patient was pyrexial for 13 days, longer than the median of 10 (95% CI 8–12 days) reported elsewhere.[7] Factors in this patient's disease course may be underlying malignancy, significant exposure to cytotoxic chemotherapy, waning levels of pembrolizumab with dissipation of immune activation, a change of viral-directed therapy from LPV/r to HCQ and azithromycin or the natural progression of a new infectious disease. We highlight that this report is limited, being a single case. The patient had a number of factors associated with favourable outcome in COVID-19, younger age, female sex, and no other significant comorbidities like diabetes mellitus, obesity, or cardiovascular disease.

We would also like to highlight potential dilemma of an acute respiratory presentation in the current climate in patients taking PD-1 inhibitors. Pembrolizumab-induced pneumonitis, although a rare complication, carries a high mortality. While prompt administration of corticosteroids is necessary in the case of pembrolizumab-induced pneumonitis, this strategy may result in worse outcomes in patients affected by COVID-19.[8] A careful risk *versus* benefit assessment using a multidisciplinary approach is advised in these cases.

Funding information

The authors received no funding for the preparation of this manuscript.

Conflicts of interest

The authors declare to have no conflicts of interest to declare regarding the present work.

Consent

Patient consent was obtained for submission.

Author contributions

All authors contributed to the writing of this article.

Brendan O'Kelly[1]
Padraig McGettrick[1,3]
Daniel Angelov[2]
Michael Fay[2]
Tara McGinty[1,3]
Aoife G. Cotter[1,3]
Gerard Sheehan[1]
John S. Lambert[1,4]

[1]*Infectious Diseases Department, Mater Misericordiae University Hospital,* [2]*Haematology Department, Mater Misericordiae University Hospital,* [3]*Centre for Experimental Pathogen Host Research, University College Dublin and* [4]*School of Medicine, University College Dublin, Dublin, Ireland.*
E-mail: okellybr@tcd.ie

Keywords: checkpoint inhibitor, COVID-19, haematological malignancy, Hodgkin lymphoma, pembrolizumab, SARS-CoV-2

First published online 25 May 2020
doi: 10.1111/bjh.16798

References

1. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncology*. 2020;**21**:335–7.
2. Yu J, Ouyang W, Chua MLK, Xie C. Transmission in patients with cancer at a tertiary care hospital in Wuhan, China. *JAMA Oncol*. 2020. https://doi.org/10.1001/jamaoncol.2020.0980 [Epub ahead of print].
3. Choi J, Lee SY. Clinical characteristics and treatment of immune-related adverse events of immune checkpoint inhibitors. *Immune Network*. 2020;**20**:e9.
4. Del Castillo M, Romero FA, Argüello E, Kyi C, Postow MA, Redelman-Sidi G. The spectrum of serious infections among patients receiving immune checkpoint blockade for the treatment of melanoma. *Clinical Infectious Diseases*. 2016;**63**:1490–3.
5. Bersanelli M, Scala S, Affanni P, Veronesi L, Colucci ME, Banna GL, et al. Immunological insights on influenza infection and vaccination during immune checkpoint blockade in cancer patients. *Immunotherapy*. 2020;**12**:105–10.
6. Bersanelli M. Controversies about COVID-19 and anticancer treatment with immune checkpoint inhibitors. *Immunotherapy*. 2020. https://doi.org/10.2217/imt-2020-0067 [Epub ahead of print].
7. Chen J, Qi T, Liu L, Ling Y, Qian Z, Li T, et al. Clinical progression of patients with COVID-19 in Shanghai, China. *J Infect*. 2020;**80**:e1–e6.
8. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet*. 2020;**395**:473–5.

Philadelphia-positive acute lymphoblastic leukaemia (ALL) in Italy during the COVID-19 pandemic: a Campus ALL study

The recent spread of the coronavirus disease 2019 (COVID-19) infection has raised important questions within the haematology community on how best to manage and treat patients with haematological malignancies, particularly acute leukaemias. Italy has witnessed a dramatic rise in infections and death rates, which has affected, in particular, certain

areas of the most populated northern regions of the country (Lombardia, Veneto, Piemonte, Emilia Romagna). Within the nationwide Campus Acute Lymphoblastic Leukaemia (ALL) programme, in the last week of March, we sent a questionnaire addressing different issues related to the management of adult patients with ALL during the COVID-19 pandemic to 40 haematology centres located across the country. Twenty-four centres were based in Northern Italy (i.e. north of Rome), which has been most affected by the COVID-19 outbreak. So far, in the large majority of centres throughout the country, patients are screened prior to being admitted as inpatients, while this procedure is not routinely carried in most centres for outpatients, unless they present with symptoms potentially ascribable to the COVID-19 infection. In the present analysis, we focussed on Philadelphia-positive (Ph+) ALL, for which a second questionnaire was sent at the beginning of April. The interest in Ph+ ALL relates to its incidence, which increases with age accounting for approximately 50% of B-lineage ALL patients aged >50 years,[1] to the key role played by tyrosine kinase inhibitors (TKIs) and to the approach taken in Italy to treat adult Ph+ ALL. We obtained information on 267 adult patients with Ph+ ALLs currently managed at these centres. A total of 128 patients came from the four regions most affected by COVID-19; 62·2% of the patients were aged 18–60 years, and 37·8% were >60 years (20 >70 years, seven >80 years). To date, only one patient has tested COVID-19 positive. Because of pneumonitis and cellulitis, this patient was transferred to the intensive care unit (ICU) and from there to a department of internal medicine, which developed a COVID-19 outbreak, where he got infected. He is now well and asymptomatic. Only one patient proved symptomatic but tested negative. This information refers to all Ph+ ALL patients managed at the different centres.

The obvious question is how Ph+ ALL patients should be treated during the COVID-19 pandemic, which is complicated by the shortage of available ICU beds. In Italy in the last 15 years all adult ALL patients enrolled in the GIMEMA (Gruppo Italiano Malattie EMatologiche dell'Adulto) nationwide trials are evaluated centrally within 1 week from diagnosis during the steroid pre-phase. Patients with Ph+ ALL are treated in induction with a TKI plus steroids, with no systemic chemotherapy.[2] The only chemotherapy is represented by the intrathecal central nervous system prophylaxis. This approach has enabled complete remission rates of 94–100%, with virtually no deaths in induction, including patients aged >70 years.[2-4] In the last GIMEMA LAL2116 front-line protocol for adult Ph+ ALL [European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) number 2016-001083-11; ClinicalTrials.gov identifier: NTC02744768), with no upper age limit, patients have been treated with an induction based on dasatinib and steroids followed by a consolidation with the bispecific monoclonal antibody, blinatumomab, and further dasatinib.[5] To date, despite the current pandemic, patients have continued their treatment as planned. The central molecular monitoring of minimal residual disease has to date been guaranteed for all patients enrolled in the LAL2116 protocol, where the primary endpoint of treatment is the rate of complete molecular responses after the dasatinib/blinatumomab induction-consolidation. The only problem mentioned by some centres has been the difficulty in allocating patients to an allogeneic stem-cell transplant when required.

This analysis allows some considerations. The likelihood of a symptomatic COVID-19 infection in adult Ph+ ALL patients in Italy is close to zero, even in the most affected regions and despite the high rate of elderly individuals in this subgroup of ALL. The strategy of inducing into remission Ph+ ALL patients with a TKI plus steroids and without systemic chemotherapy seems to be of further added value in this dramatic setting. Many patients can reduce their hospitalisation days and can be mainly managed at home with a TKI. In our dasatinib protocols,[4,5] the induction lasts for 3 months. Even at a peak of the COVID-19 pandemic this 'soft' approach allows an effective and mostly home-based treatment. In addition, a chemotherapy-free consolidation approach, in our case with blinatumomab, can further reduce the post-remission hospitalisation.

The possibility that TKIs may play a role in protecting patients from the COVID-19 infection has been suggested pre-clinically[6] and a randomised study aimed at verifying the effect of imatinib in preventing pulmonary vascular leak in patients with severe COVID-19 is ongoing (EudraCT 2020-001236-10). Finally, an immunosuppressed status may not be a risk factor for COVID-19 adverse events,[7-9] as documented also in patients with liver transplants.[10]

It becomes increasingly important that patients with Ph+ ALL are rapidly identified at diagnosis and we once again advocate for a chemotherapy-free induction strategy. It is worth recalling that with dasatinib (and steroids) alone, 20–25% of patients can become molecularly negative[4,5] and that with the addition of blinatumomab this increases to 60%.[5] Under such a TKI-based strategy in Italy, adult Ph+ ALL of all ages could continue to be managed as before even during the outbreak and peak of the COVID-19 epidemic.

Acknowledgements

The authors wish to thank all the Campus ALL colleagues who provided data of their patients. Partly supported by Associazione Italiana Ricerca sul Cancro (AIRC), Special 5 × 1000 Program Metastases (21198), Milan (Italy) to RF.

Robin Foà[1]
Massimiliano Bonifacio[2]
Sabina Chiaretti[1]
Antonio Curti[3]
Anna Candoni[4]
Carmen Fava[5]
Maria Ciccone[6]

Giovanni Pizzolo[2]
Felicetto Ferrara[7]
[1]*Department of Translational and Precision Medicine, Sapienza University of Rome, Rome,* [2]*Department of Medicine, Section of Hematology, University of Verona, Verona,* [3]*Department of Hematology/Oncology "L. and A. Seràgnoli", University of Bologna, Bologna,* [4]*Azienda Sanitaria Universitaria Integrata di Udine, Udine,* [5]*Dipartimento di Scienze Cliniche e Biologiche, Università di Torino, Torino,* [6]*Department of Medical Sciences, Section of Hematology, University of Ferrara, Ferrara and* [7]*Division of Haematology and Stem Cell Transplantation Unit, Cardarelli Hospital, Napoli, Italy.*
E-mail: rfoa@bce.uniroma1.it

Keywords: COVID-19, Ph+ acute lymphoblastic leukaemia, tyrosine kinase inhibitors, management

First published online 14 June 2020
doi: 10.1111/bjh.16758

References

1. Chiaretti S, Vitale A, Cazzaniga G, Orlando SM, Silvestri D, Fazi, P, et al. Clinico-biological features of 5202 patients with acute lymphoblastic leukemia enrolled in the Italian AIEOP and GIMEMA protocols and stratified in age cohorts. *Haematologica*. 2013;**98**:1702–10.
2. Chiaretti S, Foà R. Management of adult Ph-positive acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program*. 2015;**2015**:406–13.
3. Vignetti M, Fazi P, Cimino G, Martinelli G, Di Raimondo F,Ferrara, F, et al. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol. *Blood*. 2007;**109**:3676–8.
4. Foà R, Vitale A, Vignetti M, Meloni G, Guarini A, De Propris, M, et al. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood*. 2011;**118**:6521–8.
5. Chiaretti S, Bassan R, Vitale A, Elia L, Piciocchi A, Puzzolo, C, et al. Dasatinib-blinatumomab combination for the front-line treatment of adult Ph+ ALL patients. Updated results of the GIMEMA LAL2116 D-Alba trial. *Blood*. 2019;**134**:740.
6. Nguyen DD, Gao K, Chen J, Wang R, Wei GW. Potentially highly potent drugs for 2019-nCoV. *bioRxiv*. 2020 [Epub ahead of print]. DOI: https://doi.org/10.1101/2020.02.05.936013.
7. Sarzi-Puttini P, Giorgi V, Sirotti S, Marotto D, Ardizzone S, Rizzardini, G, et al. COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome? *Clin Exp Rheumatol*. 2020;**38**:337–42.
8. Ferro F, Elefante E, Baldini C, Bartolani E, Puxeddu I, Talarico, R, et al. COVID-19: the new challenge for rheumatologists. *Clin Exp Rheumatol*. 2020;**38**:175–80.
9. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson, JJ COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;**395**:1033–4.
10. D'Antiga L. Coronaviruses and immunosuppressed patients. The facts during the third epidemic. *Liver Transpl*. 2020 [Epub ahead of print]. https://doi.org/10.1002/lt.25756.

SARS-CoV-2 infection anxieties and general population restrictions delay diagnosis and treatment of acute haematological malignancies

Acute leukaemias remain a very serious group of diseases often associated with major complications and substantial morbidity and mortality. Diagnosis and appropriate anti-leukaemic therapy together with any needed supportive therapy should be started as soon as possible. Any delay in diagnosis or treatment increases the probability of additional medical complications, including hyperleukocytosis with related leukostasis, tumour lysis syndrome and coagulopathies or myeloid extramedullary masses. In addition, patients with acute leukaemias are highly susceptible to infectious diseases unrelated to the disease itself, to treatment side effects and to individual risk factors.

- Severe infectious diseases, such as the plague, cholera and yellow fever, have been the cause of pandemics throughout recorded human history including in the past two centuries. For example, 14 international conferences were held between 1851 and 1938 to coordinate responses to major infectious outbreaks. Restrictive measurements including quarantine and social distancing measures were established and guidelines for sanitary management of contagious disease were developed.[1] These conferences aimed to maximize protection from disease with minimum effects on trade and travel.

From its emergence in China, SARS-CoV-2 virus has spread all around the world, representing the most serious health, economic and social crisis of the new millennium.[2] Since the beginning of the SARS-CoV-2 epidemic in Italy, the Italian Government has implemented several restrictive measures to contain the spread of infection. Among these measures, the lockdown implemented on 9 March 2020 has a positive impact on disease propagation, in particular in the central and southern regions of Italy.[3] Unfortunately, the