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Supplementary appendix

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Supplemental File

Special Considerations in the Management of Adult Patients with Acute Leukaemias and Myeloid Neoplasms in the COVID-19 Era: Recommendations by an International Expert Panel

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Acute Myeloid Leukaemia (AML):

Although a new diagnosis of AML is often considered a medical emergency (e.g. hyperleucocytosis/leucostasis, coagulopathy, acute promyelocytic leukaemia [APL]), several studies have suggested that it may be safe to delay treatment initiation in many patients in order to obtain diagnostic and prognostic information (1-3). The clinician must exercise careful clinical judgement in determining whether a patient with newly diagnosed AML is an appropriate candidate for delayed initiation of treatment.

It is unclear how standard AML therapy influences the course of SARS-CoV-2 infection. The ASH COVID-19 advisory committee for AML recommended cytarabine/anthracycline-based induction chemotherapy (e.g. “7+3” or similar) in non-APL AML with the specific regimen based on risk stratification, as well as all-trans retinoic acid (ATRA) + arsenic trioxide (ATO) in non-high-risk APL patients (4). Similarly, ATRA + ATO + anthracycline/gemtuzumab ozogamicin should be administrated, as per standard, in high-risk APL patients (5). Although standardized guidelines recommend consideration of use of prophylactic corticosteroids to prevent differentiation syndrome during APL therapy, this may increase the risk of viral complications.

We recommend testing all patients with AML (Figure 1) in need of intensive induction therapy for the presence of SARS-CoV-2 infection before treatment initiation, and should infection be detected, consider delaying treatment by 10-14 days if possible. Given the limited sensitivity of SARS-CoV-2 RT-PCR (~70%) (6), we recommend repeat testing after 24 hours, especially in cases of high clinical suspicion. If the patient is SARS-CoV-2 infected and asymptomatic or only mildly symptomatic, but in need of

urgent initiation of induction therapy, he/she may be treated without delay, but with close monitoring for any evolving COVID-19-related symptoms.

There are no data on the prognosis and outcome of AML patients receiving induction chemotherapy with concomitant SARS-CoV-2 infection. If the patient has moderate or severe COVID-19 infection, the expert consensus is to await improvement in clinical status before initiating chemotherapy, if at all possible. For newly diagnosed AML patients with hyperleucocytosis with COVID-19 infection, hydroxyurea can be used to lower white blood cell count if the patient is clinically stable as a temporizing measure (7). For an AML patient with hyperleucocytosis and COVID-19 infection, differentiating whether severe hypoxemia is related to COVID-19 infection or is a manifestation of pulmonary leucostasis is extremely difficult. A careful discussion with patient and family regarding risks and benefits of urgent cytoreduction beyond hydroxyurea in this situation should occur, and should take into account the patient's age, medical comorbidities including cardiac and pulmonary status, biology of AML, and chances of cure. Extreme vigilance is required when administering cytoreductive therapies, which could potentiate viral replication or worsen the immune response due to associated tumor lysis syndrome and disseminated intravascular coagulation.

After treatment initiation, if the patient develops symptoms of COVID-19, chemotherapy discontinuation may be warranted to minimize treatment-related immunosuppression. This decision should be made in consultation with the treating haematologist. Possible amendments to consolidative strategies include consideration of deferral of allogeneic haematopoietic cell transplant (alloHCT), particularly in patients without adverse-risk disease who are measurable residual disease (MRD) negative; and a reduction in the number of chemotherapy consolidation cycles (e.g. 3 instead of 4 cycles), and in the intensity of therapy within each consolidation cycle (e.g. use of 1.5 gm/m^2 instead of 3 gm/m^2 dosing of high dose cytarabine [HiDAC]) (8), especially in patients without favourable-risk disease(4). Delaying alloHCT until it is safer and logistically more feasible is a reasonable strategy in intermediate-risk AML. With emerging data suggesting a role of azanucleosides (e.g. [oral] azacitidine) as maintenance therapy following completion

of induction (and, possibly, post-remission) therapy (9), such therapeutics may be considered instead of intensive post-remission therapy to minimize the duration of cytopenias, transfusion support, and health care encounters/needs. In addition, autologous stem cell transplantation (SCT), which is a strategy used in some cooperative groups, could be replaced by consolidation with HiDAC, as autologous SCT can result in cellular immunosuppression lasting up to three months.

In exceptional circumstances where there is a critical shortage in hospital bed capacity and support staff, patients may have to make the informed choice of opting for treatment with alternative lower intensity induction regimens such as hypomethylating agents (HMAs), combinations of HMAs or low dose cytarabine with venetoclax, or targeted therapies (i.e. oral small molecule inhibitors against *FLT3 or IDH1/2*), that can be administered in the outpatient setting (4, 10). Pre-treatment testing for SARS-CoV-2 should be considered for patients receiving such regimens, even in the outpatient setting, given the potential for catastrophic outcomes in SARS-CoV-2 positive patients receiving myelosuppressive therapy. Outpatient management of AML patients following induction therapy is known to be safe at centres with the appropriate outpatient management infrastructure, allowing patients to spend a large portion of their time until blood count recovery as outpatients (11, 12). It is important to note, however, that this strategy entails patient travel and transportation, which carries the added risk of a potential COVID-19 community exposure. Using ambulatory pumps for outpatient consolidation therapy administration is also a safe and feasible approach and should be considered as often as possible (13, 14) in centres capable of delivering such therapy.

Patients with relapsed/refractory (R/R) AML should be evaluated by cytogenetics and mutational profiling to determine optimal treatment approaches and to identify potential targeted therapy options. Participation in clinical trials is still recommended by the expert panel for patients with R/R AML if it is safe and feasible to enrol on such studies at the respective institution. Pharmacokinetic/pharmacodynamic analyses and correlative research samples may need to be adjusted and/or eliminated in conjunction with the institution’s IRB and sponsor approval given the inherent risks of these procedures and

visits during the COVID-19 pandemic. If *FLT3*, *IDH1* or *IDH2* mutations are present, these patients should be considered for oral targeted small molecule inhibitors such as gilteritinib, ivosidenib, and enasidenib, respectively, as opposed to salvage chemotherapy. While delays in alloHCT in first complete remission (CR1) may be considered during the COVID-19 pandemic, R/R patients with AML who achieve second complete remission (CR2) should be considered for alloHCT on a more urgent basis, after weighing relative risks and benefits, given the high-risk nature of the disease and the elevated risk of relapse (15).

The use of venetoclax (16) and of targeted molecular inhibitors against *IDH1* and *FLT3* mutations such as ivosidenib (17) and gilteritinib (18), respectively, and azole antifungals (as a part of anti-microbial management) requires careful consideration of potential drug-drug interactions via CYP3A4 metabolism pathway. Further, ivosidenib and gilteritinib can potentially lead to QTc prolongation; measurement of the Fridericia or Framingham corrected QT interval (as opposed to Bazett) is critical in such cases (19). Concomitant QTc prolongation from potential COVID-19 therapies, namely HCQ-azithromycin, will require careful attention especially when they are administered to patients receiving ivosidenib and gilteritinib, given the long half-life (approximately 4-5 days) of these agents (4, 20, 21).

Acute Lymphoblastic Leukaemia (ALL):

As is the case with AML, we recommend testing all patients with newly diagnosed ALL who require intensive chemotherapy for SARS-CoV-2 (Figure 1). There exists a severe SARS-CoV-2 risk in ALL patients undergoing therapy, as highlighted by a recent report of severe COVID-19 in a paediatric patient receiving chemotherapy for ALL (22). If possible, definitive treatment should be delayed by 10-14 days in patients found to be SARS-CoV-2-infected, with the exception of central nervous system symptoms where intrathecal therapies should be promptly administered.

The use of steroids, which are integral to ALL management, likely increases the risk of SARS-CoV-2 infection. While data regarding the benefit of steroids in severe COVID-19

is controversial (23), we suggest considering minimizing steroid exposure particularly, in older ALL patients, referencing data from previous studies in which steroids were associated with increased mortality and secondary infection rates in cases of influenza (24) and with increased plasma viral loads in SARS-CoV-1 (25).

The ASH advisory group recommends considering dose reductions in daunorubicin and PEG-asparaginase during the induction phase in older, less-fit patients at high risk of complications, and dose-reductions to corticosteroid therapy during the maintenance phase. The use of anti-CD20 monoclonal antibodies (e.g., rituximab) is associated with a reduction in immunoglobulins, and their use should be carefully considered and delayed if possible. Growth factor support is routinely incorporated into ALL protocols to facilitate count recovery (26) during the induction therapy phase and to maintain absolute neutrophil counts above 1000/mm^3 across all phases of ALL therapy, except in the case of a SARS-CoV-2 infected patient with severe respiratory manifestations where its use needs to be reconsidered. Numerous studies have shown that reduced-dose or chemotherapy-free strategies are possible for Philadelphia chromosome-positive (Ph+ve) ALL, particularly in older patients. Given the risk of myelosuppression in SARS-CoV-2 infection, strong consideration should be given to the use of a second-generation tyrosine kinase inhibitor (TKI) such as dasatinib with reduced dose steroids as the chemotherapy-free treatment of choice in Ph+ve ALL (27).

While delays in alloHCT in CR1 may be considered during the COVID-19 pandemic, R/R patients with ALL who achieve CR2 should be taken to alloHCT promptly, after weighing relative risks and benefits considering the high-risk nature of the disease and the elevated risk of relapse (15). The committee still recommends prompt initiation of blinatumomab to treat minimal residual disease in Philadelphia chromosome-negative (Ph-ve) B-ALL (28). For patients with R/R ALL, inotuzumab may be considered over blinatumomab as the first salvage option to reduce the duration of hospital stay (15). Clinical cellular therapy trials have been placed on hold. The decision to treat with CD19-directed CAR-T cell therapy, an approved option for use in younger adults (up to 25 years of age) with R/R ALL (29), should be based upon individual risk-benefit assessment by the treating haematologist. .

Myeloproliferative Neoplasms (MPNs):

The *BCR-ABL1*-positive MPN, chronic myelogenous leukaemia (CML), stands apart from other MPNs, as this subtype is effectively managed in the majority of patients with targeted tyrosine kinase inhibitor (TKI) therapy. CML patients receiving TKI therapy should remain on their oral treatment at the current dose and extend the interval between office visits and blood draws meant to determine molecular response. During the COVID-19 pandemic, TKI discontinuation trials should not be initiated as this requires frequent monitoring. Patients with newly diagnosed CML should be started on TKI therapy. Every effort should be made to extend intervals between visits, utilize telehealth to assess patient adherence, and assist with symptom management and utilize mobile lab draws where available. At present, there is no indication that TKIs would increase the risk of COVID-19 related complications in patients with CML. Relevantly, *in vitro* data suggest that these agents are potent inhibitors of coronavirus virus-cell membrane fusion (30, 31).

In the case of *BCR-ABL1*-negative MPNs, essential thrombocythaemia (ET) and polycythaemia vera (PV), current cytoreductive treatment with hydroxyurea, anagrelide, interferon-α, or ruxolitinib should also be maintained. At present there is no indication that hydroxyurea or anagrelide would increase the risk of COVID-19 related complications in MPN patients. Although cytoreductive therapy may be immunosuppressive, the risks of therapy discontinuation should be weighed against the theoretical risk of less immunosuppression. However, it may be appropriate to have more lenient blood cell count targets to minimize leucopenia associated with cytoreductive therapy use. In PV patients requiring control of the haematocrit by phlebotomy, a decrease in the frequency of office visits, may be considered, especially in the context of the patient's risks of and from COVID-19 infection. For PV patients that rely on phlebotomy for symptomatic relief or where higher haematocrit thresholds are unacceptable, initiation of cytoreductive therapy may be appropriate to reduce the frequency of phlebotomy.

Clinical trials evaluating the effects of JAK inhibitors such as ruxolitinib in patients infected with COVID-19 have recently been announced and are informed by a mechanism of action that leads to depression of STAT driven inflammatory cytokine production, including IL-6 (32). MPN patients receiving a JAK inhibitor should remain on therapy and

dose attenuation is not recommended. However, the ASH co-advisory committee recommends consideration of deferring initiation of JAK inhibitors in patients, as clinically appropriate, until the peak of the pandemic subsides. The extent of the competing risk of immunosuppression with ruxolitinib, for example, is unknown and is based on laboratory studies demonstrating downregulation of T-cell and dendritic cell function, as well as on clinical trial data suggesting increased risk of infections such as viral pathogens (33, 34). The role of interferon-α in the setting of COVID-19 infection is unknown but would not be anticipated to lead to an immunosuppressive state. The use of aspirin for thromboprophylaxis, particularly in high risk ET/PV should remain in place, and in the setting of acute COVID-19 infection, consideration of a change in oral anticoagulation to low molecular weight heparin (LMWH) is suggested.

Clinical trial accrual during this acute phase of the COVID-19 pandemic should be limited to patients with higher risk myelofibrosis (MF), given the lack of effective available therapies and the demonstrated poor outcome in patients that fail ruxolitinib treatment (35). Use of erythropoiesis stimulating agents (ESAs) and alternative anaemia directed agents such as danazol to reduce RBC transfusion needs may be appropriate on a case-by-case basis. Delay in alloHCT may be required in cases given current resource allocation. Patients with MPN-blast phase should be managed with HMA therapy +/- ruxolitinib as an outpatient whenever possible with a goal of alloHCT where appropriate (36). However, in this high-risk patient group, discussions about prognosis are particularly critical during the COVID-19 pandemic where resources are limited.

Myelodysplastic syndromes (MDS)

Some patients with MDS have an associated lymphopenia, which can compromise the ability to contain the virus post-infection, and is an indicator of poor prognosis in both MDS and SARS-CoV-2 infections (37, 38). Underlying neutrophil-related defects increase the risk of developing secondary bacterial superinfections, which can contribute to additional respiratory virus-related mortality (39, 40). Alterations to therapy approaches will be dictated by the specific MDS International Prognostic Risk Scoring System (IPSS-R) category. Among patients with higher-risk MDS (IPSS-R > 3.5) where the goal is disease control, preventing progression, and extending survival, the ASH co-advisory

committee still recommends prompt initiation of hypomethylating agents in newly diagnosed patients and continuation in patients already on therapy, though the schedule may require adjustment. In some patients, therapy may be delayed, while in others, a positive result should be incorporated into a risk-benefit assessment of therapy. However, close observation without definitive treatment is a reasonable strategy in patients with higher-risk MDS with only modest cytopenias (41). It is reasonable in patients being considered for therapy, especially if potentially myeloablative, to undergo testing for COVID-19 prior to treatment initiation. For patients receiving azacitidine, consideration of only subcutaneous use over intravenous should be made to decrease infusion centre time and exposures. For patients with lower-risk MDS (IPSS-R score < 3.5) in whom a 'wait-and-watch' approach can be pursued, transfusion thresholds may be altered as outlined in the 'transfusion support' section of the main article. Frequent laboratory draws for monitoring or visits for injections may require delay. Consideration should be given to using therapies which reduce transfusion needs such as ESAs in ESA-naïve patients, as well as the recently approved drug luspatercept (42). For newly-diagnosed del(5q) MDS patients, we recommend deferring lenalidomide, given the myelosuppressive risk. However, lenalidomide may be continued in patients already on therapy. Lenalidomide can now be prescribed in 56-day intervals rather than 28 for most reproductive risk groups, reducing patients' need to interact with clinic or pharmacy staff.

Myelodysplastic syndrome /Myeloproliferative neoplasm overlap syndromes (MDS/MPN):

The MDS/MPN overlap syndromes include malignancies such as chronic myelomonocytic leukaemia (CMML), MDS/MPN-unclassifiable, atypical chronic myeloid leukaemia (aCML), and MDS/MPN-ring sideroblasts and thrombocytosis (43). Among these, CMML, aCML, and MDS/MPN-U in particular, pose a unique challenge, given that a large number of patients present with proliferative features and experience leukemoid reactions during times of physiological stress (44). These patients have baseline leucocytosis, neutrophilia and monocytosis (CMML), splenomegaly, leucoerythroblastosis, and/or elevated baseline inflammatory cytokines (45). Each of

these factors may increase their risk for systemic inflammatory response syndromes (SIRS) and cytokine release syndromes (CRS), both major mechanisms underlying COVID-19 related morbidity and mortality (46, 47). Moreover, proliferative CMML is a disease that occurs due to acquisition of signal pathway mutations (*NRAS, CBL, JAK2*) in the context of age-related clonal haematopoiesis (*TET2, SRSF2, ASXL1*). There is a growing body of evidence relating the effect of these mutations in clonal haematopoiesis (48-53) and endothelial dysfunction in cardiovascular disease, often linked to an increase in inflammatory cytokines. In CMML, these elevated inflammatory cytokines (54) (clinically manifesting as constitutional symptoms, autoimmune phenomena or poly-inflammatory syndromes) and proliferation are further elevated, and clearly are factors that could accelerate complications of COVID-19, such as ARDS and MODS. In addition, similar to MDS, other factors such as RBC transfusion dependency and thrombocytopenia further compound these issues.

In cases of proliferative CMML in which the leucocytosis is mild-to-moderate (55), patients are often followed without specific cytoreductive intervention for leucocytosis. For patients with extreme leucocytosis during the pandemic, consideration should be given to lowering the WBC in asymptomatic MDS/MPN patients with low doses of hydroxyurea and careful monitoring of blood counts, given the likelihood of leukaemoid reactions, CRS, and severe ARDS if the patient was to be infected with COVID-19. Early initiation of cytokine modulators may be considered, as indicated, in such patients with symptomatic COVID-19 infection (56, 57). The role of corticosteroids is currently controversial, given that it might accentuate SARS-CoV-2 viral loads and exacerbate CMML-related leukemoid reactions.

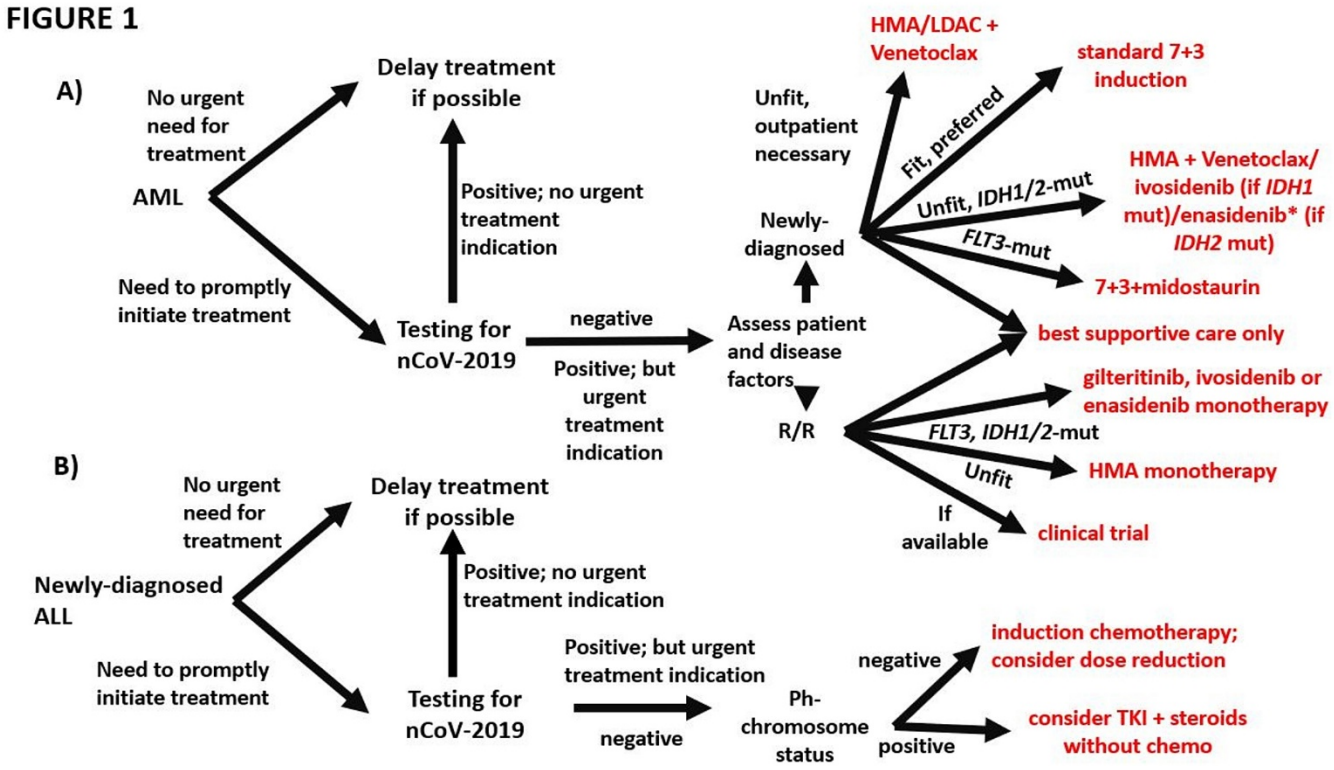
Erythropoiesis-stimulating agents can be used in the management of anaemia. Given that a high proportion of CMML and MDS/MPN overlap syndromes have splenomegaly, the committee does not recommend the routine use of G-CSF in these patients given a risk of splenic rupture (58).

Supplemental Table 1. Online resources for clinicians

Disease	Online resources for guidance and management
AML	***General management guidelines:*** American Society of Haematology (https://www.haematology.org/covid-19/covid-19-and-acute-myeloid-leukaemia) AML Working Party (http://www.cureleukaemia.co.uk/page/news/523/aml-working-party-covid-19-recommendations) National Comprehensive Cancer Network (https://www.nccn.org/covid-19/default.aspx) European Haematology Association (https://ehaweb.org/covid-19/aboutthehub/) ***Transplant considerations:*** American Society of Transplant and Cellular Therapy (https://www.astct.org/communities/public-home?CommunityKey=d3949d84-3440-45f4-8142-90ea05adb0e5) European Society for Blood and Marrow Transplantation (http://newsletters.ebmt.org/view.php?J=sdJU2X80rmN0KWiiCSsZBg&C=WKRf763y9VzwPoB0anNGjDGA)
ALL	***General management guidelines:*** American Society of Haematology (https://www.haematology.org/covid-19/covid-19-and-all) National Comprehensive Cancer Network (https://www.nccn.org/covid-19/default.aspx) European Haematology Association (https://ehaweb.org/covid-19/aboutthehub/) ***Transplant considerations:*** American Society of Transplant and Cellular Therapy (https://www.astct.org/communities/public-home?CommunityKey=d3949d84-3440-45f4-8142-90ea05adb0e5) European Society for Blood and Marrow Transplantation (http://newsletters.ebmt.org/view.php?J=sdJU2X80rmN0KWiiCSsZBg&C=WKRf763y9VzwPoB0anNGjDGA)
MPN	***General management guidelines:*** American Society of Haematology (https://www.haematology.org/covid-19/covid-19-and-myeloproliferative-neoplasms) National Comprehensive Cancer Network (https://www.nccn.org/covid-19/default.aspx) European Haematology Association (https://ehaweb.org/covid-19/aboutthehub/) ***Transplant considerations:*** American Society of Transplant and Cellular Therapy (https://www.astct.org/communities/public-home?CommunityKey=d3949d84-3440-45f4-8142-90ea05adb0e5) European Bone Marrow Transplant Society (http://newsletters.ebmt.org/view.php?J=sdJU2X80rmN0KWiiCSsZBg&C=WKRf763y9VzwPoB0anNGjDGA)
MDS	***General management guidelines:*** American Society of Haematology (https://www.haematology.org/covid-19/covid-19-and-myelodysplastic-syndromes) Aplastic Anaemia and MDS International Foundation (https://www.aamds.org/education/covid-19) MDS Foundation (https://www.mds-foundation.org/mds-and-coronavirus-covid-19/) UK MDS Forum (http://www.ukmdsforum.org.uk/documents/UK-MDS-Forum-guidance-covid.pdf) European Haematology Association (https://ehaweb.org/covid-19/aboutthehub/) ***Transplant considerations:*** American Society of Transplant and Cellular Therapy (https://www.astct.org/communities/public-home?CommunityKey=d3949d84-3440-45f4-8142-90ea05adb0e5) European Society for Blood and Marrow Transplantation

	(http://newsletters.ebmt.org/view.php?J=sdJU2X80rmN0KWiiCSsZBg&C=WKRf763y9VzwPoB0anNGjDGA)
MDS/MPN	***General management guidelines:*** *American Society of Haematology (*https://www.haematology.org/covid-19/covid-19-and-myeloproliferative-neoplasms) National Comprehensive Cancer Network (https://www.nccn.org/covid-19/default.aspx) European Haematology Association (https://ehaweb.org/covid-19/aboutthehub/) ***Transplant considerations:*** American Society of Transplant and Cellular Therapy (https://www.astct.org/communities/public-home?CommunityKey=d3949d84-3440-45f4-8142-90ea05adb0e5) European Society for Blood and Marrow Transplantation (http://newsletters.ebmt.org/view.php?J=sdJU2X80rmN0KWiiCSsZBg&C=WKRf763y9VzwPoB0anNGjDGA_

Supplemental Figure 1: Proposed treatment algorithm for patients with newly diagnosed or R/R-AML and newly diagnosed ALL in setting of COVID-19 pandemic.



All patients with AML and ALL should be tested for infection with SARS-CoV-2 before starting treatment and initiation of therapy should be delayed whenever possible in the setting of active SARS-CoV-2 infection, with the exception of hydroxyurea for control of leukocytosis or urgent cytoreduction for clinical leukostasis resulting from hyperleukocytosis. For patients with a high probability of remission, standard remission induction strategies should be offered. For older patients, reduced intensity induction strategies should be considered, such as hypomethylating agents (HMA) combined with venetoclax for AML and vincristine+prednisone+/- a tyrosine kinase inhibitor for ALL. It must be kept in mind that while HMA+venetoclax regimens are termed “less intensive,” they are strongly myelosuppressive and close monitoring, along with multi-agent antimicrobial prophylaxis, either in the hospital or as an outpatient, are required. For older AML patients with IDH1 or IDH2 mutations, single-agent therapy with targeted inhibitors could also be considered. For unfit patients with acute leukaemia and those with relapsed/refractory disease, careful and realistic assessment of the probability of attaining remission must be assessed and discussed with the patient and family prior to initiation of any treatment. These patients are at high risk for spending their last days alone in the hospital, without visitors, and careful treatment planning, as well as goals of care discussions, are essential. Post-remission therapy for patients with a high probability for cure should follow established guidelines, but dose reductions to minimize long periods of neutropenia, growth factor support, and treatment delays should be considered based on individual patient circumstances. Allogeneic stem cell transplantation may be feasible under specific circumstances, but many centres are already reluctant to offer this option in the setting of COVID-19. For older patients with AML and ALL in remission, post-remission strategies should be tailored to avoid the need for multiple follow-up visits and to avoid neutropenia and transfusion dependence as much as possible.

Abbreviations used: chemo: chemotherapy; HMA: hypomethylating therapy; LDAC: low dose cytarabine; mut: mutant; Ph-: Philadelphia; R/R: relapsed/refractory.

*-enasidenib is not FDA approved in the front-line setting

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