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 120 (2022) 106901

Contents lists available at ScienceDirect

Leukemia Research

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

Correspondence

Characteristics and clinical outcomes of SARS-CoV-2 infection in adult patients with acute leukemia in France

ARTICLE INFO

Keywords
Acute myeloid leukemia
Acute lymphoid leukemia
SARS-CoV-2

Dear editor,

We read with interest papers from Palanques-Pastor et al. [1] and Mitrovic et al. [2] describing SARS-CoV-2 infections in acute myeloid leukemia (AML) in Spain and acute leukemia in Serbia during the first wave, respectively. Indeed, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) triggered a global pandemic in December 2019, and posed a threat since it causes damage to the respiratory tract [3]. France has been affected by four epidemic waves of decreasing intensity while their duration increased during the first three waves, leading to a number of severe forms and deaths that increased with each wave, except during the fourth. Moreover, the latter occurred after half of the population had received at least one dose of vaccine. In the first, second and third waves, 20,000, 25,000 and 44,000 people died in hospital, respectively. Moreover, between the peaks of the second and third waves, i.e. during the study period, the rate of infection remained high, whereas it had fallen dramatically between the first and second waves, and between the third and fourth waves [4]. Patients infected with SARS-CoV-2 have an adverse prognosis, particularly older male patients and those suffering from cardiovascular disease, chronic respiratory diseases, cancers, neurodegenerative diseases, and immunodeficiency [5]. Most patients with SARS-CoV-2 have common symptoms, such as fever, malaise, and influenza-like features [6]. However, some patients rapidly develop acute respiratory distress syndrome (ARDS) and multiple organ failure [7]. During the pandemic, a panel of experts published special recommendations for the management of adult patients with cancer [8] and specifically for those with acute lymphoid leukemia (ALL) and AML, including shifting care to an outpatient setting [9]. This implied a decrease in the intensity of treatments, even though such strategies could potentially mean that chances to treat are lost [10]. In this setting, our group proposed recommendations for caring for patients with acute leukemia in France (Supplementary data). However, as the pandemic dragged on, management of patients was shifted back to standard of care and to the precautions dictated by the health crisis.

The current multicenter observational ambispective study included adult ALL and AML patients aged $\geq$ 18 years with a diagnosis of SARS-CoV-2 during the second and third wave in France, which started in mid-August 2020 and finished at the end of June 2021, respectively [4]. Diagnoses were made by positive PCR or association of suggestive clinical features (such as fever, cough, dyspnea, chest pain, body aches, sore throat, rhinorrhea, headache, diarrhea/abdominal pain, loss of taste) and typical CT scan patterns (such as ground-glass opacities, consolidations including pseudo-nodular ones, combination of ground-glass opacities and consolidations, reticular pattern, and crazy-paving for the most typical ones) in the absence of a differential diagnosis [11]. Patients were reported in a specific registry (NCT04452604) by the French Innovative Leukemia Organization (FILO), the Acute Leukemia French Association (ALFA) and the Group for Research in Adult Acute Lymphoblastic Leukemia (GRAALL) between June 2020 and June 2021. The study was conducted according to the tenets of the Declaration of Helsinki and institutional review board approval (2217583v0) was received. Finally, 79 patients with acute leukemia from 20 hospitals were reported with SARS-CoV-2 infection, 74 (93.7%) with positive PCR and 5 additional patients diagnosed on a clinical presentation and typical chest-CT scan features without any differential diagnosis, including opportunistic infections such as *pneumocystis jiroveci* pneumonia. Main characteristics are described in Table 1. The median age was 57 years (IQR 41–65; range 18–89) and 57.0% were male. Patients' disease was ALL in 19.0% and AML in 81.0%, including 2 patients with acute promyelocytic leukemia. The median time between acute leukemia diagnosis and SARS-CoV-2 detection was 8 months (range 0–55). SARS-CoV-2 infection led to an acute leukemia diagnosis in 7 patients. Regarding period of care, 42 (53.2%) patients were in front line, 18 (22.8%) in second line and 9 (11.4%) beyond second line with 5 patients in best supportive care. The most frequent comorbidities were chronic respiratory diseases in 13 patients (16.5%), *diabetes mellitus* in 11 patients (13.9%), cardiovascular diseases in 9 patients (11.4%) and renal insufficiency in 5 patients (6.3%). Moreover, 13 (16.5%) patients had received corticosteroids in the past 30 days. Median body mass index (BMI) was 24 (IQR 22–28; range 14–40) and 16.3% of patients had a BMI$>$ 30. At the time of SARS-CoV-2 diagnosis, 11 patients (13.9%) had recently diagnosed acute leukemia, 18 (22.8%) were receiving induction or salvage therapy, 18 (22.8%) were in the consolidation period, 14 (17.7%) were in the post hematopoietic stem cell transplantation (HSCT) period, 8 (10.1%) were in remission without HSCT and free of treatment, and 8 (10.1%) were receiving non-intensive treatment such as

https://doi.org/10.1016/j.leukres.2022.106901
Received 10 December 2021; Received in revised form 8 June 2022; Accepted 12 June 2022
Available online 20 June 2022

Table 1
Characteristics at diagnosis of SARS-CoV-2 infection in 79 patients with acute leukemia.

	Total n = 79
Age at diagnosis (years)	
Median (IQR)	57 (41–65)
Range	18–89
Sex: n (%)	
Man	45 (57.0)
Woman	34 (43.0)
Subtype of acute leukemia: n (%)	
ALL	15 (19.0)
AML	64 (81.0)
Including APL	2 (2.5)
ANC at SARS-CoV-2 diagnosis ($\times 10^9$/L)	
Median (IQR)	1.9 (0.9–4.0)
Range	0.0–20.7
$< 0.5 \times 10^9$/L [n (%)] [missing = 8]	15 (21.1)
Lymphocytes at SARS-CoV-2 diagnosis ($\times 10^9$/L)	
Median (IQR)	0.9 (0.4–1.6)
Range	0.0–9.3
Period of care: n (%)	
First line	42 (53.2)
Second line	18 (22.8)
Beyond 2nd line	9 (11.4)
Best supportive care	5 (6.3)
Period of treatment: n (%)	
Diagnostic	11 (13.9)
Induction/Salvage	18 (22.8)
Consolidation/Maintenance	18 (22.8)
Post HSCT	14 (17.7)
Follow-up without HSCT	8 (10.1)
HMA	8 (10.1)
SARS-CoV-2 route of transmission: n (%)	
Nosocomial	4 (5.1)
Familial	14 (17.7)
Other	7 (8.9)
Unknown	54 (68.3)
Risk factors: n (%)	
Corticosteroids in the past 30 days	13 (16.5)
Cardiac comorbidity	9 (11.4)
Renal comorbidity	5 (6.3)
Pulmonary comorbidity	13 (16.5)
Diabetes	11 (13.9)

IQR, interquartile range; ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; ANC, absolute neutrophil count; HSCT, hematopoietic stem cell transplantation; HMA, hypomethylating agent

hypomethylating agents. Route of transmission of SARS-CoV-2 was family-related in 14 (17.7%) patients, nosocomial in 4 (5.1%) patients, identified contact non-familial non-nosocomial in 7 patients (8.9%) and unknown in 54 (68.3%) patients. Main signs and symptoms of SARS-CoV-2 were fever (57.0%), cough and/or dyspnea (48.1%) and 12.7% evolved to an ARDS. Among the whole cohort, 30.4% of patients had radiological patterns typical of SARS-CoV-2 infection. Overall, 15 (19%) patients were admitted to an intensive care unit (ICU) including 2 (2.5%) for septic shock. Twenty-three (29.1%) patients had an ARDS, requiring mechanical ventilation in 1 (1.3%) patient, non-invasive ventilation in 4 (5%) patients, and a nasal cannula in 18 (22.8%) patients. At SARS-CoV-2 diagnosis, median absolute lymphocytes and neutrophil counts were 0.79×10^9/L (IQR 0.31–1.25; range 0.04–9.30) and 2.70×10^9/L (IQR 0.38–3.83; range 0.00–15.94) *versus* 0.95×10^9/L (IQR 0.49–1.66; range 0.03–5.03) and 1.90×10^9/L (IQR 1.14–4.27; range 0.00–20.69) for patients requiring oxygen *versus* those who did not, respectively (p = 0.64 and 0.72). Apart from dexamethasone [12] and tocilizumab in certain situations, no therapeutic strategy was recommended as specific treatment during the study period [13], most patients did not receive any specific drug for SARS-CoV-2 infection (81.0%), 9 (11.5%) received corticosteroids including 6 associated with oxygen therapy, 3 (2.5%) received hydroxychloroquine and 4 (5%) patients received monoclonal antibodies (bamlanivimab/etesevimab or casirivimab/imdevimab), since the Omicron variant was not present in France at this period (0.1% in November 2021, 5 months after the end of the study period). After a median follow-up of patients alive 16.0 months from the diagnosis of acute leukemia and 4.8 months from the diagnosis of SARS-CoV-2 infection, 19 (24.0%) patients had died (Fig. 1). Nine (11.4%) deaths were related to SARS-CoV-2 infection: 5 patients were on frontline intensive induction, 1 on frontline azacitidine, 1 in the consolidation phase, 1 in the post HSCT period in complete remission, and 1 on best supportive care. The remaining 10 patients died from acute leukemia progression or complications unrelated to SARS-CoV-2 infection.

This study performed during the second and third waves in France revealed a moderate mortality rate in a cohort of 79 adult acute leukemia patients with SARS-CoV-2 infection. As previously discussed by Palanques et al., the overall mortality of SARS-CoV-2 in hematological malignancies showed great variability that could be linked to level of experience in SARS-CoV-2 infection, since we had a relatively low rate of SARS-CoV-2 attributable mortality during the second and third waves as compared to previous studies in Spain and Serbia during the first wave. However, it cannot be excluded that COVID infection may impact the dose intensity of treatment and carry a risk of subsequent relapse, especially when patients are transferred to an ICU. Larger studies are needed to answer this question. Moreover, the vaccination campaign started in France with mRNA vaccines during the course of the study on December 27th, 2020, [14,15]. This may have had an impact on mortality that is not measurable, especially in immunocompromised patients who had access to vaccination in April, 2021, i.e. for the last three months of recruitment of the study and with a single dose for most, making impossible to analyze the impact of vaccination on the survival of this cohort. The size of our cohort and the limited number of events precluded any analysis exploring risk factors for death, even though a previous study in AML identified dyspnea, ICU admission, ANC< 1000/ml, DDimer> 500 ng/ml as risk factors [1]. As compared with other studies in the general population and in an acute leukemia population, fever, dyspnea, and cough were the most prevalent symptoms.

The main limitation of this study is the voluntary declaration by the physicians, which may have induced a selection bias. Moreover, the study did not cover the whole of France and the incidence varied from one region to another, so no epidemiological conclusions can be drawn. To conclude, during the second and third waves, acute leukemia patients

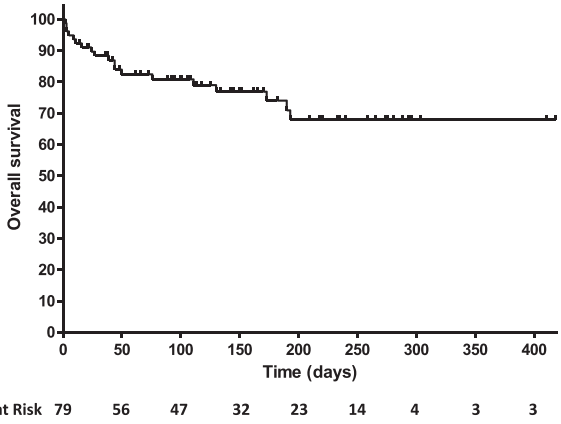

Fig. 1. Overall survival from SARS-CoV-2 diagnosis.

with SARS-CoV-2 infection had an 11.4% mortality rate related to the viral infection. This compared favorably to previous studies conducted in the first wave, probably due to a change in practice acquired by experience. Indeed, many of our patients did not receive any treatment, so the curative strategy was not involved. We think that management in an ICU such as non-invasive ventilation probably plays an important role. We are also unable to rule out the putative adverse effects of treatments used in other studies or other external factors specific to the countries in which these studies were conducted.

Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.leukres.2022.106901.

References

[1] T. Palanques-Pastor, J.E. Megías-Vericat, P. Martínez, J.L. López Lorenzo, J. Cornago Navascués, G. Rodriguez Macias, et al., Characteristics, clinical outcomes, and risk factors of SARS-COV-2 infection in adult acute myeloid leukemia patients: experience of the PETHEMA group, Leuk. Lymphoma (2021) 1–11.

[2] M. Mitrovic, N. Pantic, N. Sabljic, M. Vucic, Z. Bukumiric, M. Virijevic, et al., Acute leukemia and SARS-CoV-2 infection: clinical characteristics and risk factors for mortality, Leuk. Lymphoma 0 (0) (2021) 1–5.

[3] B. Hu, H. Guo, P. Zhou, Z.L. Shi, Characteristics of SARS-CoV-2 and COVID-19, Nat. Rev. Microbiol. 19 (3) (2021) 141–154.

[4] Santé publique France. Epidemiological update / N°72 / Situation on 16 July 2021.

[5] E.J. Williamson, A.J. Walker, K. Bhaskaran, S. Bacon, C. Bates, C.E. Morton, et al., Factors associated with COVID-19-related death using OpenSAFELY, Nature 584 (7821) (2020) 430–436.

[6] Y. Alimohamadi, M. Sepandi, M. Taghdir, H. Hosamirudsari, Determine the most common clinical symptoms in COVID-19 patients: a systematic review and meta-analysis, J. Prev. Med. Hyg. 61 (3) (2020) E304–E312.

[7] E. Barbeta, A. Motos, A. Torres, A. Ceccato, M. Ferrer, C. Cilloniz, et al., SARS-CoV-2–induced acute respiratory distress syndrome: pulmonary mechanics and gas-exchange abnormalities, Ann. Am. Thorac. Soc. 17 (9) (2020) 1164–1168.

[8] B. You, A. Ravaud, A. Canivet, G. Ganem, P. Giraud, R. Guimbaud, et al., The official French guidelines to protect patients with cancer against SARS-CoV-2 infection, Lancet Oncol. 21 (5) (2020) 619–621.

[9] E. Brissot, M. Labopin, F. Baron, A. Bazarbachi, G. Bug, F. Ciceri, et al., 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, Bone Marrow Transplant. 56 (3) (2021) 532–535.

[10] L. Wilde, A. Isidori, G. Keiffer, N. Palmisiano, M. Kasner, Caring for AML patients during the COVID-19 crisis: an American and Italian experience, Front. Oncol. 10 (2020) 1689.

[11] K. De Smet, D. De Smet, T. Ryckaert, E. Laridon, B. Heremans, R. Vandenbulcke, et al., Diagnostic performance of chest CT for SARS-CoV-2 infection in individuals with or without COVID-19 symptoms, Radiology 298 (1) (2021) E30–E37.

[12] RECOVERY Collaborative Group, P. Horby, W.S. Lim, J.R. Emberson, M. Mafham, J.L. Bell, et al., Dexamethasone in hospitalized patients with Covid-19, N. Engl. J. Med. 384 (8) (2021) 693–704.

[13] WHO Solidarity Trial Consortium, H. Pan, R. Peto, A.M. Henao-Restrepo, M. P. Preziosi, V. Sathiyamoorthy, et al., Repurposed antiviral drugs for covid-19 - interim WHO solidarity trial results, N. Engl. J. Med. 384 (6) (2021) 497–511.

[14] L.R. Baden, H.M. El Sahly, B. Essink, K. Kotloff, S. Frey, R. Novak, et al., Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine, N. Engl. J. Med. 384 (5) (2021) 403–416.

[15] F.P. Polack, S.J. Thomas, N. Kitchin, J. Absalon, A. Gurtman, S. Lockhart, et al., Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine, N. Engl. J. Med. 383 (27) (2020) 2603–2615.

Pierre-Yves Dumas[a,b,*,1], Sarah Bertoli[c,d,1], Caroline Bonmati[e], Martin Carre[f], Juliette Lambert[g], Mario Ojeda-Uribe[h], Sylvain Chantepie[i], Franciane Paul[j], Eric Jourdan[k], Stéphanie Haiat[l], Emmanuelle Tavernier[m], Pierre Peterlin[n], Jean-Pierre Marolleau[o], Kamel Laribi[p], Corentin Orvain[q,r], Quentin Cabrera[s], Pascal Turlure[t], Stéphane Girault[u], Marie Balsat[v], Marc Bernard[w], Marie-Christine Bene[x], Arnaud Pigneux[a,b], Hervé Dombret[y,z], Christian Récher[c,d,**]

[a] *CHU Bordeaux, Service d'Hématologie Clinique et de Thérapie Cellulaire, F-33000 Bordeaux, France*

[b] *BRIC (BoRdeaux Institute of onCology), UMR1312, INSERM, Univ. Bordeaux, F-33000 Bordeaux, France*

[c] *Service d'Hématologie, Centre Hospitalier Universitaire de Toulouse, Institut Universitaire du Cancer de Toulouse-Oncopole, Toulouse, France*

[d] *Cancer Research Center of Toulouse, UMR1037 INSERM, ERL5294 CNRS, Toulouse, France*

[e] *Service d'Hématologie, CHU Nancy Brabois, 54500 Vandoeuvre les Nancy, France*

[f] *Service d'Hématologie clinique, CHU Grenoble Alpes, 38700 La Tronche, France*

[g] *Service d'Hématologie, CH de Versailles, 78150 Le Chesnay, France*

[h] *GHRMSA, Hôpital E Muller, Service d'Hématologie Clinique et Unité de Thérapie Cellulaire, 68070 Mulhouse, France*

[i] *Service d'Hématologie, CHU de Caen, 14000 Caen, France*

[j] *Department d'Hématologie clinique, CHU de Montpellier, 34905 Montpellier, France*

[k] *Hématologie Clinique, Institut de Cancérologie du Gard - CHU de Nîmes, 30029 Nîmes, France*

[l] *Service d'Hématologie, CH Sud Francilien, 91106 Corbeil Essonnes, France*

[m] *Institut de Cancérologie Lucien Neuwirth, 42270 Saint-Priest-en-Jarez, France*

[n] *Service d'Hématologie clinique, Nantes University Hospital, Nantes, France*

[o] *Service d'Hématologie clinique et Thérapie cellulaire, CHU Amiens-Picardie, Amiens, France*

[p] *Department of Hematology, Centre Hospitalier Le Mans, Le Mans, France*

[q] *CHU d'Angers, Maladies du Sang, Angers, France*

[r] *Univ Angers, Inserm, CRCINA, F-49000 Angers, France*

[s] *CHU Réunion Sud - Site de Saint-Pierre, Saint-Pierre, France*

[t] *Service d'Hématologie et Thérapie Cellulaire du CHU Dupuytren, Limoges, France*

[u] *Service d'Hématologie, CH de Brive, Brive, France*

[v] *Service d'Hématologie, Hospices civils de Lyon, Lyon, France*

[w] *Service d'Hématologie clinique, CHU de Rennes, Rennes, France*

[x] *Service d'Hématologie Biologique, Nantes, France*

[y] *Hôpital Saint-Louis, Assistance Publique - Hôpitaux de Paris (AP-HP), Paris, France*

[z] *Institut de Recherche Saint-Louis, Université de Paris, Paris, France*

[*] Correspondence to: Hématologie Clinique et Thérapie Cellulaire, CHU Bordeaux, F-33000 Bordeaux, France.

[**] Correspondence to: Service d'Hématologie, Institut Universitaire du Cancer de Toulouse Oncopole, 1 avenue Irène Joliot-Curie, 31059 Toulouse Cedex 9, France.

E-mail addresses: pierre-yves.dumas@u-bordeaux.fr (P.-Y. Dumas), recher.christian@iuct-oncopole.fr (C. Récher).

[1] PYD and SB contributed equally to the work.