Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Special considerations in the management of adult patients with acute leukaemias and myeloid neoplasms in the COVID-19 era: recommendations from a panel of international experts

Amer M Zeidan, Prajwal C Boddu*, Mrinal M Patnaik, Jan Philipp Bewersdorf, Maximilian Stahl, Raajit K Rampal, Rory M Shallis, David P Steensma, Michael R Savona, Mikkael A Sekeres, Gail J Roboz, Daniel J DeAngelo, Andre C Schuh, Eric Padron, Joshua F Zeidner, Roland B Walter, Francesco Onida, Amir T Fathi, Amy DeZern, Gabriela Hobbs, Eytan M Stein, Paresh Vyas, Andrew H Wei, David T Bowen, Pau Montesinos, Elizabeth A Griffiths, Amit K Verma, Alla Keyzner, Michal Bar-Natan, Shyamala C Navada , Marina Kremyanskaya, Aaron D Goldberg, Aref Al-Kali, Mark L Heaney, Aziz Nazha, Huda Salman, Selina Luger, Keith W Pratz, Heiko Konig, Rami Komrokji, Michael Deininger, Blanca Xicoy Cirici, Vijaya Raj Bhatt, Lewis R Silverman, Harry P Erba, Pierre Fenaux, Uwe Platzbecker, Valeria Santini, Eunice S Wang, Martin S Tallman, Richard M Stone, John Mascarenhas*

The ongoing COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 is a global public health crisis. Multiple observations indicate poorer post-infection outcomes for patients with cancer than for the general population. Herein, we highlight the challenges in caring for patients with acute leukaemias and myeloid neoplasms amid the COVID-19 pandemic. We summarise key changes related to service allocation, clinical and supportive care, clinical trial participation, and ethical considerations regarding the use of lifesaving measures for these patients. We recognise that these recommendations might be more applicable to high-income countries and might not be generalisable because of regional differences in health-care infrastructure, individual circumstances, and a complex and highly fluid health-care environment. Despite these limitations, we aim to provide a general framework for the care of patients with acute leukaemias and myeloid neoplasms during the COVID-19 pandemic on the basis of recommendations from international experts.

Lancet Haematol 2020; 7: e601–12

Published Online June 18, 2020 https://doi.org/10.1016/S2352-3026(20)30205-2

*Contributed equally

Section of Hematology (A M Zeidan MBBS, P C Boddu MD, J P Bewersdorf MD, R M Shallis MD) **and Yale Comprehensive Cancer Center** (A M Zeidan, P C Boddu, J P Bewersdorf, R M Shallis), **Yale School of Medicine, Yale University, New Haven, CT, USA; Department of Hematology, Mayo Clinic, Rochester, MN, USA** (M M Patnaik MBBS, A Al-Kali MD); **Department of Hematology, Memorial Sloan Kettering Cancer Center, New York, NY, USA** (M Stahl MD, R K Rampal MD, E M Stein MD, A D Goldberg MD, Prof M S Tallman MD); **Department of Hematology, Division of Leukemia, Dana-Farber Cancer Institute, Boston, MA, USA** (D P Steensma MD, Prof D J DeAngelo MD, Prof R M Stone MD); **Department of Hematology, Vanderbilt-Ingram Cancer Center, Nashville, TN, USA** (Prof M R Savona MD); **Leukemia Program, Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, OH, USA** (Prof M A Sekeres MD); **Department of Hematology and Oncology, Weill Cornell Medicine, New York-Presbyterian Hospital, New York, NY, USA** (Prof G J Roboz MD); **Division of Medical Oncology and Hematology, University of**

Introduction

Caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the COVID-19 outbreak has spread to more than 180 countries, with the USA reporting the most confirmed cases worldwide as of May, 2020, and widespread infection (ie, reports of COVID-19 in all 50 states). The case fatality rate (believed to be at least 1%) is uncertain and might vary by country.[1] Quarantine and physical distancing measures have been implemented in most jurisdictions to slow down the spread of the virus.

Older and immunocompromised populations appear to be at a higher risk for severe, potentially life-threatening illness related to COVID-19 compared with the general population, with reported case fatality rates as high as 15% in patients aged 80 years or older.[2] This observation presents a particular concern for patients with myeloid neoplasms, including acute myeloid leukaemia, myelodysplastic syndromes, myeloproliferative neoplasms, and overlap disorders with features of both myelodysplastic syndromes and myeloproliferative neoplasms, all of which present at a median age of 65–70 years.[3,4] Although patients with acute lymphocytic leukaemia are generally younger, the age distribution at presentation is bimodal, with an increasing incidence of disease in patients older than 45 years. Moreover, treatment for acute lymphocytic leukaemia is highly immunosuppressive and often prolonged in duration; thus, the risk of complications related to COVID-19 in these patients is a concern.

Early data from the Chinese National Database Repository suggest an over-representation of patients with cancer in the COVID-19 cohort.[5] COVID-19-related case fatality rates are estimated to be 5·6% in those with cancer,[2] and patients with cancer are at a 3·5 times higher risk of severe COVID-19 compared with the general population.[5] Additionally, case fatality rates of up to 37% have been reported in patients with haematological malignancies and COVID-19.[6] One study found that case fatality rates were much higher in hospitalised patients with haematological cancers who developed COVID-19 than in hospitalised health-care providers with COVID-19.[7] However, the exact incidence of COVID-19 in patients with cancer in general, and in patients with leukaemias in particular, is unclear.

Resource allocation that prioritises the care of patients with COVID-19 will affect the care of patients with other serious medical conditions such as haematological malignancies. Compounding the problem is the disruption to the timely delivery of cancer-directed therapies because of constraints on access to healthcare and the supply of blood products, and the disruption to the supply chain of drug therapies and medical supplies during the pandemic. Moreover, the manpower and time needed in screening for SARS-CoV-2 and the risks and consequences of SARS-CoV-2 infection among health-care personnel have had an effect across all diagnostic specialities.[8] Therefore, the minimisation and rationing of oncology care, while assuring the best possible treatment for patients with cancer, requires pandemic planning and collaboration by haematology and oncology representatives, local health organisations, and policy makers.[9]

Toronto, Toronto, ON, Canada (A C Schuh MD)**; Department of Malignant Hematology, Moffitt Cancer Center, Tampa, FL, USA** (E Padron MD, Prof R Komrokji MD)**; Division of Hematology and Oncology, Lineberger Comprehensive Care Center, University of North Carolina, Chapel Hill, NC, USA** (J F Zeidner MD)**; Division of Hematology, Fred Hutchinson Cancer Research Center, Seattle, WA, USA** (R B Walter MD)**; Department of Hematology, IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy** (F Onida MD)**; Department of Hematology, Centre for Leukemia, Massachusetts General Hospital, Boston, MA, USA** (A T Fathi MD, G Hobbs MD)**; Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA** (A DeZern MD)**; MRC Molecular Haematology Unit, BRC Oxford Department of Haematology, University of Oxford, Oxford, UK** (P Vyas MD)**; Department of Clinical Haematology, Alfred Hospital, Melbourne, VIC, Australia** (A H Wei MBBS)**; Department of Haematology, Leeds Teaching Hospitals National Health Service Trust, Leeds, UK** (Prof D T Bowen MD)**; Department of Haematology, Hospital Universitario y Politecnico La Fe, Valencia, Spain** (P Montesinos MD)**; CIBERONC, Instituto Carlos III, University of Valencia, Madrid, Spain** (P Montesinos)**; Leukemia Service, Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA** (E A Griffiths MD, Prof E S Wang MD)**; Department of Oncology, Montefiore Medical Center, Albert Einstein College of Medicine, New York, NY, USA** (Prof A K Verma MD)**; Division of Hematology and Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, USA** (A Keyzner MD, M Bar-Natan MD, S C Navada MD, M Kremyanskaya MD, Prof L R Silverman MD, J Mascarenhas MD)**; Department of Hematology, Herbert Irving Comprehensive Care Centre, Columbia University, New York, NY, USA** (Prof M L Heaney MD)**; Department of Hematology, Cleveland Clinic-Taussig Cancer**

This Viewpoint provides a summary of the current challenges in caring for patients with acute leukaemias (ie, acute myeloid leukaemia and acute lymphocytic leukaemia) and other myeloid neoplasms (ie, myelodysplastic syndromes, myeloproliferative neoplasms, and overlap syndromes), and offers a consensus on clinical practice guidance for optimal care in both the university and community health-care settings. The paucity of evidence-based data to guide leukaemia management during the pandemic prompted an online discussion, which initially involved leukaemia experts from highly affected areas in the USA, in which aspects of leukaemia care during the initial days of the COVID-19 pandemic were discussed. Subsequently, sharing this collective experience with the larger community of leukaemia care providers was recognised to be prudent, given the wide and rapidly progressing effects of the pandemic. To gain further input and perspective from different parts of the USA and other countries around the world, additional authors were invited to participate in the collaborative effort on the basis of their speciality and location. The experts on our panel are haematologists and oncologists who are highly specialised in leukaemia, myeloid neoplasms, and transplant care. Discussions were held through virtual, online meetings. Given the scarcity of evidence-based data on the management of leukaemias in the context of COVID-19, recommendations in this Viewpoint are based largely on expert opinion and experience, and complement the guidelines issued by relevant medical societies.

Because of the fluid health-care situation amid a rapidly evolving outbreak, the actions and contingency plans proposed in this Viewpoint should be considered in the context of disruptions to the local health system. We address various aspects of clinical management and provide specific suggestions to optimise the treatment of patients with haematological malignancies during the COVID-19 pandemic (panel 1).[10–13]

Resource allocation

Patients with haematological malignancies undergoing therapy require expert supportive care services that can be severely strained during a pandemic. Despite preparedness plans prioritising the support and safety of the health-care staff, a considerable number of health-care personnel will probably become unavailable because of sickness, mandated quarantines, fear of exposure, or concerns about family safety.[8,14] Furthermore, some personnel will be required to, or volunteer to, take on additional patient care responsibilities, could come to work regardless of a high personal risk (eg, from old age or comorbid conditions), adopt not yet fully proven mitigation strategies, or inadvertently expose other essential colleagues, which is a particular risk given the high incidence of subclinical infections.[15]

Challenges in resource allocation are likely to be greatest at institutions already functioning at their maximum workforce capacity.[8] Physical distancing measures and efforts to minimise the exposure of patients with comorbidities, such as haematological malignancies, to health-care environments will have detrimental downstream effects on the delivery of healthcare, including fewer in-person patient visits, delays in timely laboratory testing, interruptions to chemotherapy administration (despite many treatments depending on timely, cyclic administration), and delays to surgical and radiation therapy planning.[16] Patients with haematological malignancies should follow standard precautions related to COVID-19 and minimise physical contact, similar to the recommendations for older patients.

Specific to patients with haematological malignancies, physical distancing measures and fear of infection have an effect on the willingness and ability of volunteers to donate blood products, resulting in potential shortages of red blood cells, platelets, and plasma factors. Consequently, institutions could implement more restrictive transfusion guidelines, liberalise the use of erythroid growth factors, or do both, to decrease transfusion needs. Delaying the administration of therapies, including cellular and immunological approaches, for which supportive interventions (eg, tocilizumab) might be commandeered to manage SARS-CoV-2 infections, needs to be considered.

Strategies to reduce nosocomial SARS-CoV-2 transmission

To maximise the effect of physical distancing measures, in-person hospital visits should be minimised as much as possible for the safety of both the patients and the staff.[17] It is also recommended that all personnel involved in the care of patients with haematological malignancies (including patients asymptomatic for COVID-19), in addition to using appropriate personal protective equipment and infection control procedures, be routinely tested for SARS-CoV-2 if logistically possible, and the frequency of which should be based on the local patterns and frequency of SARS-CoV-2 infections.[16,17] Additionally, we strongly recommend that COVID-19 areas and oncology departments in hospitals are strictly separated, with a view towards keeping the cancer wards and clinics free of COVID-19. One approach, in such cases, might be to have separately staffed wards: one for patients who are positive for SARS-CoV-2, one for patients who are negative for SARS-CoV-2, and a third to isolate patients until their COVID-19 status is known. Each nursing unit should develop and follow pre-emptive strategies to avoid patient–patient and staff–patient transmission, especially in wards with patients who are immunosuppressed and in whom the adverse consequences of such transmission might be serious. Limiting in-person visits for patients in an in-house palliative care unit can have a considerable effect on both patients and families, with respect to quality of life.

The implementation of non-traditional strategies to deliver healthcare, such as telehealth platforms, has the potential to partially mitigate the negative effect physical

Panel 1: Summary of key recommendations

Shifting care to the outpatient setting

Leukaemia providers should determine how long patients can be managed for without in-person follow-up, blood tests, and therapies, including blood product support. The frequency of clinic visitations should be individualised and will vary by the acuity of the illness, the need for close monitoring of potential complications during therapy, and blood product and medication supply, among other factors.

Telehealth services (eg, telemedicine and video conferencing) provide valuable delivery platforms to facilitate adherence to physical distancing guidelines and should be preferred for patient–provider encounters that do not require infusional therapy, transfusions, or laboratory tests.

Ethics, resource allocation, and advance care planning

Haematologists caring for patients under crisis standards of care are advised to consult with the centralised hospital ethics committee to address complex ethical issues involving the rationing of lifesaving interventions when the situation arises.

Although the overarching goal is to offer potentially curative treatments when appropriate, the futility of further treatment in patients with advanced, multi-line refractory disease, who have exhausted standard-of-care options and are without access to clinical trials, must be considered.

Haematologists should have goals-of-care discussions with all patients with haematological malignancies under their care, particularly older patients (>60 years) and those with a haematological malignancy associated with a poor prognosis. Such goals-of-care discussions in the COVID-19 era, by stressing the potential resource limitations, might considerably reduce the proportion of patients with advanced disease who elect for intubation, thereby resulting in the modification of current treatment goals, preventing inappropriate escalation of care.[10]

Blood product and transfusion management

During times of blood product shortages, we recommend maintaining a haemoglobin serum concentration of more than 7 g/dL for patients with haematological malignancies requiring red blood cell transfusion, with a higher threshold for those with burdensome symptoms or serious comorbidities such as active cardiopulmonary disease. Consider increasing the intervals between transfusion episodes, with more red blood cell units transfused per episode.

We recommend a phased response for platelet transfusions on the basis of the estimation of available blood bank resources. During times of severe shortage, avoiding prophylactic transfusions even if platelet concentration is less than 10 000 platelets per µL (in the absence of bleeding), with consideration of the prophylactic use of antifibrinolytics, could be considered.

Growth factor support

The benefit of minimising the duration of neutropenia with growth factors must be balanced against the rare, but potential, risk of worsening the pulmonary complications related to COVID-19.[11] There is a theoretical risk of worsening pulmonary inflammatory injury by the use of growth factors in moderate-to-severe, active COVID-19, one setting in which the use of growth factors should be reconsidered.[12,13]

Clinical trials

Continued participant accrual in clinical trials investigating drugs of probable therapeutic benefit and in late salvage trials offering the only viable option for patients with advanced leukaemia is recommended, whenever logistically possible.

Enrolment in clinical trials, in which patients are randomly assigned to commercially available standard-of-care therapies, might place patients at unnecessary risk to comply with study-related procedures, and therefore continued enrolment in these trials, in the pandemic, should be re-evaluated.

For patients with relapsed or refractory haematological malignancies for whom clinical trials represent the only viable treatment option, the decision to participate in a trial will need to be pursued on a case-by-case basis.

Onsite monitoring is inconsistent with physical distancing goals, and protocol deviations are unavoidable; the US Food and Drug Administration, the European Medicines Agency, Health Canada, and other regulatory agencies have issued guidance on the safe conduct of trials during the pandemic.

General approach to treatment and legal ramifications

Careful clinical judgment must balance the risks and benefits of various treatment options and patient burden to allow for the best possible outcomes. The goal should still be to not compromise care for patients whose cancer is curable, despite the pandemic.

Substituting standard-of-care intensive chemotherapy with potentially suboptimal, less intensive treatment regimens to reduce inpatient bed and intensive care bed use requires a transparent discussion between the patient and the provider.

Discussions with patients regarding deviations in therapy from the standard of care to lessen the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, proceeding with therapy with the possibility of greater morbidity in the event of a SARS-CoV-2 infection, or deviations in planned therapy if cancer centre resources are compromised unexpectedly, should be endorsed at a unit level and documented in the patient notes to show the process for these decisions.

Research agenda

The American Society of Hematology has launched a global registry initiative intended to provide periodically updated summaries of observational data to physicians. We encourage physicians who treat patients with leukaemia to submit their data on patients with haematological malignancies and COVID-19 to this publicly accessible resource.

Institute, Cleveland, OH, USA (A Nazha MD); **Department of Internal Medicine, Stony Brook University Cancer Center, Stony Brook, NY, USA** (H Salman MD); **Department of Medicine, Hematology and Oncology Division, University of Pennsylvania, Philadelphia, PA, USA** (Prof S Luger MD, K W Pratz MD); **Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Division of Hematology and Oncology, Indiana University, Indianapolis, IN, USA** (H Konig MD); **Huntsman Cancer Institute, Department of Medicine, Division of Hematology and Hematologic Malignancies, University of Utah, Salt Lake City, UT, USA** (Prof M Deininger MD); **Clinical Haematology Department, Josep Carreras Leukaemia Research Institute, Universitat Autònoma de Barcelona, Barcelona, Spain** (B X Cirici MD); **Fred and Pamela Buffett Cancer Center, Department of Oncology and Hematology, University of Nebraska Medical Center, Omaha, NE, USA** (V R Bhatt MD); **Duke Cancer Institute, Department of Medicine, Division of Hematologic Malignancies and Cellular Therapies, Durham, NC, USA** (Prof H P Erba MD); **Department of Hematology, Hôpital St Louis, Assistance Publique-Hôpitaux de Paris, Paris, France** (Prof P Fenaux MD); **Department of Haematology, Paris University, Paris, France** (P Fenaux MD); **Department of Medicine, Division of Translational Hematology, Leipzig University Hospital, Leipzig, Germany** (Prof U Platzbecker MD); **and Department of Medicine, University of Florence Medical School, Florence, Italy** (Prof V Santini MD)

Correspondence to:
Dr Amer M Zeidan, Section of Hematology, Department of Internal Medicine, Yale Comprehensive Cancer Center and Smilow Cancer Hospital, Yale School of Medicine, Yale University, New Haven, CT 06510, USA
amer.zeidan@yale.edu

For more on **reports of COVID-19** see https://coronavirus.jhu.edu/us-map

For more on this **global registry initiative** see https://www.ashresearchcollaborative.org/covid-19-registry

distancing has on the delivery of cancer care.[18] However, for patients with haematological malignancies, remote healthcare is often insufficient, given their need for frequent phlebotomies, transfusion support, and scheduled treatments. Health-care providers will need to prioritise patients on the basis of the urgency and the goals of care. In some cases, treatment and assessment can be safely delayed, and in-person visits can be avoided via the use of telehealth or remote communication approaches. In other cases, such as for patients who require urgent, life-sustaining or potentially curative therapies, in-person visits are essential. If possible, patients should receive therapy in their local area to minimise travel to large academic centres.

Ethical considerations

Because of rising demand and scarce resources, hospital systems face ethical challenges in the rationing of health-care resources.[19] Rationing access to, and services for, intensive care units to those who are critically ill and near the end of life poses a challenge for, and disrupts the equipoise of, the health-care provider. Rationing these lifesaving, yet finite, resources is an ethically complex decision making process that requires balancing and rectifying ethically competing goals.[9,19] Community-based guidelines have been put in place during crisis standards of care to deal with the issues of resource use that could arise if lifesaving measures are in short supply.[20] We strongly advise haematologists and intensive care physicians caring for patients under crisis standards of care to consult with centralised hospital ethics committees who can provide guidance in cases where complex ethical issues involving the rationing of lifesaving interventions might arise. Although various a priori approaches have been suggested to facilitate resource triage during a pandemic, fair resource allocation at the patient level should be based on judgment by experienced intensive care physicians using established evidence-based prognostic scores. Useful online resources and publications exist that outline frameworks for identifying key ethical issues during a pandemic and guidelines on ways to navigate these issues.[21,22] The availability of adequate and timely intensive care support is crucial for oncology and haematology treatment programmes (eg, intensive chemotherapy and allogeneic haematopoietic stem-cell transplantation). In these circumstances, not only should any uncertainties regarding the availability of intensive care unit support be considered during treatment planning discussions, but the haematologist must be prepared to deliver precise information on life expectancy and potential long-term individual outcomes to the intensive care provider. The haematologist should be willing to appropriately advocate for the treatment of their patients with curable haematological malignancies in cases of overzealous restriction of resources. In essence, we must recognise that some patients with haematological malignancies who require admission to intensive care units for reasons related or unrelated to COVID-19 have cancers that are still curable, so deprioritising their access to intensive care units should be avoided.

Transfusion support

Blood product transfusion support is an integral aspect of supportive care, and many curative therapies (eg, intensive induction and allogeneic haematopoietic stem-cell transplantation) require that patients reliably receive blood product transfusion support during protracted myelosuppression. Conversely, patients without the prospect of cure might still glean clinical benefit from non-intensive therapies or best supportive care, and transfusion support is often fundamental for these patients.[23] Patients receiving chronic transfusion support not only represent a considerable logistical challenge to the hospital system's blood bank capability, but are also a potential source of SARS-CoV-2 transmission because of frequent exposure to other patients and staff.

Concerns over blood donor safety in the COVID-19 era, taken together with physical distancing and quarantining initiatives, have prompted donor deferral to the detriment of the pool of blood product donors. An inherently high demand for blood products among patients with haematological malignancies, coupled with a diminished donor pool and a reduction in blood bank service providers, places severe strain on the cancer centre's capacity to provide transfusions.

Although most blood management groups generally follow restrictive thresholds for transfusion based on national guidelines (ie, transfusion is not indicated until the haemoglobin serum concentration is 7–8 g/dL),[24] this approach might not be appropriate for certain populations at high risk of complications related to anaemia, including those who are older (>60 years) and those who have cardiovascular disease.[25] Controversy remains about the appropriate haemoglobin trigger threshold for red blood cell transfusion in patients with various myeloid neoplasms,[26] resulting in a wide variation in transfusion practices among physicians and institutions.[27] Regardless, contingency plans for emergency transfusion might require the adoption of increasingly restrictive transfusion thresholds to match the constraints on blood product supply. Consideration should also be given to increasing the interval between transfusion episodes and increasing the number of transfusion units given per episode, thereby reducing the number of patient visits to health-care institutions.[28] Where possible, community-based blood draws for blood count and cross-matching should be implemented. Nonetheless, a severe shortage of blood products and uncertainty about future supply should prompt clinicians to discuss risks and benefits with their patients, especially if intensive myelosuppressive chemotherapy is under consideration.

Given the short shelf life of platelets, platelet availability is particularly problematic in the event of blood product shortages.[28] We propose a stepwise

approach to platelet transfusion in patients with haematological malignancies on the basis of the estimation of resources in the local blood bank. If platelet resources are unaffected locally, continue with local institutional policies. If platelet availability is reduced, initial strategies to conserve platelet stocks include avoiding prophylactic platelet transfusions for surgical interventions by deferring non-urgent procedures and establishing an inpatient and outpatient threshold for prophylactic platelet transfusions of less than 10 000 platelets per µL for the overall population with chronic needs. For situations in which the available pool of platelet products is very low, we advocate for a strategy of non-prophylactic platelet transfusion on the basis of data showing no survival benefit for prophylactic platelet transfusions among patients with haematological malignancies undergoing chemotherapy.[29,30] Additional strategies, in times of serious shortage, could include avoiding prophylactic platelet transfusions with rare exceptions (eg, disseminated intravascular coagulation and coagulopathy of acute promyelocytic leukaemia), and considering the use of prophylactic antifibrinolytics, such as aminocaproic acid or tranexamic acid, if the risk of bleeding is high in patients negative for SARS-CoV-2 infection.[31]

Although early studies[32,33] have presented conflicting data on the detection of SARS-CoV-2 RNA and infectious virus in blood specimens, and blood borne transmission of SARS-CoV-2 has yet to be reported, the US Food and Drug Administration (FDA) recommends donor deferral measures to prevent the transmission of SARS-CoV-2 via blood components.[34] These measures include the careful screening of blood donors for symptoms of COVID-19 and the recalling of untransfused blood products from infected donors. To address the urgent need for blood components in certain areas, the FDA has revised these recommendations by, for example, reducing the deferral period in populations at high risk, such as men who have sex with men and donors who have travelled to or from COVID-19 endemic areas, to encourage more blood donations.[35]

Growth factor support and prophylactic antimicrobials

The use of prophylactic antimicrobials constitutes an important aspect of leukaemia management for disease-induced and chemotherapy-induced neutropenia.[36] Many chemotherapy protocols for myeloid neoplasms do not incorporate the routine use of haematopoietic colony-stimulating factors (eg, granulocyte colony-stimulating factor) to prevent chemotherapy-induced neutropenia. The use of growth factors, such as granulocyte colony-stimulating factor or other myeloid growth factors, should probably be avoided in patients with moderate-to-severe SARS-CoV-2 infection given the potential risk of exacerbating inflammatory pulmonary injury, especially in the case of patients with disorders that have overlap between myelodysplastic syndromes and myeloproliferative neoplasms.[12,13]

Although patients with haematological malignancies and neutropenia are potentially at a higher risk of having severe COVID-19 compared with the general population because of an immunocompromised state, the differential diagnosis for neutropenic fever remains broad, and empirical antibacterial therapy should be initiated promptly pending further workup. We recommend screening for SARS-CoV-2 in all patients with haematological malignancies and a fever whenever possible, and before haematopoietic stem-cell transplantation, cellular therapy (such as with chimeric antigen receptor T cells), and chemotherapy. We recommend that when SARS-CoV-2 is identified in a patient with neutropenic fever (with or without respiratory symptoms), well established protocols of broad-spectrum (and even antifungal) agent administration should be applied, along with COVID-19 therapies specific to the institution.

Given the safety concerns surrounding hepatotoxicity and QT interval prolongation (corrected for heart rate) with some of the agents used to treat patients with COVID-19, such as hydroxychloroquine and azithromycin, we do not recommend prophylaxis with these agents for patients with haematological malignancies negative for SARS-CoV-2. However, several ongoing clinical trials in North America and elsewhere should provide further guidance on this point (eg, NCT04330495 and NCT04329923).

Because of the increasing concern that microthrombosis is contributing to the pathophysiology of COVID-19, many institutions are now adopting prophylactic or therapeutic anticoagulation as a part of their treatment algorithms for the infection.[37] Careful consideration and frequent monitoring of coagulation markers and platelet counts, in the context of acute leukaemia, should be undertaken when making decisions regarding the administration of anticoagulation.

Clinical trial participation

Minimising the disruption to clinical care and preserving the integrity of clinical trials is a major challenge during a pandemic. Physical distancing and other mitigation efforts in the community negatively affect several standard clinical trial procedures, including patient accrual, the optimal delivery of interventions, patients' adherence to medical treatments, patient monitoring and adverse event reporting, and the evaluation of outcome measures.[38,39] In addition, most laboratories that do correlative studies, such as biomarker assessments, pharmacokinetic assays, and pharmacodynamic assays, are closed. The effect of these important mitigation measures on preclinical research should also be recognised because leukaemia translational laboratories are suspending or drastically scaling back operations to comply with physical distancing requirements.[40]

***Panel 2*: Summary of treatment guidelines for the management of adult acute myeloid leukaemia**

General recommendations

- Consider delaying treatment unless there is an urgent need to initiate treatment[44]
- Screen all patients in need of intensive induction treatment for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) before treatment initiation:
  - If the test is positive, consider delaying treatment by 10–14 days, with careful consideration of cytoreductive agents in the interim; consult with infectious disease specialists regarding the criteria to clear the patient for chemotherapy (ie, two negative COVID-19 tests and an absence of symptoms)
  - If the test is negative, repeat the test after 24 h if there is high clinical suspicion because the RT-PCR test has a sensitivity of about 70%[45]
  - If the patient is positive for SARS-CoV-2 and there is an urgent need to initiate induction treatment, consider treatment with close monitoring for any evolving and related COVID-19 symptoms
- Consider treatment discontinuation if the patient develops symptoms of COVID-19; early initiation of cytokine modulators could be considered for patients with COVID-19 who are symptomatic from COVID-19[46,47]
- Prioritise outpatient management following induction therapy once the necessary follow-up is ensured[48]

Induction

- For younger (18–65 years) or fit patients (who are deemed eligible for intensive chemotherapy on the basis of general health and performance status) who are newly diagnosed:
  - Treatment induction with cytarabine and an anthracycline (eg, 7 days of cytarabine infusion and 3 days of an anthracycline infusion, or similar) in non-acute promyelocytic leukaemia, with a specific regimen based on risk stratification, and all-trans retinoic acid with arsenic trioxide in non-high-risk acute promyelocytic leukaemia, should remain standard[49]
  - Use caution with prophylactic corticosteroids to prevent differentiation syndrome during therapy for acute promyelocytic leukaemia
  - If there are severe shortages in hospital bed capacity, support staff, or both, alternative low intensity, outpatient induction regimens (eg, a hypomethylating agent and venetoclax) might be necessary[49,50]
- For older patients (>65 years) deemed eligible for intensive chemotherapy:
  - Outpatient treatment with a hypomethylating agent with or without venetoclax or targeted inhibitors should be strongly considered[49,50]

Consolidation

- Consider deferring patients without adverse risk disease who need allogeneic haematopoietic stem-cell transplants when they test negative for minimal residual disease
- Consider reducing the number of chemotherapy consolidation cycles with high-dose cytarabine and the cumulative cytarabine dose within each cycle[49,51]
- Consider maintenance therapy with a hypomethylating agent as an alternative to intensive post-remission therapy after careful consideration of the risks versus the benefits[52]
- Consider high-dose cytarabine consolidation as an alternative to autologous haematopoietic stem-cell transplantation

Supportive care

- The benefit of minimising the duration of neutropenia with growth factors must be balanced against the rare, but potential, risk of worsening the pulmonary complications related to COVID-19;[49] the use of growth factors in patients with moderate-to-severe COVID-19 should be reconsidered
- Follow transfusion contingency plans
- Monitor patients for drug–drug interactions between venetoclax, ivosidenib, gilteritinib, and azole antifungals and COVID-19 therapies (eg, hydroxychloroquine and azithromycin)

To ease the burden on participating health-care facilities now prioritising COVID-19 studies, academic centres and drug sponsors have begun to suspend patient enrolment in many ongoing interventional trials. Some centres have needed to put accrual to phase 3 trials and some phase 2 trials on hold when a viable standard-of-care option exists. However, we must maintain and support continuing clinical intervention trials whenever possible, including the continued accrual of new participants, while ensuring patient safety and study feasibility.[39] This support should apply to randomised trials investigating the effects of interventions of proven clinical benefit and trials involving multi-line refractory patients who have exhausted all alternative standard-of-care options.

Recognising the challenges affecting standard protocol procedures, the FDA and Health Canada have issued guidance for doing clinical trials during the COVID-19 pandemic, particularly emphasising patient safety.[41,42] In Europe, a COVID-19 pandemic task force set up by the European Medicines Agency in collaboration with the Clinical Trials Facilitation and Coordination Group has been established to take quick and coordinated regulatory action related to COVID-19 medicines.[43]

In accordance with good clinical practice, drug sponsors, protocol investigators, local institutional review boards, and ethics committees should continue to establish memoranda of policies that explain how clinical trial activities can be done effectively while allowing for possible disruptions in usual care at the study sites.[42] Disruptions related to the pandemic, including when patients become symptomatic from a SARS-CoV-2 infection during therapy, might necessitate protocol

Panel 3: Summary of treatment guidelines for the management of adult acute lymphocytic leukaemia

General recommendations

- Consider delaying treatment if possible, given the risks of developing severe COVID-19 with chemotherapy[53]
- Test all patients for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) before treatment initiation:
  - If the test is positive, consider delaying treatment by 10–14 days, except intrathecal therapies for CNS symptoms
  - If the test is negative, repeat the test after 24 h if there is high clinical suspicion because the RT-PCR test has a sensitivity of about 70%[45]
  - If the patient is positive for SARS-CoV-2 and initiation of induction treatment is urgently needed, consider treatment with close monitoring for any evolving and related COVID-19 symptoms; institute appropriate precautions (eg, use personal protective equipment) and obtain goals of care before initiating therapy
- Consider treatment discontinuation if the patient develops symptoms of COVID-19; early initiation of cytokine modulators could be considered for patients with COVID-19 who are symptomatic from COVID-19[46,47]

Induction

- In older patients (>65 years), consider minimising steroid exposure because of the concern that steroids could increase the risk of severe COVID-19[54,55]
- In older patients (>65 years), consider reducing the dose of daunorubicin and PEGylated asparaginase during treatment induction
- Delay treatment with anti-CD20 monoclonal antibodies if possible because these agents reduce immunoglobulin concentrations
- Consider second-generation tyrosine kinase inhibitors with reduced dose steroids in Philadelphia chromosome-positive disease[56]

Consolidation

- Consider blinatumomab if patients are positive for minimal residual disease after two cycles of chemotherapy
- Consider advancement to maintenance if patients are negative for minimal residual disease and have already received most of their treatment

Maintenance

- In older patients (>65 years), consider reducing the dose of steroids and avoiding vincristine[57]
- Pending further evidence, prompt initiation of blinatumomab to treat minimal residual disease in Philadelphia chromosome-negative B-cell acute lymphocytic leukaemia remains standard[58]

Relapsed or refractory disease and transplantation

- Consider inotuzumab over blinatumomab as the first salvage option to reduce the duration of hospital stay[57]
- Consider delaying allogeneic haematopoietic stem-cell transplantation for patients in first complete remission
- Patients with relapsed or refractory acute lymphocytic leukaemia in second complete remission should have an allogeneic haematopoietic stem-cell transplant promptly, considering the high-risk nature of disease and the high risk of relapse[57]
- If feasible, consider delaying therapy with T cells with chimeric antigen receptors directed to B-lymphocyte antigen CD19 for patients with relapsed or refractory acute lymphocytic leukaemia younger than 25 years for whom this therapy is approved by the US Food and Drug Administration

Supportive care

- Consider liberal use of growth factor support in patients without COVID-19 to facilitate the recovery of neutrophil count[11] and to maintain an absolute neutrophil count of more than 1000 cells per µL across all phases of therapy; the use of growth factors in moderate-to-severe COVID-19 should be reconsidered given the potential risk of worsening the pulmonary complications related to COVID-19
- Follow transfusion contingency plans
- Monitor for drug–drug interactions between the drugs used to treat acute lymphocytic leukaemia and any potential therapies for COVID-19

deviations. Suspension of all non-essential procedures related to the trial that do not directly ensure safety should be considered. For example, extended hospital visits for pharmacokinetic and pharmacodynamic studies and non-crucial response assessments should be eliminated during the height of the COVID-19 pandemic, when the risk of exposure in the cancer centre outweighs any immediate direct benefit to the patient. Continuing patient access to the study drug, when approved by both the sponsor and the institutional review board, might include shipping the study drug directly to patients, mobile laboratory blood draws, and the approval of telehealth study visits.

Treating adult patients with acute leukaemias and myeloid neoplasms during the COVID-19 pandemic

In the absence of evidence-driven clinical guidelines in the COVID-19 setting, the health-care provider must carefully balance the risks and the benefits when making a treatment recommendation. The administration of intensive chemotherapy amid an active pandemic can place patients at a high risk of contracting a severe SARS-CoV-2 infection, with potentially fatal consequences, and might lead to the need for intensive care. Considering the challenges faced by the oncology community in

***Panel 4*: Summary of treatment guidelines for the management of adult myeloproliferative neoplasms**

Chronic myeloid leukaemia

- We do not recommend any changes in management with tyrosine kinase inhibitors at this point
- Patients with newly diagnosed disease should be started on tyrosine kinase inhibitor treatment as usual, extending visits and mobile laboratory blood draws where available; ensure patients have routine lab monitoring for cytopenias induced by treatment with a tyrosine kinase inhibitor and a 1–3 month supply of tyrosine kinase inhibitor to minimise pharmacy visits
- We do not recommend doing trials of tyrosine kinase inhibitor discontinuation during the COVID-19 pandemic
- In accelerated phase or blast phase disease, consider non-aggressive regimens with tyrosine kinase inhibitors

Philadelphia chromosome-negative myeloproliferative neoplasms

- Patients with essential thrombocythaemia or polycythaemia vera should continue current cytoreductive treatment with hydroxycarbamide, anagrelide, interferon alfa, or ruxolitinib
- Ensure that patients have a 3-month supply of agents to minimise pharmacy visits
- Whenever possible, avoid stopping ruxolitinib, especially in the setting of the COVID-19 pandemic, because ruxolitinib helps to prevent possible immune cytokine release syndrome
- Consider deferring the initiation of JAK inhibitors because of these agents' immunosuppressive effects[59]
- Continue aspirin for thromboprophylaxis in patients with high-risk essential thrombocythaemia or polycythaemia vera; consider switching patients from oral anticoagulation to low-molecular-weight heparin in the setting of acute COVID-19
- Use erythropoiesis-stimulating agents and danazol to reduce the need for red blood cell transfusion on a case-by-case basis
- Delaying allogeneic haematopoietic stem-cell transplantation might be required given the current restrictions on resource allocation
- Consider a hypomethylating agent with or without ruxolitinib or venetoclax in blast phase disease, in the outpatient setting whenever possible, with a goal of doing allogeneic haematopoietic stem-cell transplantation when appropriate[60]

treating adult patients with myeloid neoplasms, major medical societies, including the American Society of Hematology, have released resources to help providers to care for patients with haematological malignancies (appendix pp 13–14). These intervention strategies are mainly aimed at mitigating the risk of inducing an immunocompromised state that can predispose patients to a potentially fatal SARS-CoV-2 infection, and reducing the effect of the pandemic on hospital bed capacity and intensive care capacity by decreasing the intensity and the length of chemotherapy exposure.

See Online for appendix

We have outlined a proposed general approach to the treatment of adult patients with acute myeloid leukaemia and acute lymphocytic leukaemia during the pandemic (appendix pp 15–16). We would like to emphasise that the situation remains fluid and individual clinical practice needs to be adapted to the local circumstances (eg, resource availability and local disease epidemiology) and to the individual patient. We have summarised the key considerations of the management approaches for patients with acute myeloid leukaemia (panel 2), acute lymphocytic leukaemia (panel 3), myeloproliferative neoplasms (panel 4), and myelodysplastic syndromes and overlap syndromes (panel 5) in the setting of the COVID-19 pandemic. Many of our recommendations align with those of the COVID-19 advisory panels of the American Society of Hematology. We have outlined a detailed discussion on the rationales and available evidence supporting these recommendations in the appendix (pp 3–12). The underlying principles behind these recommendations are the need to minimise the risk of contracting SARS-CoV-2 and reduce the severity of ensuing COVID-19 for patients by avoiding health-care exposure and periods of immunosuppression and providing effective disease-directed treatment. We acknowledge that these recommendations reflect a compromise and partly deviate from routine practice in the non-COVID-19 setting. As the evidence base evolves, these recommendations should be critically re-evaluated and additional adjustments will probably become necessary in the future.

Many of the mitigation strategies and risk assessments we have outlined will be similar to those for lymphoid malignancies and plasma cell neoplasms. Consideration must be given to dose-attenuated regimens and careful growth factor use in the older population (>65 years) to reduce the risk of myelosuppression and the duration of hospitalisation. Suitable alternative regimens suggested by the National Comprehensive Cancer Network that can be managed on an outpatient basis might be preferred.[64] Specific additional considerations for patients with COVID-19, including the use of immunomodulatory therapeutic strategies to overcome T-cell immune dysfunction induced by therapies for multiple myeloma and lymphomas,[65–69] should be addressed. A detailed discussion regarding changes to management approaches in aggressive and indolent lymphomas, chronic lymphocytic leukaemia, multiple myeloma, and allogeneic haematopoietic stem-cell transplantation is beyond the scope of this Viewpoint and we refer the reader to other resources in which these topics are reviewed in more detail.[70]

Call for research on the effect of COVID-19 on patients with haematological malignancies

Many clinical trials are underway to investigate the efficacy of vaccines and various antiviral therapies targeting SARS-CoV-2, but the inclusion of patients with haematological malignancies in these trials is variable. Early and emerging data suggest that convalescent serum samples might be beneficial either for the prophylaxis of infection or the treatment of COVID-19, and it is hoped that patients with haematological malignancies will also be eligible for this intervention.[71,72] Trials evaluating agents intended to dampen harmful inflammatory responses to SARS-CoV-2, such as JAK inhibitors (eg, NCT04320277), anti-IL-6 monoclonal antibodies (eg, NCT04322773), BET inhibitors (eg, NCT03936465), and

BTK inhibitors (eg, NCT04346199), are prospectively evaluating treatment responses in patients with COVID-19 and a diagnosis of cancer. With the emergency use authorisation of remdesivir, made on the basis of early efficacy data, haematological effects, especially among patients receiving chemotherapy, should be considered.[73] Until effective antiviral strategies are supported by data and made available, physical distancing, minimising hospital and office visits, telemedicine, and careful tailoring of individual treatment plans are essential strategies to mitigate the potential complications from COVID-19 in patients with haematological malignancies. These measures can be especially challenging for older patients (>65 years) who might need increased assistance with daily care, transportation to clinic visits, or technological support.

With the COVID-19 outbreak likely to last months, and possibly recur in the future in a cyclical pattern,[74] epidemiological and outcome data defining populations at high risk of contracting severe COVID-19 will inform the development of a framework that incorporates pre-emptive strategies, such as the use of vaccines and antiviral drugs, to optimise outcomes for patients with haematological malignancies. Identifying patients who might have immunity to SARS-CoV-2, perhaps from previous exposure, is similarly important, and reliable serological testing is therefore eagerly anticipated. These important research agendas will warrant investigation under controlled clinical trial settings that will explore not only their immediate benefits, but also other crucial aspects of administration, such as drug interactions between antiviral therapies and leukaemia treatments. Delineation of the effects of SARS-CoV-2 on haematopoiesis will have broader implications on haematopoietic stem-cell mobilisation and the use of growth factor support.[75] Research on the effect of the COVID-19 outbreak on leukaemia outcomes, including the role of delays in treatment, the selection of potentially suboptimal chemotherapy regimens, and complications directly related to COVID-19, will become feasible with the growing pool of infected patients and ongoing efforts to centralise these data.

Conclusions

The COVID-19 pandemic has severely strained the oncology community and the delivery of optimal care for patients with leukaemia and associated myeloid neoplasms. With local policy makers implementing various contingency measures to minimise the potential effect of this pandemic, the rationing of oncology care services has become a reality. The need to treat patients with potentially lifesaving, intensive chemotherapy presents an enormous challenge; the population's associated immunocompromised state places an already susceptible population at even greater risk for contracting severe COVID-19. Setting early goals of care and discussing code status for all patients with haematological malignancies is imperative. Ethical issues surrounding the allocation of lifesaving interventions to critically ill patients, and the determination of treatment futility among patients without viable treatment options outside of a clinical trial, will need to be continually addressed.

***Panel 5*: Summary of treatment guidelines for the management of adult myelodysplastic syndromes and adult syndromes with overlap between myelodysplastic disease and myeloproliferative neoplasms**

General recommendations

- Treatment decisions should be based on category in the revised international prognostic scoring system
- Established and newly diagnosed patients being considered for potentially myeloablative therapy should undergo testing for COVID-19 before treatment initiation with the same considerations as for patients with acute myeloid leukaemia
- The goals-of-care discussion and the importance of physical distancing should be emphasised because a large proportion of the patient population are older individuals (>65 years) with comorbidities who are at a high risk of mortality if diagnosed with COVID-19

High-risk myelodysplastic syndromes

- Close observation without definitive treatment is a reasonable strategy in patients with only modest cytopenias[61]
- Start newly diagnosed patients requiring treatment on a hypomethylating agent and continue treatment in patients already receiving these agents[62]
- Consider lengthening the duration between treatment cycles and reducing dosing within each cycle for patients that have had a response; maintain normal intervals until patients respond
- Avoid a delay of more than 6 weeks between cycles of hypomethylating agents
- Subcutaneous azacitidine is preferred over intravenous azacitidine to decrease the time spent at infusion centres and in contact with COVID-19 exposures

Lower risk myelodysplastic syndromes

- We recommend a watch-and-wait approach for most patients
- Erythropoiesis-stimulating agents (for patients naive to these agents) and luspatercept[63] should be considered to minimise the need for red blood cell transfusions
- Consider deferring the initiation of lenalidomide in newly diagnosed patients with del(5q) disease given the risk for myelosuppression

Overlap syndromes

- We recommend a watch-and-wait approach for patients with proliferative chronic myelomonocytic leukaemia and mild-to-moderate leucocytosis; given the likelihood of leukaemoid reactions, cytokine release syndrome, and severe acute respiratory distress syndrome with COVID-19 in this group, the careful lowering of white blood cell count in cases of extreme leucocytosis in asymptomatic patients should be done with low doses of hydroxycarbamide while monitoring for the emergence of cytopenias
- Early initiation of cytokine modulators, such as anakinra and tocilizumab, could be considered for patients symptomatic for COVID-19[46,47]
- Erythropoiesis-stimulating agents or erythropoiesis maturation agents should be used in the management of anaemia to minimise transfusion burden

Supportive care

- Erythropoiesis-stimulating agents or erythropoiesis maturation agents should be used in the management of anaemia to minimise transfusion burden
- Transfusion contingency plans should be followed
- Use of granulocyte colony-stimulating factor should be carefully considered; we do not recommend routine use in patients with splenomegaly given the associated risk of splenic rupture

Search strategy and selection criteria

We searched PubMed for publications related to COVID-19, SARS-CoV-2, cancer, and haematological malignancies published in English between Dec 1, 2019, and May 10, 2020. To gather further references, we searched the reference lists of articles identified from the PubMed search. Because the focus of cancer management is minimising inpatient hospital stays and frequent visitations to cancer centres, most of the references included in this Viewpoint are from previous available literature that supports the safety of such management approaches.

We acknowledge that the recommendations provided in this Viewpoint might not be generalisable because of regional differences in health-care infrastructure and individual circumstances. That said, the guidance we have provided in this Viewpoint is adapted from available literature supporting guidelines for oncological management that minimise patient–provider interactions and inpatient hospital stays.

Disease-specific advisory groups have started to issue guidance on how to best provide care in the face of a rapidly accelerating outbreak, but these recommendations are based largely on expert consensus. Robust data substantiating these recommendations are currently scarce. Reporting of patient outcomes and epidemiological data in the context of COVID-19 is urgently needed to support the evidence-based management of patients with haematological malignancies in the future. Now, more than ever, patients with leukaemia need the support of the oncological community to help balance the risks and benefits and allow for the best possible outcomes in these extraordinary circumstances.

Contributors

AMZ, PCB, and JM contributed to the conception, design, and writing of the manuscript. MMP, JPB, MS, RKR, RMSh, DPS, MRS, MAS, GJR, DJD, ACS, EP, JFZ, ESW, MST, and RMSt contributed to the writing, reviewing, and editing of the manuscript. RBW, FO, ATF, ADZ, GH, EMS, PV, AHW, DTB, PM, EAG, AKV, AK, MB-N, SCN, MK, ADG, AA-K, MLH, AN, HS, SL, KWP, HK, RK, MD, BXC, VRB, LRS, HPE, PF, UP, and VS provided expert and analytical feedback and were involved in reviewing and editing the manuscript.

Declaration of interests

AMZ received research funding (institutional) from Celgene (Bristol-Myers Squibb), AbbView, Astex, Pfizer, Medimmune (AstraZeneca), Boehringer-Ingelheim, Trovagene, Incyte, Takeda, Novartis, Aprea, and ADC Therapeutics; participated in advisory boards or had a consultancy with, and received honoraria from, AbbVie, Otsuka, Pfizer, Celgene (Bristol-Myers Squibb), Jazz, Incyte, Agios, Boehringer-Ingelheim, Novartis, Acceleron, Astellas, Daiichi Sankyo, Cardinal Health, Taiho, Seattle Genetics, BeyondSpring, Trovagene, Takeda, Ionis, Amgen, Janssen, Epizyme, and Tyme; served on steering and independent data review committees for clinical trials for Novartis and Janssen; and received travel support for meetings from Pfizer, Novartis, and Trovagene. MMP is on the advisory board for Stem Line Pharmaceuticals. RKR has received consulting fees from Constellation, Incyte, Celgene, Promedior, CTI, Jazz Pharmaceuticals, Blueprint, and Stemline; and research funding from Incyte, Constellation, and Stemline. MRS is on the advisory boards for AbbView, Bristol-Myers Squibb, Celgene, Sierra Oncology, Ryvu, Takeda, and TG Therapeutics; is a consultant for Karyopharm and Ryvu; and receives grants and research support from Astex, Incyte, and TG Therapeutics, royalties from Bohringer-Ingelheimand, and equity from Karyopharm. MAS is on the advisory boards for Bristol-Myers Squibb and Takeda (Millenium). RMSt has served on independent data safety monitoring committees for trials supported by Celgene, Takeda, and Argenix; has consulted for AbbVie, Actinium, Agios, Amgen, Arog, Astellas, AstraZeneca, Biolinerx, Celgene, Daiichi Sankyo, Fujifilm, Janssen, Juno, Macrogenics, Novartis, Ono, Orsenix, Pfizer, Roche, Stemline, Sumitomo, Takeda, and Trovagene; and has received research support (to the institution) for clinical trials sponsored by AbbVie, Agios, Arog, and Novartis. JFZ has received honoraria from AbbVie, Agios, AsystBio Laboratories, Celgene, Daiichi Sankyo, Genentech, Pfizer, and Takeda; is a consultant and is on advisory boards for, or has received research funding from AROG Pharmaceuticals, Celgene, Forty Seven, Merck, Takeda, and Tolero. ATF is consulting for Celgene (Bristol-Myers Squibb), Novartis, Agios, Astellas, Pfizer, Takeda, Amgen, Daiichi Sankyo, Kite, Trovagene, Forty Seven, NewLink Genetics, and AbbVie; and receives clinical trial support from Celgene and Agios. EMS has served on advisory boards for AbbVie, Agios, Amgen, Astellas, Celgene, Daiichi Sankyo, Genentech, Novartis, and Seattle Genetics, and has received research support (to his institution) from Agios, Amgen, Bayer, Biotheryx, Celgene, Syndax, and Syros. GH has served on advisory boards for SAB Incyte, Agios, Jazz, Bristol-Myers Squibb, and Celgene; has received research support from Bayer, Merck, Incyte, and Constellation; and has received grants from ASH-AMFDP, K-12 CA087723, and the Sanchez Ferguson Award. GJR has served on independent data safety monitoring committees for trials supported by AbbVie, Actinium, Agios, Amphivena, Argenx, Array Biopharma, Astex, Astellas, AstraZeneca, Bayer, Celgene, Celltrion, Daiichi Sankyo, Eisai, Epizyme, Helsinn, Janssen, Jasper Therapeutics, Jazz, and MEI Pharma; has served as chair for independent data monitoring committees for Novartis, Orsenix, Otsuka, Pfizer, Roche (Genentech), Sandoz, Takeda, IRC Chair, and Trovagene; and receives research support from Cellectis. ACS has acted as a consultant or served on advisory boards for, or received research support from, AbbVie, Agios, Amgen, Astellas, Celgene (Bristol-Myers Squibb), GlycoMimetics, Jazz, Novartis, Phebra, Pfizer, and Teva. EP has received research funding from Bristol-Myers Squibb, Kura, and Incyte, and has received honorarium from Novartis, Blueprint, and Stemline. ESW served on advisory boards or provided consulting for AbbVie, Astellas, Daiichi Sankyo, Dava Oncology (Arog), Genentech, Jazz, Kite Pharmaceuticals, Kura Oncology, Macrogenics, Pfizer, PTC Therapeutics, and Stemline; served on independent data review committees for clinical trials for AbbVie, Genentech, and Rafael Pharmaceuticals; and serves as a speaker for Stemline and Pfizer. MLH received research funding (institutional) from Blueprint, Celgene (Bristol-Myers Squibb), CTI Biopharma, Deciphera, Novartis, Phizer, Roche (Genentech), and Sierra Oncology, and participated in advisory boards or had a consultancy with, and received honoraria from, AbbVie, Blueprint, CTI Biopharma, Incyte, Novartis, and Partner Therapeutics. VRB reports receiving consulting fees from Agios, Incyte, Partner Therapeutics, Omeros, Takeda, and AbbVie; research funding from Incyte, Jazz, Tolero Pharmaceuticals, and the National Marrow Donor Program; and funding support for a trial from Oncoceutics. HK served on advisory boards or provided consulting for Agios, Novartis, and Pfizer. SL reports grants to her institution from Biosight, Celgene, Hoffman La Roche, Kura, and Onconova; and honoraria from Acceleron, Agios, Daichii-Sankyo, Bristol-Myers Squibb, and Jazz. KWP receives institutional research funding from AbbVie, Agios, Daiichi Sankyo, and Millennium; and is an advisory board member for AbbVie, Astellas, Celgene, and Boston BioMedical. RK serves on the speaker bureau for JAZZ, Agios, and AbbVie; and served on advisory boards or provided consulting for JAZZ, Agios, AbbVie, Celgene, and Acceleron. PF receives research support from Celgene (Bristol-Myers Squibb), Janssen, AbbVie, Agios, and Novartis. UP consulted, attended an advisory board, or received honoraria from Amgen, Celgene, AbbView, Novartis, and Takeda. EAG has received institutional research funding from Genentech, Astex (Otsuka), Apellis, Celldex Therapeutics, and Celgene (Bristol-Myers Squibb); and has participated in advisory boards for AbbVie, Astex (Otsuka), Celgene (Bristol-Myers Squibb), and Alexion Pharmaceuticals. AN has received honoraria from Mount Sinai Hospital and the University of Toronto; research support from Jazz

Pharmaceutical, Meriani, Raffael pharmaceutical, PTC Therapeutics, Tolero Pharmaceuticals, Millennium Pharmaceuticals, Syros Pharmaceuticals, Pfizer, Seattle Genetics, Diiachi Sanykyo, Celgene, Imago BioScience, Sierra Oncology, Geron Corporation, Samumed, Clear Creek Bio, Forty Seven, AbbView, MacroGenics, Glycomimetics, CTI BoiPharma, Incyte Corporation, Aprea Therapeutics, Kura Oncology, and Selvitape; is on the speaker bureau for Incyte Corporation and Novartis; is part of a data monitoring committee for MEI Pharma; has served on the advisory board or has consulted for Karyopharma, AbbView, and Daiichi Sankyo; and is a consultant for Guidepoint, the American Society of Hematology, the Physicians' Education Resource, Medicom WorldWide, and Hemedicus. AA-K received research support to their institution from Novartis, Onconova, Celgene (Bristol-Myers Squibb), Astex, Medimmune (AstraZeneca), Aprea, Daiichi Sankyp, and H3B Biomedicine. ADG served on advisory boards for, or was a consultant for, AbbVie, Aptose, Celgene, Daiichi Sanyko, and Genentech; received institutional research funding from AbbVie, A.D.C Therapeutics, Aprea, AROG Pharmaceuticals, Daiichi Sanyko, and Pfizer; and received honoraria from Dava Oncology. JM received institutional research funding from Incyte, CTI Biopharma, Novartis, Merck, Roche, Kartos, Promedior, Janssen, Merus, and Arog and consulting honoraria from Celgene, Prelude, Galecto, Roche, Constellation, and Incyte. All authors with competing interests declare that none of these relationships were related to the development of this manuscript. All other authors report no competing interests.

Acknowledgments

The experts on this panel are haematologists and oncologists who specialise in leukaemia and transplant care, and discussions were held through virtual, online meetings. No external support was received for this Viewpoint. Amer M Zeidan is a Leukaemia and Lymphoma Society scholar in clinical research and is also supported by a National Cancer Institute's Cancer Clinical Investigator Team Leadership Award. Research reported in this publication was in part financially supported by the National Cancer Institute of the National Institutes of Health under award number P30 CA016359. The content of this Viewpoint is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health. This publication was not funded by the National Institutes of Health. The funder of the publication had no role in the writing of the report. The corresponding author had final responsibility for the decision to submit for publication.

References

1 Centre for Evidence-Based Medicine. Global Covid-19 case fatality rates. March 17, 2020. https://www.cebm.net/covid-19/global-covid-19-case-fatality-rates/ (accessed April 14, 2020).

2 Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020; **323:** 1239–42 .

3 Shallis RM, Wang R, Davidoff A, Ma X, Zeidan AM. Epidemiology of acute myeloid leukemia: recent progress and enduring challenges. *Blood Rev* 2019; **36:** 70–87.

4 Zeidan AM, Shallis RM, Wang R, Davidoff A, Ma X. Epidemiology of myelodysplastic syndromes: why characterizing the beast is a prerequisite to taming it. *Blood Rev* 2019; **34:** 1–15.

5 Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020; **21:** 335–37.

6 Mehta V, Goel S, Kabarriti R, et al. Case fatality rate of cancer patients with COVID-19 in a New York hospital system. *Cancer Discov* 2020; published online May 1. DOI:10.1158/2159-8290.CD-20-0516.

7 He W, Chen L, Chen L, et al. COVID-19 in persons with haematological cancers. *Leukemia* 2020; **34:** 1637–45.

8 The Lancet. COVID-19: protecting health-care workers. *Lancet* 2020; **395:** 922.

9 Persad G, Wertheimer A, Emanuel EJ. Principles for allocation of scarce medical interventions. *Lancet* 2009; **373:** 423–31.

10 Volandes AE, Levin TT, Slovin S, et al. Augmenting advance care planning in poor prognosis cancer with a video decision aid: a preintervention-postintervention study. *Cancer* 2012; **118:** 4331–38.

11 Perl AE. The most novel of the novel agents for acute myeloid leukemia. *Curr Opin Hematol* 2018; **25:** 81–89.

12 Wiedermann FJ. Acute lung injury during G-CSF-induced neutropenia recovery: effect of G-CSF on pro- and anti-inflammatory cytokines. *Bone Marrow Transplant* 2005; **36:** 731.

13 Karlin L, Darmon M, Thiéry G, et al. Respiratory status deterioration during G-CSF-induced neutropenia recovery. *Bone Marrow Transplant* 2005; **36:** 245–50.

14 Qureshi K, Gershon RR, Sherman MF, et al. Health care workers' ability and willingness to report to duty during catastrophic disasters. *J Urban Health* 2005; **82:** 378–88.

15 Song JY, Yun JG, Noh JY, Cheong HJ, Kim WJ. Covid-19 in South Korea—challenges of subclinical manifestations. *N Engl J Med* 2020; **382:** 1858–59.

16 Ueda M, Martins R, Hendrie PC, et al. Managing cancer care during the COVID-19 pandemic: agility and collaboration toward a common goal. *J Natl Compr Canc Netw* 2020; **18:** 1–4.

17 Centor RM, Marrazzo J. Annals on call—protecting health care workers from COVID-19. *Ann Intern Med* 2020; **172:** OC1.

18 Ebrahim SH, Ahmed QA, Gozzer E, Schlagenhauf P, Memish ZA. Covid-19 and community mitigation strategies in a pandemic. *BMJ* 2020; **368:** m1066.

19 Scheunemann LP, White DB. The ethics and reality of rationing in medicine. *Chest* 2011; **140:** 1625–32.

20 Commonwealth of Massachusetts. COVID-19 State of Emergency. Updates, emergency orders, and guidance associated with the COVID-19 State of Emergency. https://www.mass.gov/info-details/covid-19-state-of-emergency (accessed April 14, 2020).

21 WHO. Guidance for managing ethical issues in infectious disease outbreaks. 2016. https://apps.who.int/iris/handle/10665/250580 (accessed May 10, 2020).

22 Schopper D, Ravinetto R, Schwartz L, et al. Research ethics governance in times of Ebola. *Public Health Ethics* 2017; **10:** 49–61.

23 Fetscher S, Mertelsmann R. Supportive care in hematologic malignancies: hematopoietic growth factors, infections, transfusion therapy. *Curr Opin Hematol* 2000; **7:** 255–60.

24 Carson JL, Guyatt G, Heddle NM, et al. Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. *JAMA* 2016; **316:** 2025–35.

25 Docherty AB, O'Donnell R, Brunskill S, et al. Effect of restrictive versus liberal transfusion strategies on outcomes in patients with cardiovascular disease in a non-cardiac surgery setting: systematic review and meta-analysis. *BMJ* 2016; **352:** i1351.

26 Mueller MM, Van Remoortel H, Meybohm P, et al. Patient blood management: recommendations from the 2018 Frankfurt Consensus Conference. *JAMA* 2019; **321:** 983–97.

27 Pine AB, Lee EJ, Sekeres M, et al. Wide variations in blood product transfusion practices among providers who care for patients with acute leukemia in the United States. *Transfusion* 2017; **57:** 289–95.

28 O'Brien KL, Mohammed M, Uhl L. Management of a hospital transfusion service during a nationwide blood product shortage. *Arch Pathol Lab Med* 2018; **142:** 779–81.

29 Stanworth SJ, Estcourt LJ, Powter G, et al. A no-prophylaxis platelet-transfusion strategy for hematologic cancers. *N Engl J Med* 2013; **368:** 1771–80.

30 Wandt H, Schaefer-Eckart K, Wendelin K, et al. Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study. *Lancet* 2012; **380:** 1309–16.

31 Estcourt LJ, McQuilten Z, Powter G, et al. The TREATT Trial (TRial to EvaluAte Tranexamic acid therapy in Thrombocytopenia): safety and efficacy of tranexamic acid in patients with haematological malignancies with severe thrombocytopenia: study protocol for a double-blind randomised controlled trial. *Trials* 2019; **20:** 592.

32 Zhang W, Du RH, Li B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. *Emerg Microbes Infect* 2020; **9:** 386–89.

33 Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature* 2020; **581:** 465–69.

34 US Food and Drug Administration. Updated information for blood establishments regarding the novel coronavirus (COVID-19) outbreak. May 11, 2020.https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/updated-information-blood-establishments-regarding-novel-coronavirus-covid-19-outbreak (accessed April 14, 2020).

35 US Food and Drug Administration. Coronavirus (COVID-19) update: FDA provides updated guidance to address the urgent need for blood during the pandemic. April 2, 2020. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-provides-updated-guidance-address-urgent-need-blood-during-pandemic (accessed April 14, 2020).

36 Gafter-Gvili A, Fraser A, Paul M, et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. *Cochrane Database Syst Rev* 2012; **1:** CD004386.

37 Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost* 2020; **18:** 1023–26.

38 McDermott MM, Newman AB. Preserving clinical trial integrity during the coronavirus pandemic. *JAMA* 2020; **323:** 2135.

39 Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med* 2014; **371:** 1507–17.

40 Arnold C. COVID-19: biomedical research in a world under social-distancing measures. *Nat Med* 2020; published online March 26. DOI:10.1038/d41591-020-00005-1.

41 Government of Canada. Management of clinical trials during the COVID-19 pandemic: notice to clinical trial sponsors. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/management-clinical-trials-during-covid-19-pandemic.html (accessed April 14, 2020).

42 US Food and Drug Administration. FDA guidance on conduct of clinical trials of medical products during COVID-19 pandemic. March, 2020. https://bit.ly/3b1sORI (accessed April 14, 2020).

43 Europe Medicines Agency. Mandate, objectives and rules of procedure of the COVID-19 EMA pandemic Task Force (COVID-ETF). March 31, 2020. https://www.ema.europa.eu/en/documents/other/mandate-objectives-rules-procedure-covid-19-ema-pandemic-task-force-covid-etf_en.pdf (accessed April 14, 2020).

44 Röllig C, Kramer M, Schliemann C, et al. Time from diagnosis to treatment does not affect outcome in intensively treated patients with newly diagnosed acute myeloid leukemia. *Blood* 2019; **134** (suppl 1)**:** 13 (abstr).

45 Fang Y, Zhang H, Xie J, et al. Sensitivity of chest CT for COVID-19: comparison to RT-PCR. *Radiology* 2020; published online Feb 19. DOI:10.1148/radiol.2020200432.

46 Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395:** 1033–34.

47 Le RQ, Li L, Yuan W, et al. FDA approval summary: tocilizumab for treatment of chimeric antigen receptor t cell-induced severe or life-threatening cytokine release syndrome. *Oncologist* 2018; **23:** 943–47.

48 Allen MR, Aljitawi OS, He J, et al. Outpatient cytarabine administration is safe and effective for consolidation in acute myeloid leukemia. *Blood* 2013; **122:** 5030.

49 Tallman M, Rollig C, Zappasodi P, et al. COVID-19 and acute myeloid leukemia: frequently asked questions. https://www.hematology.org/covid-19/covid-19-and-acute-myeloid-leukemia (accessed April 14, 2020).

50 The National Cancer Research Institute Acute Myeloid Leukaemia Working Party. Recommendations for the management of patients with AML during the COVID19 outbreak. http://www.cureleukaemia.co.uk/page/news/523/aml-working-party-covid-19-recommendations (accessed April 14, 2020).

51 Burnett AK, Russell NH, Hills RK, et al. Optimization of chemotherapy for younger patients with acute myeloid leukemia: results of the medical research council AML15 trial. *J Clin Oncol* 2013; **31:** 3360–68.

52 Wei AH, Döhner H, Pocock C, et al. The QUAZAR AML-001 maintenance trial: results of a phase III international, randomized, double-blind, placebo-controlled study of CC-486 (oral formulation of azacitidine) in patients with acute myeloid leukemia (AML) in first remission. *Blood* 2019; **134** (suppl 2)**:** LBA-3 (abstr).

53 Chen Z, Xiong H, Li JX, et al. COVID-19 with post-chemotherapy agranulocytosis in childhood acute leukemia: a case report. *Zhonghua Xue Ye Xue Za Zhi* 2020; **41:** 341–43 (in Chinese).

54 Ni YN, Chen G, Sun J, Liang BM, Liang ZA. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. *Crit Care* 2019; **23:** 99.

55 Lee N, Allen Chan KC, Hui DS, et al. Effects of early corticosteroid treatment on plasma SARS-associated coronavirus RNA concentrations in adult patients. *J Clin Virol* 2004; **31:** 304–09.

56 Ravandi F. How I treat Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood* 2019; **133:** 130–36.

57 Stock W, Patel A, O'Dwyer K, et al. COVID-19 and ALL: frequently asked questions. https://www.hematology.org/covid-19/covid-19-and-all (accessed April 14, 2020).

58 Gökbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. *Blood* 2018; **131:** 1522–31.

59 Heine A, Held SA, Daecke SN, et al. The JAK-inhibitor ruxolitinib impairs dendritic cell function in vitro and in vivo. *Blood* 2013; **122:** 1192–202.

60 Rampal RK, Mascarenhas JO, Kosiorek HE, et al. Safety and efficacy of combined ruxolitinib and decitabine in accelerated and blast-phase myeloproliferative neoplasms. *Blood Adv* 2018; **2:** 3572–80.

61 Komrokji RS, Al Ali N, Sallman DA, et al. What is the optimal time to initiate hypomethylating agents (HMA) in higher risk myelodysplastic syndromes (MDS)? *Blood* 2018; **132** (suppl 1)**:** 3098 (abstr).

62 Mikkael A, Sekeres MA, Steensma DP, DeZern A, Roboz G, Garcia-Manero G, Komrokji R. COVID-19 and myelodysplastic syndromes: frequently asked questions. https://www.hematology.org/covid-19/covid-19-and-myelodysplastic-syndromes (accessed April 14, 2020).

63 Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Engl J Med* 2020; **382:** 140–51.

64 National Comprehensive Cancer Network. NCCN guidelines. https://www.nccn.org/professionals/physician_gls/default.aspx (accessed May 10, 2020).

65 Hutchins NA, Unsinger J, Hotchkiss RS, Ayala A. The new normal: immunomodulatory agents against sepsis immune suppression. *Trends Mol Med* 2014; **20:** 224–33.

66 Francois B, Jeannet R, Daix T, et al. Interleukin-7 restores lymphocytes in septic shock: the IRIS-7 randomized clinical trial. *JCI Insight* 2018; **3:** 98960.

67 Lv S, Han M, Yi R, Kwon S, Dai C, Wang R. Anti-TNF-α therapy for patients with sepsis: a systematic meta-analysis. *Int J Clin Pract* 2014; **68:** 520–28.

68 Shakoory B, Carcillo JA, Chatham WW, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase III trial. *Crit Care Med* 2016; **44:** 275–81.

69 Meisel C, Schefold JC, Pschowski R, et al. Granulocyte-macrophage colony-stimulating factor to reverse sepsis-associated immunosuppression: a double-blind, randomized, placebo-controlled multicenter trial. *Am J Respir Crit Care Med* 2009; **180:** 640–48.

70 Gavillet M, Carr Klappert J, Spertini O, Blum S. Acute leukemia in the time of COVID-19. *Leuk Res* 2020; **92:** 106353.

71 Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. *J Clin Invest* 2020; **130:** 1545–48.

72 Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA* 2020; **323:** 1582.

73 Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. *N Engl J Med* 2020; published online April 10. DOI:10.1056/NEJMoa2007016.

74 Dowell SF, Ho MS. Seasonality of infectious diseases and severe acute respiratory syndrome—what we don't know can hurt us. *Lancet Infect Dis* 2004; **4:** 704–08.

75 Eichenberger EM, Soave R, Zappetti D, et al. Incidence, significance, and persistence of human coronavirus infection in hematopoietic stem cell transplant recipients. *Bone Marrow Transplant* 2019; **54:** 1058–66.