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.

Challenges in lung cancer therapy during the COVID-19 pandemic

Dr P Marazzi/SPL

Published Online
April 9, 2020
https://doi.org/10.1016/
S2213-2600(20)30170-3

Coronavirus disease 2019 (COVID-19), caused by the newly identified strain of the coronavirus family severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly evolved into a worldwide pandemic and caused a public health emergency of major international concern.[1,2] As a result, a profound reorganisation of hospital wards and clinical activities is happening worldwide to deal with the increasing number of COVID-19-positive patients who require hospitalisation and intensive care support.[3] This comprehensive reallocation of health resources is of particular concern in patients such as those with underlying chronic diseases, including cancer.

The prioritisation of health support towards patients with COVID-19 is raising apprehension within the medical oncology community, in which physicians are increasingly being forced to select which patients should receive anticancer therapy on the basis of who is most likely to have a positive outcome.[4] In this context, the threat of COVID-19 infection might also factor into decision making—a role which could possibly be lessened by knowledge of the COVID-19 status of patients suitable for anticancer therapy.[4] This already dismal scenario seems to be even more severe for patients with lung cancer because of the high risk of interference of COVID-19 with their effective diagnostic and therapeutic management by treating physicians.

Clinical manifestations of COVID-19 range from asymptomatic, to mild symptoms (such as cold, fever, cough, or other non-specific signs), to severe pneumonia leading to acute respiratory distress syndrome, which occurs in 17–29% of infected individuals.[2] Mortality due to COVID-19 has been reported in about 3% of COVID-19-positive patients in the Chinese population,[5] while higher mortality rates are being reported in Italy,[6] which is, after the USA, currently the country with the second highest number of confirmed COVID-19 cases worldwide.[7]

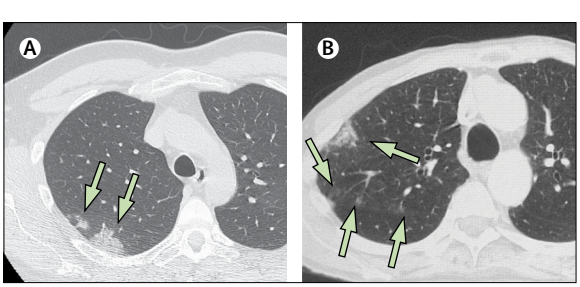

Figure: **CT scans of pneumonia due to COVID-19 and immune checkpoint inhibitor therapy**
(A) Axial lung image (without intravenous contrast) of 49-year-old man with COVID-19, showing two sub-solid areas in the upper right lobe (arrows). (B) Axial lung image (without intravenous contrast) of an immune checkpoint inhibitor-treated 76-year-old man with metastatic melanoma, showing a sub-solid area and ground-glass opacities with a rounded morphology in the upper right lobe (arrows). COVID-19=coronavirus disease 2019.

In the early phase of COVID-19-induced pneumonia, the main CT findings include multifocal peripheral and basal ground-glass opacities, crazy paving patterns, traction bronchiectasis, and air bronchogram signs. A progressive transition to consolidation, together with pleural effusion, extensive small lung nodules, irregular interlobular or septal thickening, and adenopathies, characterise the more advanced phase of the disease.[8,9] These radiological manifestations can overlap with CT findings that are often found in patients with lung cancer upon disease progression or onset of concomitant pneumonia due to overlapping opportunistic infections. Regarding clinical manifestations, the worsening of pulmonary symptoms during lung cancer progression can be similar to that typical of COVID-19, adding further complexity to the thorough assessment of the course of disease in lung cancer patients. Together, these similarities can pose a major challenge to clinicians in distinguishing lung cancer evolution from a potential COVID-19 super-infection on the basis of radiological and clinical evidence, and, importantly, these specific conditions require very different therapeutic approaches.

Adding further complexity to this scenario, pneumonitis can also be induced by immune checkpoint inhibitor therapy, an effective and widely used standard-of-care treatment for lung cancer in various treatment lines and settings.[10] Immune checkpoint inhibitor-related pneumonitis has been reported in about 2% of cancer patients,[11] with a seemingly higher incidence in patients with lung cancer.[12] Similar to COVID-19 infection, the clinical symptoms of immune checkpoint inhibitor-induced pneumonitis are often not specific, consisting mainly of cough (or its worsening), chest

pain, dyspnoea, and fever. Additionally, CT assessment of immune checkpoint inhibitor-related pneumonitis shows radiological findings similar to those typical of COVID-19-induced pneumonia (figure), thus hindering discrimination between the two clinical entities. Similarly, tyrosine kinase inhibitors can induce radiological patterns of interstitial-like pneumonitis, which develops in 4% of patients with epidermal growth factor receptor-mutant lung cancer treated with osimertinib.[13]

In this scenario, standard chemotherapy does not seem to represent a suitable or potentially safer alternative to immune checkpoint inhibitor therapy—neither for treating physicians who want to avoid the overlapping immune checkpoint inhibitor-related and COVID-19-related radiological and clinical changes, or for patients who are unsuitable for immune checkpoint inhibitor therapy. First, combinations of chemotherapies and immunotherapies have shown the best efficacy and represent the standard of care in a large group of patients without oncogene-driven lung cancer and without high PD-L1 expression in tumour cells. Second, the development of chemotherapy-associated pneumonitis is known to occur in up to 16% of treated patients,[14] and cytotoxic chemotherapy has immunosuppressive activity.[15] Notably, administration of chemotherapy within the month preceding COVID-19 diagnosis has been shown to be associated with a higher risk of severe infection-related complications.[16]

The clinical and biological aggressiveness of lung malignancies clearly does not allow for anticancer therapy to be withheld or postponed. Thus, while awaiting specific evidence-based guidelines, the comprehensive management of patients with lung cancer during the COVID-19 pandemic should involve specific and careful attention to their clinical and radiological pulmonary signs, more so than for patients with other types of tumour. From a practical viewpoint, it seems reasonable to suggest that patients with lung cancer undergo systematic testing for SARS-CoV-2 at the beginning of treatment and whenever it is deemed necessary by the treating physician in the course of therapy. This strategy might become more feasible with the increasing availability and progressive use of real-time PCR assays that can provide COVID-19 status results within an hour.[17] Furthermore, the availability of laboratory IgM or IgG testing to evaluate the exposure and immunity to SARS-CoV-2 infection will be helpful when the COVID-19 pandemic begins to decline. Allocating resources for these methodological approaches to patients with lung cancer should facilitate the most appropriate clinical management by multidisciplinary lung cancer care teams.

LC has served as consultant or advisor to Bristol-Myers Squibb and Merck Sharp and Dohme. SP has received education grants, provided consultation, attended advisory boards, or provided lectures for AbbVie, Amgen, AstraZeneca, Bayer, Biocartis, Bioinvent, Blueprint Medicines, Boehringer-Ingelheim, Bristol-Myers Squibb, Clovis, Daiichi Sankyo, Debiopharm, Eli Lilly, F Hoffmann-La Roche, Foundation Medicine, Illumina, Janssen, Merck Sharp and Dohme, Merck Serono, Merrimack, Novartis, Pharma Mar, Pfizer, Regeneron, Sanofi, Seattle Genetics, Takeda, and Vaccibody, from whom she has received honoraria (all fees to institution). J-CS was employee for AstraZeneca from September, 2017, to December, 2019, and has shares in Gritstone. AMDG has served as a consultant or advisor to Incyte, Pierre Fabre, GlaxoSmithKline and Bristol-Myers Squibb, Merck Sharp Dohme, and Sanofi. FB has served as a consultant, advisor, or lecturer for AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, Eli Lilly Oncology, F Hoffmann-La Roche, Novartis, Merck, Merck Sharp and Dohme, Pierre Fabre, Pfizer, and Takeda. CG has received honoraria as consultant or advisor or speaker bureau member for AstraZeneca, Bristol-Myers Squibb, F Hoffmann-La Roche, and Merck Sharp and Dohme, and has received funds (to organisation) from Merck Sharp and Dohme. MR has served as a consultant and provided lectures for Amgen, AbbVie, AstraZeneca, Bristol-Myers Squibb, Boehringer-Ingelheim, Celgene, Merck, Merck Sharp and Dohme, Novartis, Pfizer, Roche, Samsung. MM has served as a consultant or advisor to Roche, Bristol-Myers Squibb, Merck Sharp and Dohme, Incyte, AstraZeneca, Amgen, Pierre Fabre, Eli Lilly, GlaxoSmithKline, Sciclone, Sanofi, Alfasigma, and Merck Serono. AC, MA, and VV declare no competing interests. We thanks Nicholas Landini of the Diagnostic Radiology Department of Ca' Foncello Regional Hospital (Treviso, Italy), for providing the CT scan images of a COVID-19-positive patient with pneumonia. NR declares no competing interests.

*Luana Calabrò, Solange Peters, Jean-Charles Soria, Anna Maria Di Giacomo, Fabrice Barlesi, Alessia Covre, Maresa Altomonte, Virginia Vegni, Cesare Gridelli, Martin Reck, Naiyer Rizvi, *Michele Maio*
mmaiocro@gmail.com

Center for Immuno-Oncology, Medical Oncology and Immunotherapy, Department of Oncology, University Hospital of Siena, 53100 Siena, Italy (LC, AMDG, AC, MA, MM); NIBIT Foundation Onlus, Siena, Italy (MM); Centre Hospitalier Universitaire Vaudois, Oncology Department, Lausanne University, Lausanne, Switzerland (SP); Gustave Roussy Cancer Campus, Villejuif, France (J-CS, FB); Université Paris-Saclay, Orsay, France (J-CS); Aix Marseille University, CNRS, INSERM, CRCM, Marseille, France (FB); Radiology Unit, Rugani Hospital, Siena, Italy (VV); Division of Medical Oncology, S.G. Moscati Hospital, Avellino, Italy (CG); LungenClinic, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany (MR); and Division of Hematology/Oncology, Department of Medicine, Columbia University, New York, NY, USA (NR)

1 Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* 2020; **20:** 425–34.
2 Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395:** 507–13.
3 Emanuel EJ, Persad G, Upshur R, et al. Fair allocation of scarce medical resources in the time of COVID-19. *N Engl J Med* 2020; published online March 23. DOI:10.1056/NEJMsb2005114.
4 Ueda M, Martins R, Hendrie PC, et al. Managing cancer care during the COVID-19 pandemic: agility and collaboration toward a common goal. *J Natl Compr Canc Netw* 2020; published online March 20. DOI:10.6004/jnccn.2020.7560.
5 Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet* 2020; **395:** 470–73.

6 Ministero della Salute. Novel coronavirus. http://www.salute.gov.it/nuovocoronavirus. (accessed April 2, 2020; in Italian).

7 Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): cases in the US. https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html (accessed April 2, 2020).

8 Bernheim A, Mei X, Huang M, et al. Chest CT findings in coronavirus disease-19 (COVID-19): relationship to duration of infection. *Radiology* 2020; published online Feb 20. DOI:10.1148/radiol.2020200463.

9 Pan F, Ye T, Sun P, et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. *Radiology* 2020; published online Feb 13: 10.1148/radiol.2020200370.

10 Remon J, Passiglia F, Ahn MJ, et al. Immune checkpoint inhibitors in thoracic malignancies: review of the existing evidence by an IASLC expert panel and recommendations. *J Thorac Oncol* 2020; published online March 13. DOI:10.1016/j.jtho.2020.03.006.

11 Nishino M, Ramaiya NH, Awad MM, et al. PD-1 inhibitor-related pneumonitis in advanced cancer patients: Radiographic patterns and clinical course. *Clin Cancer Res* 2016; **22:** 6051–60.

12 Delaunay M, Prévot G, Collot S, Guilleminault L, Didier A, Mazières J. Management of pulmonary toxicity associated with immune checkpoint inhibitors. *Eur Respir Rev* 2019; **28:** 190012.

13 Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small cell lung cancer. *N Engl J Med* 2018; **378:** 113–25.

14 Magee DE, Hird AE, Klaassen Z, et al. Adverse event profile for immunotherapy agents compared with chemotherapy in solid organ tumors: a systematic review and meta-analysis of randomized clinical trials. *Ann Oncol* 2020; **31:** 50–60.

15 Lehne G, Lote K. Pulmonary toxicity of cytotoxic and immunosuppressive agents. A review. *Acta Oncol* 1990; **29:** 113–24.

16 Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020; **21:** 335–37.

17 US Food & Drug Administration. Emergency use authorizations: in vitro diagnostics EUAs. https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations (accessed April 2, 2020).

Immunomodulation in COVID-19

Published Online
May 4, 2020
https://doi.org/10.1016/S2213-2600(20)30226-5

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to spread globally despite unprecedented social isolation and restrictions resulting in widespread economic decline. More than 3·2 million people have been infected and more than 230 000 of them have died. To date, no treatments have been definitively shown to be effective; however, a multipronged approach to mitigate transmission, morbidity, and mortality is ongoing.[1] While upstream prevention strategies such as vaccination are ideal, these strategies are unlikely to be available in time to address current clinical need. Instead, fast-tracking of drug development and repurposing of approved drugs[2] has facilitated and expedited clinical trials that might hasten effective therapeutics. Many of these drugs act, at least in part, to directly limit viral replication. By contrast, the use of interleukin-6 (IL-6) inhibition might have benefits by controlling the pathological immune response to the virus. Here, we expand on the theoretical basis of IL-6 inhibition and propose potential benefits from other immunomodulators that could, in theory, prove more efficacious.

For the latter phase of convalescence, hospitalised patients with COVID-19 can develop a syndrome of dysregulated and systemic immune overactivation described as a cytokine storm or hyperinflammatory syndrome that worsens acute respiratory distress syndrome and can lead to multisystem organ failure.[3–5] The scarce systematic data available have shown an association between ferritin, lactate dehydrogenase, IL-6, IL-1, d-dimer, and C-reactive protein and severe disease.[6–8] If this group can be identified before decompensation, early and aggressive immunomodulatory treatment might prevent need for intubation and extracorporeal membrane oxygenation. To date, observational studies[9] suggest a possible benefit but results of placebo-controlled randomised clinical trials are not yet available. Given the methodological limitations of existing studies, more evidence is needed. With the rapidly expanding number of critically ill patients, there is an urgent need to identify multiple putative biological targets. While IL-6 inhibition attenuates key aspects of the cytokine cascade, we posit other immune targets of inhibition to be considered and their potential to be more efficacious in the setting of COVID-19, specifically IL-1 inhibitors and Janus kinase (JAK) inhibitors.

Observational data show overlapping clinical features in severe COVID-19 with macrophage activating syndrome (MAS) and secondary haemophagocytic lymphohistiocytosis (HLH).[7] Hyperinflammatory states, specifically in fatal cases, highlight why consideration of HLH and MAS therapies are warranted. Furthermore, the pathogenesis underlying SARS-CoV-2 involves several key pathways that can be manipulated, and use of these therapies can mitigate the propagation of an overdriven inflammatory response (figure).[10] Although few patients with severe COVID-19 would meet criteria for MAS, it is proposed that they are on the spectrum and that MAS or secondary HLH therapies might be of benefit. IL-1 inhibitors are key therapeutics in the treatment of