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PERSPECTIVE

Management of patients with acute leukemia during the COVID-19 outbreak: practical guidelines from the acute leukemia working party of the European Society for Blood and Marrow Transplantation

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Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the novel coronavirus first detected in Wuhan, China. It causes an infection named coronavirus disease 2019 (COVID-19), and is now spreading worldwide. Currently, there are no approved treatment options in Europe and there is no available vaccine. Reports from China, Europe, and USA suggest a high mortality rate and stretched intensive care unit (ICU) capacity [1–3]. It has been found that the main risk factors for death are obesity, hypertension, diabetes, male gender, and older age. Moreover, Liang et al. reported that 1% of COVID-19 patients had a history of cancer, higher than that of the overall Chinese population (0.29%), with lung cancer being the most frequently found. Moreover, patients with cancer seemed to have a higher risk of severe events (ICU admission, need of assisted ventilation, death), reaching 39% versus 8% in those not suffering from a neoplasia [4]. Their study suggests that hospital admission and recurrent outpatient visits, inherent to cancer patients' management, are potential risk factors for SARS-CoV-2 infection. Another aspect which may probably be even more relevant in cancer patients is their inability to receive the necessary care in time, under the changed scenario of a viral pandemic management.

Scarce data are available on patients with hematological malignancies. Although some recommendations for

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Table 1 Recommendation for management of patients with acute leukemia during the COVID-19 outbreak.

General points			
● Screening for COVID-19 infection before initiating chemotherapy.			
● Cytogenetics and molecular biology should be awaited before starting treatment.			
● MRD molecular remission should be useful to consider omitting one cycle of consolidation.			
● Outpatient visits should be as much as possible deferred or substituted with telemedicine visites.			
AML	Patient FIT for intensive therapy	Favorable and intermediate cytogenetics risk	Induction: "3+7" should be considered
			Consolidation: cytarabine should be reduced to 1.5 mg/m^2
		Adverse cytogenetic risk	Consider if real chance of going to allo-HSCT exists
	Patient UNFIT for intensive therapy	Azacytidine or low dose of cytarabine in monotherapy, hydroxycarbamide, palliative care	
ALL	Maintaining recommended dose of glucocorticoids, especially during prephase, induction and consolidation.		
Allo-HSCT	Discuss indication for allo-HCT on case-by-case.		
	Nonurgent allo-HCT should be deferred as much as possible.		
	High-risk allo-HCT such as for refractory AL or patient with a high risk of NRM should not proceed.		

ALL acute lymphoblastic leukemia, *Allo-HSCT* allogeneic stem cell transplantation, *AML* acute myeloid leukemia, *MRD* measurable/minimal residual disease, *"3 + 7"* daunorubicin and cytarabine.

management of those with solid cancer and hematologic neoplasms have been published, more practical guidelines may be required for individual types of malignancies [5]. Particularly acute leukemia (AL) patients who suffer from a profound and long-lasting humoral and cellular immune deficiency [6], may benefit from tailored recommendations. Moreover, AL patients under intensive chemotherapy are at a high risk of requiring ICU care, and of mortality in case of complications [7]. Therefore, special attention should be paid to this specific population during the ongoing COVID-19 outbreak. Here, we summarize some recommendations to help AL patients' management in the current situation. The aims are to minimize the requirement for ICU admission, without compromising the patient's chance of being adequately treated.

General principle

Patients should be aware of their frailty to COVID-19 infection and specific hygiene measures and importance of social distancing should be explained.

All journeys outside the hematological department should be discussed and adapted for the situation. For example, it should be ensured that outpatient transportation services bring patients to the scheduled time of their consultation, in order to minimize the time spent in the waiting area. For those requiring oral or subcutaneous treatment administration, one needs to minimize hospital visits. Possible strategies for this are offering telephone or video consultations, cutting nonessential face-to-face follow-up, using home-delivery services for medicines, and using local services for blood tests.

Screening

Given that percentage of asymptomatic cases of COVID-19 can be high [8], all newly diagnosed patients with acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) should be screened for COVID-19 infection by PCR and high-resolution thoracic computerized tomography scan before initiating chemotherapy [9] (Table 1). The screening should be repeated before each course of chemotherapy. If positive, the decision to initiate or continue the treatment needs to made on a case-by-case basis.

Clinical research

In terms of clinical research, most clinical trials have been suspended during the pandemic. However, in some cases, clinical trials allow access to off-label drugs or combinations which can be highly beneficial. For patients already included in clinical trials, their participation should, in principle, continue. Nevertheless, the patients' safety must remain the priority and, similarly to the recommendation for those treated outside clinical trials, outpatient visits must be replaced by e-health assessment whenever possible. Furthermore, for those receiving oral treatment in the frame of a clinical trial, most clinical research organizations now organize home delivery of the investigated medication to

avoid hospital visits. Alternatively, hospital pharmacies should be authorized to deliver 2 or 3 months' worth of medication, rather than the standard one. Whenever possible, follow-up by e-health assessment should be preferred to avoid hospital visits.

Acute myeloid leukemia

Patients fit to receive intensive therapy

For patients with favorable or intermediate risk acute myeloid leukemia (AML) [10] who are fit to receive intensive chemotherapy, the standard "3 + 7" induction should be considered [11]. For AML with FLT3ITD mutation, midostaurin may be added to induction and consolidation as it prolongs OS and EFS [12].

For consolidation, the dose of cytarabine could be reduced to 1.5 g/m^2 instead of 3 g/m^2 for all patients. Indeed, prospective studies showed that consolidation, in association with anthracycline, with either intermediate or high dose of cytarabine, did not result in significant differences in the 5-year overall survival, whereas prolongation of neutropenia and higher transfusion demands were observed in the high dose cytarabine arm [13–15]. The use of G-CSF should be recommended after each cycle to reduce the duration of neutropenia. In patients who have negative measurable/minimal residual disease (MRD) after two cycles of chemotherapy, omission of the fourth cycle of consolidation should be discussed. In this case, the MRD should be very closely monitored, and maintenance therapy considered, especially in those cases.

Patients with an adverse cytogenetic risk should receive intensive therapy if a real chance of going to allogeneic stem cell transplantation exists.

In the case of acute promyelocyte leukemia (APL), chemotherapy should be initiated without delay. Patients with standard-risk APL (white blood cells $<10 \times 10^9$/L) should receive all-trans-retinoic acid (ATRA) and arsenic trioxide (ATO) as frontline following the standard guideline for APL management (i.e., avoidance of G-CSF for the risk of differentiation syndrome). For high-risk APL, induction should be performed with idarubicine, ATRA, and ATO.

Patients unfit to receive intensive therapy

Newly diagnosed patients with AML, who are unfit for intensive treatment, hypomethylating agents (HMA) or low-dose cytarabine monotherapy (LDAC) could be given in the case of no-proliferative disease. The addition of venetoclax should be discussed on a case-by-case basis, considering the positive impact on CR rate and OS in combination with HMA or LDAC, but also the risk of tumor lysis syndrome and myelosuppression (https://www.fda.gov/drugs/fda-approves-venetoclax-combination-aml-adults). After the first cycle with this combination, if medullary blast infiltration is <5%, dose adjustments, duration of venetoclax, and/or the use of G-CSF are recommended to avoid prolonged cytopenia. Taking into account age, comorbidities, and disease characteristics, patients could also be managed with supportive care and, possibly, eventually hydroxycarbamide.

For patients with relapsed or refractory AML, each team should carefully assess the risks and benefits of pursuing a curative approach on a case-by-case basis. Molecular targeted therapy (e.g., enasidenib, ivosidenib, sorafenib, gilteritinib, etc.) should be discussed, considering the rate of complete remission and the duration of the response that can be expected, with a view to postponing an intensive treatment or allogeneic hematopoietic cell transplantation (allo-HCT).

Acute lymphoblastic leukemia

In ALL, one major question is the use of glucocorticoids, as they remain essential components of ALL therapy. They appeared to be effective in reducing immunopathological damage [16], but there are concerns about their possible promotion of viral rebound and adverse events. Taking into account the major role of glucocorticoids in the treatment of ALL, and the paucity of information on their potential negative role in COVID-19 infections, physicians should use the recommended dose of glucocorticoids, especially during, the prephase, induction, and consolidation, with a major concern on preventing bacterial and fungal infections. The use of asparaginase should be carefully monitored considering the inherent risk of thrombotic complications of this drug, especially knowing that COVID-19 can lead to systemic coagulation disorders, and thrombotic complications. The use of blinatumomab or inotuzumab should not be delayed as their benefit in terms of survival has been established.

For Philadelphia-chromosome positive ALL, inhibitors of tyrosine kinase should be maintained considering their positive impact on OS and EFS.

Stem cell transplantation

The EBMT recommendations for management of allo-HCT during the COVID-19 outbreak have been recently published [17]. Nonurgent allo-HCT procedures should be deferred as much as possible. Due to the rapidly changing situation, access to a stem cell donor may be restricted by the fact that the donor may become infected at the harvest centers in the middle of a strained health care system, or by

travel restrictions across international borders. It is, therefore, strongly recommended to have secured stem cell product access, by cryopreserving the product before the start of conditioning. In situations when this is not possible, an alternative back-up donor should be identified. The impact of COVID-19 on a timely graft availability, on cellular therapy unit organization, and on ICU capacity should be considered for each patient with allo-HCT indication. It is necessary to highlight the yet unknown impact of COVID-19 infection on outcomes, when counseling patients on the benefits and risks of the allo-HCT procedure.

All patients who have a high risk of disease progression without allo-HCT should still be considered candidates for the procedure according to standard clinical practice. More controversial allo-HCT indications such as refractory AL, or patients with a high risk of non-relapse mortality should be avoided.

Overall, the management of patients with AL in the COVID-19 outbreak is a major challenge, as this hematological malignancy requires rapid treatment, which may result in a requirement for admission to an ICU unit. Physicians should therefore carefully balance the risk of COVID-19 infection itself against the benefit of antileukemic intensive treatment on a case-by-case basis, within the individual resources of each medical institution.

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Compliance with ethical standards

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