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.

Leukemia Research 92 (2020) 106353

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Correspondence

Acute leukemia in the time of COVID-19

The occurrence of the current COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an unparalleled challenge for the medical community and we must all rise to be of best service to the patients and our communities.

COVID-19's mortality rate is difficult to quantify as it varies with the characteristics of the considered population, notably patients' demographics and health-care resources. Mortality rises among older people and those with underlying conditions. The true impact of underlying immunosuppression is controversial. Initial reports from China suggested that patients with cancer had a higher risk of severe events (ICU admission, invasive ventilation or death) as compared to patients without cancer (39 % vs 8 %) [1]. Other data, based on post-transplantation cohorts, argue that, unlike common viral agents, coronaviruses do not cause more severe disease in immunosuppressed patients as the host innate immune response appears to be the main driver of lung tissue damage during infection [2].

With the present paper, we intend to delineate the possible impact of the current COVID-19 pandemic on patients with acute leukemia in terms of diagnosis, chemotherapy, bone marrow transplantation, maintenance treatments, supportive measures and targeted therapies, as well as ways to mitigate it.

1. Missed or delayed diagnosis

Most current recommendations for SARS-CoV-2 screening aim at limiting diagnostic testing to symptomatic, high-risk patients; others are instructed to self-isolation/quarantine. Full blood counts will be performed only in patients with signs of severity and confirmed SARS-CoV-2 infection. As 50–75 % of patients with acute leukemia are febrile at diagnosis [3], they are at high risk of missed or delayed diagnosis. This also applies to other oncological conditions such as primary mediastinal lymphoma or lung cancer, which often present with a cough with or without fever, symptoms that are likely to be considered trivial after a negative SARS-CoV-2 test.

2. Delay or deferral in chemotherapy

In addition to diagnosis delay, most patients may suffer from postponed chemotherapy, due to a shortage of isolation beds and blood products or the wish to avoid immunosuppressive treatments. Delay in chemotherapy initiation may negatively affect prognosis, particularly in young (< 60 years-old) patients with favorable- or intermediate-risk disease. Indeed, they could progress to high-risk disease following the acquisition of additional genetic anomalies, and hyperleukocytosis (or increased blasts count in MDS) [4,5]. More treatments may then be needed to achieve a deep complete remission before allogeneic stem cell transplantation.

3. Delay or deferral in hematopoietic stem cell transplantation (HSCT)

Hematopoietic stem cell transplantation is particularly affected by the COVID-19 pandemic, as both donor and recipient must be healthy for the procedure to be feasible and successful. Delays in the identification of compatible donors are expected and represent a particular challenge when siblings are abroad. The use of home swab kits is a vital resource to enable HLA testing, particularly when access to hospitals for family is restricted. All future donors need to be tested for COVID-19. These aspects have recently been reviewed in detail elsewhere [6,7]. Deferring allogeneic HSCT is recommended if possible; however, transmission from donor to recipient, either in the transfusion of blood products or cellular therapies, has not been yet reported [8]. Literature data on the impact of delayed transplant is ambiguous, obscured by differences in stem cell source and disease subtype. However, if a delay in transplant results in the reappearance of a significant minimal residual disease (MRD), a negative impact on survival is well established [9]. Furthermore, to ensure the possibility of the graft, EBMT strongly recommends securing stem cell product by freezing HSCs prior to conditioning, or to have a back-up donor [7]. It is not presently known if cryo-conservation would negatively impact engraftment success; the use of less favorable stem cell sources in case of optimal donor unavailability might.

4. Shortfall of blood products

Blood products shortage has already begun in most affected countries. Volunteer donors are desisting due to self-isolation, travel restriction and fear of virus transmission. Furthermore, cautious eviction of any symptomatic donor is applied; whereas conditions for safely resuming donation after a suspect or confirmed SARS-CoV-2 infection are uncertain. Cancellation of elective surgery, and to a lesser extent, cessation of activities with confinement, help to reduce the need for blood products. Nonetheless, most transfusion societies call for conservative transfusions policies in strict adherence to evidence-based guidelines for patient's blood management [10].

5. Interruption of maintenance therapy

Most treatment protocols for acute lymphoblastic leukemia (ALL) include up to two years of maintenance therapy [11]. As of March 19th, GRAALL-14 investigators instruct physicians to omit vincristine and prednisone in maintenance therapy whilst continuing 6-mercaptopurine and methotrexate. The impact on patient survival and relapse rate of dose-reduction and/or drug eviction is not known.

https://doi.org/10.1016/j.leukres.2020.106353
Received 24 March 2020
Available online 26 March 2020

6. Targeted therapies

Recently, the therapeutic landscape has evolved towards targeted therapies. They are used in addition to standard chemotherapy in fit patients, or as monotherapy in frail patients. The first breakthrough in AML therapy was represented by the approval of midostaurin for FLT3-mutated AML [12]. *Princeps* study, in addition to chemotherapy backbone, showed no difference in infectious complications or neutropenia [12]. The next-generation, more potent and selective FLT3 inhibitors quizartinib, crenolanib, gilteritinib are under clinical evaluation, showing similar profiles.

Isocitrate dehydrogenase (IDH) inhibitors, ivosidenib or enasidenib may be active, in AML with IDH1 or IDH2 mutations, respectively [13]. Both inhibitors act as differentiating agents with the occurrence, in 10–20 % of patients, of a differentiation syndrome, which requires prompt corticosteroid administration and often intensive care support. No information is yet available on the risk of severe respiratory failure in patients treated with these agents and exposed to SARS-CoV-2.

Similar severe respiratory adverse effects frequently occur in patients with promyelocytic leukemia treated with arsenic trioxide (ATO) and all-trans retinoic acid (ATRA), in the absence of chemotherapy. The association of chemotherapy and ATRA, as induction therapy, may be less risky during the pandemic, with the same survival benefit, than ATRA and ATO association [14,15]. ATO could be used in consolidation therapy to achieve a low relapse rate [15].

Importantly, ivosidenib and ATO can both prolong QTc increasing the risk for severe arrhythmia. Recently, non-randomized clinical trials reported a potential benefit for chloroquine on the prognosis of severe COVID-19. Other anti-viral drugs, such as remdesivir, are currently under study. As both of these drugs can also prolong QTc, clinicians should be aware of these potential severe adverse effects in COVID-19 patients treated with ATO, IDH inhibitor or any tyrosine kinase inhibitor (TKI) that may prolong QTc interval.

Tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib, and ponatinib) are currently included in the treatment of Philadelphia positive ALL, improving response rate and survival [16]. The addition of a TKI to chemotherapy and in maintenance after HSCT adds minimal infectious toxicity. However, the use of dasatinib in post-HSCT settings may increase the risk of CMV reactivation [17], which in addition to adverse effects, such as pleural effusions and lung infiltrates, demands cautious use in the COVID-19 pandemic.

Venetoclax is a highly selective, oral, B cell leukemia/ lymphoma 2 (BCL-2) inhibitor with demonstrated efficacy in AML patients either alone or in combination with 5-azacitidine or decitabine [18]. However, prolonged neutropenia with increased risks of bacterial or fungal lung infections, is observed in AML patients treated with venetoclax [19]. Since this combined treatment is most frequently indicated in elderly AML patients unfit for intensive therapy and allogeneic transplantation, the risk of respiratory failure may be highly increased if they contract COVID-19.

7. Investigational therapies and clinical studies

As illustrated by the waiving of maintenance therapy in the GRAAL-14 protocol, other ongoing clinical studies are likely to be affected by modification in therapy protocol, increased subject withdrawal, and excess SARS-CoV-2-related mortality. These elements will permanently impact studies, impairing the strength of the results and rendering their interpretation complex.

8. Prophylactic measures

Patients with recent or ongoing treatment for leukemia are to be protected from COVID-19, isolated at home, given the opportunity to work in home office whenever possible, and tested for SARS-CoV-2 infection following local or WHO guidelines. If possible, consultation appointments should be reduced to a vital minimum to avoid spread infection of SARS-CoV-2 infection in the hematology clinic.

Leukemia patients are immunocompromised and should have up-to-date, vaccination status, notably against *Streptococcus pneumoniae* [20]. Bacterial secondary infection can complicate viral infections, a situation well known in influenza, and plausible for COVID-19 infection. The benefit of vaccination against *Streptococcus pneumonia*, may be worth investigating in clinical trials.

In conclusion, COVID-19 will result in numerous casualties. Acute leukemia patients are at a higher risk of severe complications for several reasons. As the presenting symptoms can be similar, health care practitioners should imperatively keep the possibility of acute leukemia in mind. Intensive chemotherapies and transplantations may be waived, or delayed, due to resources shortages or in line with the recommendations of transplantation societies. Targeted therapies could potentially be used. However, physicians should be aware of their interactions with other drugs used to treat SARS-CoV-2-related infections/complications such as antibiotics, anti-viral drugs and various other drugs that prolong QTc or impact targeted-therapy pharmacokinetics. The points discussed above should be considered in all patients with acute leukemia in order to best tailor individual therapeutic decisions and, whenever possible, mitigate the impact of the pandemic.

Author contribution

SB and MG conceived the study, performed the research and literature review, and wrote the manuscript. JCK wrote the manuscript. OS supervised the study conception and wrote the manuscript. All authors read and approved the final manuscript.

Funding

No government or private funding contributed to this research.

Declaration of Competing Interest

The study authors have no conflicts of interest to disclose.

References

[1] W. Liang, W. Guan, R. Chen, et al., Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China, Lancet Oncol. (2020) 335–337.
[2] L. D'Antiga, Coronaviruses and immunosuppressed patients. The facts during the third epidemic, Liver Transpl. (2020).
[3] P.J. Burke, H.G. Braine, H.K. Rathbun, A.H. Owens Jr., The clinical significance and management of fever in acute myelocytic leukemia, Johns Hopkins Med. J. (1976) 1–12.
[4] H. Dohner, E. Estey, D. Grimwade, et al., Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel, Blood (2017) 424–447.
[5] P.L. Greenberg, H. Tuechler, J. Schanz, et al., Revised international prognostic scoring system for myelodysplastic syndromes, Blood (2012) 2454–2465.
[6] B. Dholaria, B.N. Savani, How do we plan hematopoietic cell transplant and cellular therapy with the looming COVID-19 threat? Br. J. Haematol. (2020).
[7] EBMT, Coronavirus Disease COVID-19: EBMT Recommendations (UPDATE MARCH 16, 2020), Available from: (2020) https://www.ebmt.org/ebmt/news/coronavirus-disease-covid-19-ebmt-recommendations-update-march-16-2020.
[8] L. Chang, Y. Yan, L. Wang, Coronavirus disease 2019: coronaviruses and blood safety, Transfus. Med. Rev. (2020).
[9] S.A. Buckley, B.L. Wood, M. Othus, et al., Minimal residual disease prior to allogeneic hematopoietic cell transplantation in acute myeloid leukemia: a meta-analysis, Haematologica (2017) 865–873.
[10] C.A. Schiffer, K. Bohlke, M. Delaney, et al., Platelet transfusion for patients with Cancer: American society of clinical oncology clinical practice guideline update, J. Clin. Oncol. (2018) 283–299.
[11] F. Huguet, S. Chevret, T. Leguay, et al., Intensified therapy of acute lymphoblastic leukemia in adults: report of the randomized GRAALL-2005 clinical trial, J. Clin. Oncol. (2018) 2514–2523.
[12] R.M. Stone, R.A. Larson, H. Dohner, Midostaurin in FLT3-mutated acute myeloid leukemia, N. Engl. J. Med. (2017) 1903.
[13] E.M. Stein, C.D. DiNardo, D.A. Pollyea, et al., Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia, Blood (2017) 722–731.
[14] F. Lo-Coco, G. Avvisati, M. Vignetti, et al., Retinoic acid and arsenic trioxide for

acute promyelocytic leukemia, N. Engl. J. Med. (2013) 111–121.
[15] L. Ades, X. Thomas, A.G. Bresler, et al., Arsenic trioxide is required in the treatment of newly diagnosed acute promyelocytic leukemia. Analysis of a randomized trial (APL 2006) by the French Belgian Swiss APL group, Haematologica (2018) 2033–2039.
[16] F. Gruber, S. Mustjoki, K. Porkka, Impact of tyrosine kinase inhibitors on patient outcomes in Philadelphia chromosome-positive acute lymphoblastic leukaemia, Br. J. Haematol. (2009) 581–597.
[17] D.P. Prestes, E. Arbona, A. Nevett-Fernandez, et al., Dasatinib use and risk of cytomegalovirus reactivation after allogeneic hematopoietic-cell transplantation, Clin. Infect. Dis. (2017) 510–513.
[18] C.D. DiNardo, K. Pratz, V. Pullarkat, et al., Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia, Blood (2019) 7–17.
[19] M. Reinwald, J.T. Silva, N.J. Mueller, et al., ESCMID study group for infections in compromised hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (Intracellular signaling pathways: tyrosine kinase and mTOR inhibitors), Clin. Microbiol. Infect. (2018) S53–S70.
[20] L.G. Rubin, M.J. Levin, P. Ljungman, et al., IDSA clinical practice guideline for vaccination of the immunocompromised host, Clin. Infect. Dis. 2014 (2013) e4s4–100.

Mathilde Gavillet*, Jeanette Carr Klappert, Olivier Spertini, Sabine Blum
Service and Central Laboratory of Hematology, Department of Oncology and Department of Laboratory Medicine and Pathology, Lausanne University Hospital (CHUV), Lausanne, Switzerland
E-mail address: mathilde.gavillet@chuv.ch (M. Gavillet).

* Corresponding author at: Service and Central Laboratory of Hematology, Department of Oncology and Department of Laboratory Medicine and Pathology, Lausanne University Hospital (CHUV), 1011, Lausanne, Switzerland.