REVIEW

Should we screen patients with hematologic malignancies for COVID-19?

Elie Rassy[1†] [ID] | Rita-Maria Khoury-Abboud[1†] | Nathalie Ibrahim[1] | Tarek Assi[1] [ID] | Bachar Samra[2] | Colette Hanna[1] | Fadi El Karak[1] | Marwan Ghosn[1]

[1]Hematology and Oncology Department, Saint Joseph University, Lebanon

[2]Department of Leukemia, the University of Texas MD Anderson Cancer Center, Houston, Texas

Correspondence
Elie Rassy, MD, MSc, Hematology and Oncology Department, Saint Joseph University, Lebanon.
Email: elie.rassy@hotmail.com

Abstract

The coronavirus disease (COVID-19) pandemic has posed several challenges to the hematology community to re-organize the medical care of patients with hematologic malignances. Whereas the oncology societies favored a more or less conservative approach which considered the possibility of delaying treatment administration on a case-by-case basis, the hematology community guidelines were less stringent and recommended adequate individualized regimens. As countries are de-escalating the lockdown and the medical community is unable to foresee the end of the current outbreak will and whether the pandemic would eventually come back as a seasonal infection, there is interest in screening of patients with hematology malignancies with COVID-19 instead of limiting access to curative treatments. The rapidly accumulating knowledge about COVID-19 allows a better understanding of the diagnostic tools that may be potentially used in screening. Herein, we briefly review the pathophysiology of COVID-19, the rationale of screening of patients with hematologic malignancies, tools for screening, and available guidelines.

KEYWORDS
COVID-19, leukemia, lymphoma, multiple myeloma, polymerase chain reaction, screening

1 | INTRODUCTION

Just over 6 months after the first reports of the coronavirus disease (COVID-19) in Wuhan, China, the COVID-19 pandemic has become a serious pandemic leading to over three million cases which overloaded the healthcare systems and lead to an alarming figure of death numbers.[1] Since COVID-19 is a novel disease, guidance by scientific evidence is limited and impactful decisions are inevitably based on expert opinions that recommend isolation and quarantine given the highly infectious attribute of the virus. The early reports of patients with COVID-19 showed that higher rates of severe illness occurred in older patients (mean 63.1 vs 48.7 years; $P < 0.001$), those with a smoking history (22 vs 7%; $P = 0.032$), and those with cancer (39 vs 8%; $P = 0.0003$).[2,3] In the multivariate analysis, cancer was the highest

individual risk factor for severe events (OR = 5.4; 95% CI 1.8-16.2).[3] As a result, oncologists were challenged to reorganize the oncological care of patients with solid and hematological malignancies without compromising cancer outcomes.[4,5]

The understanding of the COVID-19 process in patients with solid malignancies is increasing, whereas the reports of patients with hematologic malignancies remain scarce. Patients with hematologic malignancies are at increased risk of COVID-19 due to the disease biology and associated therapy. Moreover, the immunocompromised patients with COVID-19 may also be at higher risk of superimposed bacterial or fungal pneumonia.[6(p19)] A cohort study on 128 hospitalized patients with hematologic malignancy did not show a higher rate of COVID-19 (10 vs 7%, $P = 0.322$) but reported a higher death rate (63 vs 0%, $P = 0.002$) compared to healthy healthcare providers.[7] A recent French observational study reporting on 48 patients with hematological malignancies tested for COVID-19 based on clinical suspicion.[8]

† Equal contribution

Twenty-five patients (of whom 20 had lymphoid malignancy including 10 multiple myeloma patients) tested positive with suggested possible nosocomial infection in 40%, acute respiratory distress syndrome occurred in 52%, and mortality rate at one month was 60%.[8] Consequently, patients with hematologic malignancies are more susceptible to severe forms of COVID-19. As we write this paper, countries are attempting to deescalate the confinement measures, which raise interest in the potential benefit of screening measures for COVID-19 in asymptomatic patients with hematologic malignancies.

2 | PATHOPHYSIOLOGY OF COVID-19

The currently available data on the COVID-19 physiopathology point out to a two-phase clinical course for the disease. The first phase occurs within the first days, consists of non-specific symptoms such as fever, fatigue, and diarrhea, and during which the lymphocyte and neutrophil counts seem to remain within the normal ranges.[9,10] The second phase occurs 7-14 days after symptom appearance, likely corresponding to a second viral lynching, characterized by a cytokine storm responsible for both severe interstitial lung inflammation and extrapulmonary multiorgan damage.[11] During this phase, there is a significant decrease in the B and T lymphocytes that is associated with adverse outcomes.[10,12] As a result, patients with hematologic malignancies may be particularly at a higher risk of developing COVID-19 for multiple reasons associated with profound and prolonged neutropenia,[13,14] lymphopenia,[15] the high-dose corticosteroids used in the majority of lymphoma and multiple myeloma regimens, and the frequent and long hospitalization for chemotherapy or transfusions.[16]

3 | RATIONALE FOR SCREENING

At this moment, it is not foreseeable when the current outbreak will end and whether the pandemic would eventually come back as a seasonal infection. To date, there are no evidence-based guidelines for the screening of patients with hematologic malignancies, and the recommended measures are based on previous experiences from other infectious diseases. The available data in cancer patients show that those undergoing chemotherapy are at higher risk of severe COVID-19.[4] Moreover, patients with hematologic malignancies have the additional impact of the acquired disease-related secondary immunodeficiency, the common use of corticosteroids in myeloma and lymphoma regimens, and the use of monoclonal antibodies. Other potential considerations for which clear impact has not been yet established include the use of tyrosine kinase inhibitors (TKI) and colony-stimulating factors.

4 | ACQUIRED DISEASE-RELATED SECONDARY IMMUNODEFICIENCY

The pathophysiology of acquired immunodeficiency in lymphoproliferative disorders is in part inherent to the disease itself.

Hematologic malignancies are accompanied by dysfunction in both cellular and humoral immunity, with B cell, T cell, NK cells, and dendritic-cell function, neutropenia due to marrow infiltration, and hypogammaglobulinemia.[17-19] In patients with CLL, the secretion of TGFβ and high IL2 levels are responsible for B-cell proliferation inhibition and T-helper cell downregulation, respectively, partly explaining the resulting various immune deficiencies.[18] In multiple myeloma, reduced levels of uninvolved immunoglobulins are a hallmark of the disease[20] but are not the sole actors of the acquired immunodeficiency in patients. Impaired dendritic cell and NK cell functions, as well as neutropenia and impaired lymphocyte function, are main contributors.[17,21]

5 | CORTICOSTEROIDS

Corticosteroids are a mainstay in the treatment of lymphomas and multiple myelomas; however, they predictably result in neutrophilic leucocytosis, smaller elevations in monocyte, and reductions in both lymphocytes and eosinophils. Moreover, corticosteroids reduce the ability of leukocytes to adhere to vascular endothelium and exit from the circulation as well as inhibit the phagocytic function, T cell functions, and immunoglobulin production by B cells.

The past experiences with previous coronaviruses show controversial outcomes that limit clear conclusions.[22] The corticosteroid use was associated with a delayed virus clearance from blood and respiratory tract for Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), respectively.[23,24] However, it was not associated with a statistically significant difference in mortality.[25]

The current evidence for the use of corticosteroids in patients with COVID-19 is limited to small retrospective case series. A retrospective study including 15 patients with COVID-19 pneumonia and requiring intensive care unit hospitalization, hydrocortisone (400 mg daily for a mean 9.5 days) was beneficial in terms of oxygenation but did not improve ICU mortality.[26] A larger retrospective cohort of 46 patients with severe COVID-19 pneumonia found no difference in mortality between the group of 26 patients who received methylprednisone (1-2 mg/kg/day for 5-7 days) and the group not receiving corticoid treatment. Patients treated with methylprednisone had a significantly shorter length of hospital stay, faster oxygenation improvement, and were less likely to require mechanical ventilation.[27] As such, the fifth version of the Chinese National Health Commission treatment scheme for COVID-19 pneumonia includes low-dose methylprednisone for 3-5 days in the list of adjuvant treatments.[28]

6 | TARGETED THERAPIES: MONOCLONAL ANTIBODIES AND TYROSINE KINASE INHIBITORS

The available evidence concerning the safety of monoclonal antibodies such as rituximab and ofatumumab (anti-CD20), inotuzumab ozogamycine (anti-CD22), brentuximab vedotin (anti-CD30), and

alemtuzumab (anti-CD52) is lacking in patients with/or at risk of COVID-19. However, the labels of these drugs report an increased risk of new viral infections or reactivations. Notably, lymphoma patients receiving rituximab whether alone or in combination with chemotherapy failed to produce effective protective antibody titers after receiving an Influenzae A vaccine.[29] Safety data concerning TKI are also inexistent with reports showing an off-target inhibition of kinases important in B-cell signaling, reduction of memory B-cell frequencies, and impairment of B cell responses in CML patients treated with TKI.[30] For instance, bruton TKI was associated with an impaired innate immune response as well as B- and T-cell functions [6(p19)]. However, a case series of six patients with Waldenstrom macroglobulinemia with COVID-19 did not report on the occurrence of severe cases which was attributed to the shift from an M1 – (inflammation promoters) to an M2 (inflammation inhibitors) – polarized macrophage response induced by ibrutinib.[31,32] Other tyrosine kinase inhibitors such as FLT3 inhibitors (approved in acute myeloid leukemia), PI3K inhibitors (approved in chronic lymphocytic leukemia), and BCL-2 inhibitors (approved in acute myeloid leukemia and chronic lymphocytic leukemia) are known to increase the risk of upper respiratory tract infection and should be avoided if possible.[33-35] Many other targeted therapies, such as proteasome inhibitors and immunomodulatory imide drugs (approved in multiple myeloma), IDH inhibitors (approved in acute myeloid leukemias), and BRAF inhibitors (approved in hairy cell leukemia), lack safety data for COVID-19.

7 | USE OF COLONY-STIMULATING FACTORS

The preclinical data on the use of colony-stimulating factors show a transient worsening of lymphopenia thought to be controlling viral infections.[5] Clinical evidence has reported cases of worsening lung injury upon the recovery of neutropenia following colony-stimulating factor use mainly due to immune reconstitution.[36,37] The available evidence concerning the impact of colony-stimulating factors in the particular case of patients with COVID-19 is limited to a higher level colony-stimulating factors in patients with severe COVID-19 suggesting a potential risk of inflammatory cytokine storm.[38] Nevertheless, the guidelines favor the systematic use of granulocyte colony-stimulating factors support to minimize neutropenia risk.[28,39]

8 | TOOLS FOR THE SCREENING OF COVID-19 IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES

The knowledge of the COVID-19 pathogenesis has led to a better understanding of the COVID-19 diagnostic tests. Three types of diagnostic tests are commonly in use including reverse transcriptase-polymerase chain reaction (RT-PCR), IgM and IgG enzyme-linked immunosorbent assay (ELISA), and chest CT scan.[40,41] The most commonly used and reliable test is RT-PCR which measures the viral RNA

load in the nasopharyngeal swab. The virus is detectable from day 1 on symptoms, peaks within the first week of symptom onset, and declines by week 3 before becoming undetectable. RT-PCR positivity declines more slowly in sputum and stool. A positive test usually presents less than 40 cycle threshold which is the number of replication cycles to produce a fluorescent signal; thus, it reflects the detection of viral DNA and does not necessarily indicate the presence of a viable virus.[42] On the other hand, false-negative results were attributed to inaccurate sampling techniques or inappropriate timing of sample collection.[40] Serological testing is mainly important in the diagnosis of patients who present after 2 weeks of symptom onset. The screening role of this tool encloses the testing of individuals that became immune to the virus, especially asymptomatic patients from highly endemic areas.[43,44] IgM and IgG seroconversion occur as early as the fourth day after symptom onset with higher levels in the second and third week of illness.[45] Last, chest imaging mainly using a chest CT scan was used is some centers to screening for COVID-19. It is widely available, easily performed, and allows a fast diagnosis.[19] Radiologically suggestive features include patchy ground-glass opacities in the two lower lobes bilaterally.[46] Although the available evidence supports a higher sensitivity for chest CT scan over RT-PCR, the American College of Radiology advised against the use of chest CT scan for screening and diagnostic purposes of COVID-19.[47,48]

The time course of RT-PCR testing positivity, seroconversion, and imaging findings is most probably delayed in patients with hematologic malignancies because of the inherent immunosuppression to their malignancy and to the effect of chemotherapy, targeted therapy, and immunotherapy (as discussed previously). Subsequently, it is elusive to consider that diagnostic testing presents the same pre- and post-test values during the same time course in patients with hematological malignancies. As these tools seem to present a low yield in detecting the virus in asymptomatic patients, it is common sense that their sensitivity would be lower in asymptomatic patients with hematological malignancies.[40]

9 | GUIDELINES FOR SCREENING COVID-19 IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES

Given the high transmissibility rate of COVID-19, it is the responsibility of cancer centers to adapt the treatment regimens to reduce the number of hospitalizations and to prevent anticancer treatment-induced complications of COVID-19.[5] Subsequently, there is more rationale for less intensive but effective therapies that require fewer and shorter hospitalizations over reducing patient access to cancer centers and using therapies with unproven benefit in curable diseases.[6] As a result, international hematology societies have issued their recommendations according to this perspective. Several screening steps have been adopted in several cancer centers in Europe such as calling patients 24 hours before hospital admission to screen for any COVID-19 symptoms and screening them upon arrival to the hospital for COVID-19 symptoms.[5] In the absence of any evocative signs

or symptoms, patients can be admitted to the hematology ward where healthcare workers can also be screened weekly for COVID-19. The initial evaluation should include exposure history, clinical examination, basic blood exams, and radiological evaluation preferably using a chest CT scan given that up to 75% of patients at risk of a delayed or missed diagnosis.[49-52] Testing of caregivers preferably using serologic testing, to ensure the protection of patients, and the presence of sufficient qualified personnel has also been suggested.[53]

The European Hematology Association (ESH) and American Hematology Association (ASH) issued screening guidelines in patients with acute leukemias.[39,54] The ESH guidelines recommend RT-PCR screening in newly diagnosed acute leukemia cases and before every treatment cycle even among asymptomatic patients.[54] The ASH guidelines were less stringent and considered RT-PCR testing all patients for COVID-19 before induction initiation for both acute myeloid and lymphoid leukemias.[39] Both guidelines did not issue any recommendation concerning the screening role of chest CT scan.[39,54] In patients with chronic myeloid leukemia, ASH did not suggest screening recommendations whereas ESH considered screening all newly diagnosed patients using RT-PCR is ideal but should be discussed depending on test availabilities.[39,54] In regard to lymphomas and multiple myeloma, the practices differ depending on the prevalence of COVID-19 and the availability of screening, but there is not any direct recommendation in this regard.[39,55,56] Some centers are beginning to screen patients beginning therapy, especially those with Hodgkin's lymphoma because of the concerns for bleomycin-induced lung toxicity which might be problematic during the pandemic.[39]

The European Society for Blood and Marrow Transplantation (ESBMT) and American Society for Transplantation and Cellular Therapy guidelines recommend screening all donors and patients within 72 hours before undergoing conditioning chemotherapy (after patient and donor home isolation for four and 2 weeks, respectively in the ESBMT guidelines).[57,58] Concerning CAR-T cell therapies, experts consider RT-PCR testing within 48-72 hours before apheresis and 48-72 hours before lymphodepleting chemotherapy. Repeat evaluation of RT-PCR within 72 hours of CAR-T cell infusion to detect interim COVID-19 and perform serologic testing for COVID-19 seroconversion once available.[59,60]

10 | CONCLUSIONS AND FUTURE PERSPECTIVES

The management of patients with hematologic malignancies during the COVID-19 pandemic may be challenging. By reviewing the pathogenesis of hematologic malignancies and the impact of chemotherapy and steroids, we have shown that patients with hematologic malignancies are undoubtedly a very vulnerable population to COVID-19. These patients present profound and prolonged neutropenia and lymphopenia, especially following intensive chemotherapy leading lo frequent and long hospitalizations. In addition, the available evidence, mainly some preclinical data, alludes to an immune dysregulation from targeted therapies that may increase the risk for COVID-19, but the clinical data are lacking. We believe that optimal preventive measures,

mainly social distancing, reduce the risk of COVID-19. However, the severity of COVID-19 in patients with hematologic malignancies remains considerable. Efforts to keep hematology departments COVID-19-free zones should be prioritized by screening the staff and the patients as well as limiting patient visits. We have previously proposed, in addition to other international societies, a screening strategy for COVID-19 according to a risk-level-based on management.[19] Unfortunately, solid scientific data are lacking on how to screen patients for COVID-19 with all the discussed limitations of RT-PCR and serologic testing. Whereas the international hematology community has shared and discussed expert opinions that provide the roadmap in the short term, the oncology community should close the large knowledge gap in screening for COVID-19 to enable evidence-based algorithms and ensure the safe management of patients with hematologic malignancies.

ORCID
Elie Rassy https://orcid.org/0000-0002-7906-0991
Tarek Assi https://orcid.org/0000-0002-5579-5264

REFERENCES

1. Coronavirus Update (Live): 3,515,743 Cases and 245,617 Deaths from COVID-19 Virus Pandemic - Worldometer. Accessed May 3, 2020. https://www.worldometers.info/coronavirus/

2. Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720. https://doi.org/10.1056/NEJMoa2002032.

3. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol*. 2020;21(3):335-337. https://doi.org/10.1016/S1470-2045(20)30096-6.

4. Rassy E, Khoury-Abboud R-M, Ibrahim N, Kattan C, Assi T, Kattan J. What the oncologist needs to know about COVID-19 infection in cancer patients. *Future Oncol* Published online. April 23, 2020;16:1153-1156. https://doi.org/10.2217/fon-2020-0312.

5. van de Haar J, Hoes LR, Coles CE, et al. Caring for patients with cancer in the COVID-19 era. *Nat Med*. 2020;26(5):665-671. https://doi.org/10.1038/s41591-020-0874-8.

6. Paul S, Rausch CR, Jain N, Kadia T, Ravandi F, DiNardo CD, Welch MA, Dabaja BS, Daver N, Garcia-Manero G, Wierda W, Pemmaraju N, Montalban Bravo G, Thompson P, Verstovsek S, Konopleva M, Kantarjian H, Jabbour E Treating Leukemia in the time of COVID-19. *Acta Haematol* 11, 2020:1–13. doi:https://doi.org/10.1159/000508199 Published Online May

7. He W, Chen L, Chen L, Yuan G, Fang Y, Chen W, Wu D, Liang B, Lu X, Ma Y, Li L, Wang H, Chen Z, Li Q, Gale RP COVID-19 in persons with haematological cancers. *Leukemia* 24, 2020:1–9. doi:https://doi.org/10.1038/s41375-020-0836-7 Published Online April

8. Malard F, Genthon A, Brissot E, et al. COVID-19 outcomes in patients with hematologic disease. *Bone Marrow Transplant*. 2020; 6:1-5. https://doi.org/10.1038/s41409-020-0931-4.

9. Zhang W, Du R-H, Li B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. *Emerg Microbes Infect*. 2020;9(1):386-389. https://doi.org/10.1080/22221751.2020.1729071.

10. Li T, Lu H, Zhang W. Clinical observation and management of COVID-19 patients. *Emerg Microbes Infect*. 2020;9(1):687-690. https://doi.org/10.1080/22221751.2020.1741327.

11. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'cytokine storm' in COVID-19. *J Infect* Published online. April 10, 2020;80: 607-613. https://doi.org/10.1016/j.jinf.2020.03.037.

12. Henry BM. COVID-19, ECMO, and lymphopenia: a word of caution. *Lancet Respir Med*. 2020;8(4):e24. https://doi.org/10.1016/S2213-2600(20)30119-3.

13. Sureda A, Domingo-Domenech E, Gautam A. Neutropenia during frontline treatment of advanced Hodgkin lymphoma: incidence, risk factors, and management. *Crit Rev Oncol Hematol*. 2019;138:1-5. https://doi.org/10.1016/j.critrevonc.2019.03.016.

14. Pettengell R, Schwenkglenks M, Leonard R, et al. Neutropenia occurrence and predictors of reduced chemotherapy delivery: results from the INC-EU prospective observational European neutropenia study. *Support Care Cancer off J Multinatl Assoc Support Care Cancer*. 2008; 16(11):1299-1309. https://doi.org/10.1007/s00520-008-0430-4.

15. Tadmor T, Polliack A. Lymphopenia a simple prognostic factor in lymphoma and other cancers: why not use it more as a guide? *Leuk Lymphoma*. 2010;51(10):1773-1774. https://doi.org/10.3109/10428194.2010.508825.

16. Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 transmission in patients with cancer at a tertiary Care Hospital in Wuhan, China. *JAMA Oncol* Published online. March 25, 2020;6:1108. https://doi.org/10.1001/jamaoncol.2020.0980.

17. Friman V, Winqvist O, Blimark C, Langerbeins P, Chapel H, Dhalla F. Secondary immunodeficiency in lymphoproliferative malignancies. *Hematol Oncol*. 2016;34(3):121-132. https://doi.org/10.1002/hon.2323.

18. Ravandi F, O'Brien S. Immune defects in patients with chronic lymphocytic leukemia. *Cancer Immunol Immunother CII*. 2006;55(2):197-209. https://doi.org/10.1007/s00262-005-0015-8.

19. Assi T, Samra B, Dercle L, et al. Screening strategies for COVID-19 in patients with hematologic malignancies. *Front Oncol*. 2020;10:1267. https://doi.org/10.3389/fonc.2020.01267.

20. Sanchez E, Gillespie A, Tang G, et al. Soluble B-cell maturation antigen mediates tumor-induced immune deficiency in multiple myeloma. *Clin Cancer Res off J Am Assoc Cancer Res*. 2016;22(13):3383-3397. https://doi.org/10.1158/1078-0432.CCR-15-2224.

21. Pratt G, Goodyear O, Moss P. Immunodeficiency and immunotherapy in multiple myeloma. *Br J Haematol*. 2007;138(5):563-579. https://doi.org/10.1111/j.1365-2141.2007.06705.x.

22. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet Lond Engl*. 2020;395(10223):473-475. https://doi.org/10.1016/S0140-6736(20)30317-2.

23. 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 off Publ Pan Am Soc Clin Virol*. 2004;31(4):304-309. https://doi.org/10.1016/j.jcv.2004.07.006.

24. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *Am J Respir Crit Care Med*. 2018;197(6):757-767. https://doi.org/10.1164/rccm.201706-1172OC.

25. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med*. 2006;3(9):e343. https://doi.org/10.1371/journal.pmed.0030343.

26. Zhou W, Liu Y, Tian D, et al. Potential benefits of precise corticosteroids therapy for severe 2019-nCoV pneumonia. *Signal Transduct Target Ther*. 2020;5(1):18. https://doi.org/10.1038/s41392-020-0127-9.

27. Wang Y, Jiang W, He Q, et al. A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia. *Signal Transduct Target Ther*. 2020;5:57. https://doi.org/10.1038/s41392-020-0158-2.

28. ESMO. ESMO management and treatment adapted recommendations in the COVID-19 era: Diffuse large B-cell lymphoma, Mantle cell lymphoma and Aggressive T-cell lymphomas. Accessed May 3, 2020. https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/haematological-malignancies-dlbcl-mcl-and-aggressive-t-cell-lymphoma-in-the-covid-19-era

29. Yri OE, Torfoss D, Hungnes O, et al. Rituximab blocks protective serologic response to influenza a (H1N1) 2009 vaccination in lymphoma patients during or within 6 months after treatment. *Blood*. 2011;118(26):6769-6771. https://doi.org/10.1182/blood-2011-08-372649.

30. de Lavallade H, Khoder A, Hart M, et al. Tyrosine kinase inhibitors impair B-cell immune responses in CML through off-target inhibition of kinases important for cell signaling. *Blood*. 2013;122(2):227-238. https://doi.org/10.1182/blood-2012-11-465039.

31. Fiorcari S, Maffei R, Audrito V, et al. Ibrutinib modifies the function of monocyte/macrophage population in chronic lymphocytic leukemia. *Oncotarget*. 2016;7(40):65968-65981. https://doi.org/10.18632/oncotarget.11782.

32. Treon SP, Castillo JJ, Skarbnik AP, et al. The BTK inhibitor ibrutinib may protect against pulmonary injury in COVID-19-infected patients. *Blood*. 2020;135(21):1912-1915. https://doi.org/10.1182/blood.2020006288.

33. Davids MS, Hallek M, Wierda W, et al. Comprehensive safety analysis of Venetoclax monotherapy for patients with relapsed/refractory chronic lymphocytic Leukemia. *Clin Cancer Res*. 2018;24(18):4371-4379. https://doi.org/10.1158/1078-0432.CCR-17-3761.

34. Brown JR, Byrd JC, Coutre SE, et al. Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110δ, for relapsed/refractory chronic lymphocytic leukemia. *Blood*. 2014;123(22):3390-3397. https://doi.org/10.1182/blood-2013-11-535047.

35. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid Leukemia with a FLT3 mutation. *N Engl J Med*. 2017;377(5):454-464. https://doi.org/10.1056/NEJMoa1614359.

36. Azoulay E, Attalah H, Yang K, et al. Exacerbation with granulocyte colony-stimulating factor of prior acute lung injury during neutropenia recovery in rats. *Crit Care Med*. 2003;31(1):157-165. https://doi.org/10.1097/00003246-200301000-00025.

37. Wiedermann FJ, Mittermayr M, Hoffmann G, Schobersberger W. Recombinant granulocyte colony-stimulating factor (G-CSF) in infectious diseases: still a debate. *Wien Klin Wochenschr*. 2001;113(3–4): 90-96.

38. Zhou Y, Fu B, Zheng X, et al. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. *Natl Sci Rev* Published online March. 2020;13:998-1002. https://doi.org/10.1093/nsr/nwaa041.

39. COVID-19 Resources. Accessed May 23, 2020. https://www.hematology.org:443/covid-19

40. Sethuraman N, Jeremiah SS, Ryo A. Interpreting diagnostic tests for SARS-CoV-2. *Jama* Published online. May 6, 2020;323:2249. https://doi.org/10.1001/jama.2020.8259.

41. Fang Y, Zhang H, Xie J, et al. Sensitivity of chest CT for COVID-19: comparison to RT-PCR. *Radiology*. Published online February 19, 2020;296:200432. https://doi.org/10.1148/radiol.2020200432

42. Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature* Published online. April 1, 2020;581:1-5. https://doi.org/10.1038/s41586-020-2196-x.

43. Place des tests sérologiques dans la stratégie de prise en charge de la maladie COVID-19. Haute Autorité de Santé. Accessed May 23, 2020. https://www.has-sante.fr/jcms/p_3179992/fr/place-des-tests-serologiques-dans-la-strategie-de-prise-en-charge-de-la-maladie-covid-19

44. CDC. Information for laboratories about coronavirus (COVID-19). *Centers for Disease Control and Prevention*. Published February 11, 2020. Accessed May 23, 2020. https://www.cdc.gov/coronavirus/2019-ncov/lab/serology-testing.html

45. Lou B, Li T, Zheng S, et al. Serology characteristics of SARS-CoV-2 infection since the exposure and post symptoms onset. *medRxiv*. Published online March 27, 2020:March 23, 2020.20041707. doi:https://doi.org/10.1101/2020.03.23.20041707

46. Raptis CA, Hammer MM, Short RG, et al. Chest CT and coronavirus disease (COVID-19): a critical review of the literature to date. *Am J Roentgenol*. 2020;26:1-4.

47. Bao C, Liu X, Zhang H, Li Y, Liu J. Coronavirus disease 2019 (COVID-19) CT findings: a systematic review and meta-analysis. *J Am Coll Radiol* Published online. March 25, 2020;17:701-709. https://doi.org/10.1016/j.jacr.2020.03.006.

48. American College of Radiology (ACR). *ACR Recommendations for the Use of Chest Radiography and Computed Tomography (CT) for Suspected COVID-19 Infection*. ACR Website. www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Recommendations-for-Chest-Radiography-and-CTfor-Suspected-COVID19-Infection. Updated 2020.

49. Burke PJ, Braine HG, Rathbun HK, Owens JA. The clinical significance and management of fever in acute myelocytic leukemia. *Johns Hopkins Med J*. 1976;139(1):1-12.

50. Hirsch HH, Martino R, Ward KN, Boeckh M, Einsele H, Ljungman P. Fourth European conference on infections in leukaemia (ECIL-4): guidelines for diagnosis and treatment of human respiratory syncytial virus, parainfluenza virus, metapneumovirus, rhinovirus, and coronavirus. *Clin Infect Dis*. 2013;56(2):258-266.

51. Dignan FL, Clark A, Aitken C, et al. BCSH/BSBMT/UKclinical virology network guideline: diagnosis and management of common respiratory viral infections in patients undergoing treatment for haematological malignancies or stem cell transplantation. *Br J Haematol*. 2016;173(3):380-393.

52. Gavillet M, Carr Klappert J, Spertini O, Blum S. Acute leukemia in the time of COVID-19. *Leuk Res*. 2020;92:106353. https://doi.org/10.1016/j.leukres.2020.106353.

53. ecancer. What to expect. Oncology's response to coronavirus in Italy - ecancer. *Accessed April*. 2020;27. http://ecancer.org/en/news/17495-what-to-expect-oncologys-response-to-coronavirus-in-italy.

54. EHA guidelines. *Recommendations for Specific Hematologic Malignancies*.https://ehaweb.org/covid-19/covid-19-recommendations/recommendations-for-specific-hematologic-malignancies/.

55. Al Saleh AS, Sher T, Gertz MA. Multiple myeloma in the time of COVID-19. *Acta Haematol*. 2020;17:1-7.

56. Mian H, Grant SJ, Engelhardt M, et al. Caring for older adults with multiple myeloma during the COVID-19 pandemic: perspective from the international forum for optimizing Care of Older Adults with myeloma. *J Geriatr Oncol Published Online*. 2020;11:764-768.

57. Styczynski JMM, Ljungman P.*EBMT Recommendation on: CORONAVIRUS DISEASE COVID-19: EBMT; 2020 [Updated 03/08/2020*.

58. *COVID-19 Resource Community - ASTCT. Accessed* May 23, 2020. https://www.astct.org/communities/public-home?CommunityKey=d3949d84-3440-45f4-8142-90ea05adb0e5

59. Bachanova V, Bishop MR, Dahi P, et al. Chimeric antigen receptor T cell therapy during the COVID-19 pandemic. *Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant* Published online. April 14, 2020;26:1239-1246. https://doi.org/10.1016/j.bbmt.2020.04.008.

60. Frey NV, Shaw PA, Hexner EO, et al. Optimizing chimeric antigen receptor T-cell therapy for adults with acute lymphoblastic leukemia. *J Clin Oncol*. 2020;38(5):415-422.