicine are some ways to safely provide effective treatment. There is a large knowledge gap on how to treat COVID-19-positive patients due to lack of experience. However, treatment decisions need to be individualized based on patient-related factors, the risk of added toxicity from chemotherapy, and the feasibility of treatment administration. Ongoing studies will help define the biological implications of immune dysregulation associated with leukemia and current targeted therapies, such as JAK-STAT or BTK inhibitors, in the immune response and disease features of COVID-19.

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