COMMENT

Repurposing anticancer drugs for COVID-19-induced inflammation, immune dysfunction, and coagulopathy

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Three cardinal manifestations of neoplasia, namely inflammation, immune dysfunction, and coagulopathy are also seen in patients with severe SARS-CoV-2 infection, providing a biological rationale for testing selected anticancer drugs for their ability to control the symptoms and/or modify the course of COVID-19.

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MAIN

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has resulted in >5.9 million infections and 363,000 deaths as of 29 May 2020.

Although SARS-CoV-2 primarily infects the upper and lower respiratory tract, it can also affect the intestine, heart, liver, kidney, brain, and other organs. Among 1482 patients with confirmed COVID-19 in the United States, the most common signs and symptoms included cough (86%), fever or chills (85%), shortness of breath (80%), diarrhoea (26%), and nausea or vomiting (24%).

No treatment has shown convincing benefit yet for patients with COVID-19, but the Food and Drug Administration (FDA) recently granted emergency use authorisation for the repurposed investigational anti-Ebola drug remdesivir for COVID-19. Repurposing refers to the use of approved or investigational drugs beyond the scope of the original medical indication. Repurposing, not only of antiviral drugs but also those used in other diseases such as cancer, is worthy of consideration to shorten timelines for identifying an effective therapy for COVID-19.

Inflammation, immune dysfunction, and coagulopathy in COVID-19 and cancer

Although many of the details regarding the SARS-CoV-2 virus and its effects on humans are yet to be elucidated, a few interesting commonalities between the pathophysiology of COVID-19 and cancer are beginning to emerge. Notably, both these diseases exhibit the triad of inflammation, immune dysregulation, and coagulopathy.

The intracellular entry of SARS-CoV-2 is facilitated by the angiotensin-converting enzyme 2 receptor, which is expressed in type II alveolar cells of lung, cholangiocytes, oesophageal keratinocytes, ileal and colonic enterocytes, myocardial cells, renal proximal tubule cells, bladder urothelial cells, fibroblasts, endothelial cells, oral mucosal epithelium, and haematopoietic cells, including monocytes and macrophages. Crosstalk between monocytes, macrophages, and other antigen-presenting cells could explain some features of inflammation and immune dysfunction in severe COVID-19.

Dysregulated immune responses in critically ill patients with COVID-19 is reflected by lymphopenia, affecting mostly CD4+ T cells, including effector, memory, and regulatory T cells, and decreased IFN-γ expression in CD4+ T cells. Exhaustion of cytotoxic T lymphocytes, activation of macrophages, and a low human leukocyte antigen-DR expression on CD4+ monocytes has been noted in patients with COVID-19.

A marked pro-coagulant tendency has been observed in patients with severe COVID-19 and may present as microvascular or macrovascular thrombosis affecting the lung, heart, intestine, kidney, or other organs, with elevated D-dimer, fibrin/fibrinogen degradation products, fibrinogen level, or disseminated

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Table 1. Approved anticancer agents being tested in patients with COVID-19.

| Class                        | Agent         | Mechanism                                                                 | US FDA approval for cancer type or cancer symptom                                                                 | COVID-19 trial identifier |
|------------------------------|---------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|---------------------------|
| Interleukin (IL) inhibitor   | Tocilizumab   | Competitive blockade of the IL-6 binding site                            | Cytokine release syndrome                                                                                     | NCT04361552, NCT04313795 |
|                              | Siltuximab    | Prevents the binding of IL-6 to both soluble and membrane-bound IL-6 receptors | Multicentric Castleman's disease                                                                           | NCT04329650, NCT04300638 |
| Corticosteroid               | Prednisolone  | Anti-inflammatory and immunosuppressive                                   | Lymphomas, leukaemias                                                                                       | NCT04273321, NCT04263402 |
|                              | Dexamethasone | Anti-inflammatory and immunosuppressive                                   | Lymphomas, leukaemias                                                                                       | NCT04325061, NCT04327401 |
|                              | Hydrocortisone| Anti-inflammatory and immunosuppressive                                   | Palliation of leukaemias and lymphomas                                                                     | NCT04348305, NCT02735707 |
| Anticoagulant                | Enoxaparin    | Binds to antithrombin to irreversibly inactivate clotting factor Xα       | Prophylaxis of deep vein thrombosis in abdominal surgery or medical patients with severely restricted mobility during acute illness | NCT04345848, NCT04359277 |
| Interferon                   | IFN-α         | Immunomodulator                                                           | Hairy cell leukaemia, melanoma, follicular lymphoma                                                          | NCT04320238, NCT04254874 |
| Checkpoint inhibitor         | Nivolumab     | Blocks programmed death-1 receptor                                       | Melanoma, non-small cell lung cancer, renal cell cancer, Hodgkin's lymphoma, squamous cell cancer of the head and neck, urothelial cancer, colorectal cancer, hepatocellular cancer | NCT04333914, NCT04365208 |
|                              | Pembrolizumab | Blocks programmed death-1 receptor                                       | Melanoma, non-small cell lung cancer, head and neck squamous cell cancer, Hodgkin's lymphoma, primary mediaslial large B-cell lymphoma, urothelial cancer, microsatellite instability-high cancer, gastric cancer, cervical cancer, hepatocellular cancer, Merkel cell cancer | NCT04335305 |
| Anti-vascular endothelial growth factor | Bevacizumab | Binds circulating vascular endothelial growth factor | Colorectal cancer, non-squamous non-small cell lung cancer, glioblastoma, Renal cell cancer | NCT04305106, NCT04275414 |
| Kinase inhibitor             | Ruxolitinib   | Inhibits Janus kinase (JAK) 1 and 2                                       | Primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis | NCT04339858, NCT04354714 |
|                              | Imatinib      | Inhibits bcr-abl tyrosine kinase                                           | Chronic myeloid leukaemia, acute lymphoblastic leukaemia, gastrointestinal stromal tumours                  | NCT04355713, NCT04346147 |
|                              | Acalabrutinib | Inhibits Bruton’s tyrosine kinase                                          | Mantle cell lymphoma                                                                                        | NCT04346199 |
|                              | Duvelisib     | Inhibits phosphoinositide-3 kinase δ and γ                               | Chronic lymphocytic leukaemia, small lymphocytic lymphoma, follicular lymphoma                              | NCT04372602 |
| Immunomodulator              | Thalidomide   | Immunomodulatory, antiangiogenic, and modulation of tumour necrosis factor-α | Multiple myeloma                                                                                            | NCT04273529, NCT04273581 |
|                              | Lenalidomide  | Immunomodulatory, antiangiogenic                                           | Multiple myeloma                                                                                            | NCT04361643 |
| Nuclear export inhibitor     | Selinexor     | Binds to exportin 1                                                       | Multiple myeloma                                                                                            | NCT043555676, NCT04349099 |
| Granulocyte, macrophage-colony stimulating factor | Sargramostim | Haematopoietic growth factor and immune modulator                        | Shorten neutrophil recovery after induction chemotherapy                                                    | NCT04326920 |
| Retinoid                     | Isotretinoin  | Induces apoptosis                                                          | High-risk neuroblastoma                                                                                     | NCT04361422, NCT043553180 |
| Interleukin                  | IL-2          | Expansion and activation of regulatory T cells                            | Melanoma, renal cell cancer                                                                                 | NCT04357444 |
| Cytotoxic chemotherapy       | Etoposide     | Topoisomerase II inhibitor                                                | Testicular tumours, small cell lung cancer                                                                  | NCT04356690 |
|                              | Methotrexate  | Antimetabolite, inhibits dihydrofolate reductase                          | Breast cancer, epidermoid cancers of the head and neck, cutaneous T cell lymphoma, squamous cell lung cancer, small cell lung cancer, non-Hodgkin's lymphoma | NCT04352465 |
| Radiotherapy                 | External beam radiation | DNA damage                                            | Multiple cancer types                                                                                      | NCT04366791 |

A maximum of two representative trials have been included for a given agent.

intravascular coagulation. Out of 184 patients admitted with COVID-19, 31% had thrombotic complications despite standard thromboprophylaxis, with pulmonary embolism being the most common event. A multifactorial process termed as microvascular COVID-19 lung vessel obstructive thromboinflammatory syndrome could play a role in the rapid evolution of multiorgan injury. Important manifestations of severe COVID-19 infection are shared with neoplasia, namely inflammation, immune dysfunction, and coagulopathy. Inflammation has been long known to play a central role in cancer pathogenesis, and in 2011, Hanahan and Weinberg labelled tumour-promoting inflammation as a hallmark of cancer. Chronic inflammation is both a risk factor and a consequence of cancer. Innate cytotoxic cells as well as the adaptive immune cells are dysfunctional in cancer, allowing neoplastic cells to avoid detection and elimination by the immune system. Thromboembolism is recognised as a leading cause of death in patients with cancer, with the risk of venous thrombosis increased several fold.
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Repurposing anticancer drugs against COVID-19

The clinical development of a new drug or vaccine usually takes several years. Given the urgent need to quickly find efficacious therapies for COVID-19, existing drugs are being repurposed and tested in clinical trials, potentially substantially accelerating development timelines. The pharmaceutical industry, contract research organisations (CROs), and academia have spent decades developing drugs for cancer-induced inflammation, immune dysfunction, and coagulopathy; given that this triad is also seen in patients affected by COVID-19, it is reasonable to consider testing selected anticancer agents in a rational manner against this viral illness.

Several drugs that have been approved for a cancer indication by the US FDA are now in COVID-19 clinical trials (see Table 1). These include the anti-interleukin tocilizumab, which competitively blocks the IL-6-binding site and is approved for multicentric Castleman’s disease; corticosteroids like prednisolone and dexamethasone, which are used in lymphomas and leukaemias; enoxaparin used for the prophylaxis of deep vein thrombosis in patients with cancer; bevacizumab, which binds vascular endothelial growth factor and is approved for several solid cancers; immunomodulators like thalidomide and lenalidomide used for multiple myeloma; IFN-α used for hairy cell leukaemia, myeloproliferative neoplasms, melanoma, and follicular lymphoma; checkpoint inhibitors like the programmed death receptor-1 inhibitors nivolumab and pembrolizumab that are approved for several types of cancers; tyrosine kinase inhibitors like imatinib, duvelisib, and acalabrutinib; antimetabolites; topoisomerase II inhibitors; and even radiotherapy. In addition, CAR therapeutic agents, approved for some haematological cancers, is also being studied in COVID-19-infected patients (clinicaltrials.gov identifier NCT04324996).

Finally, there are several drugs and cell and gene therapies in clinical development for a cancer indication that are now being tested for efficacy against COVID-19.

Preliminary safety and efficacy data are currently available for only a few of these approved anticancer agents currently being tested in patients with COVID-19. In the CORIMUNO-19 trial, 129 patients with moderate or severe COVID-19 pneumonia received either tocilizumab plus standard treatment or standard treatment alone. The primary efficacy endpoint (a combination of the need for ventilation or death on day 14) was achieved in a significantly lower proportion of patients in the tocilizumab arm according to a pre-publication announcement.15 Preliminary data for 21 of the 25 patients treated with siltuximab in the SiSCO trial showed that 76% of the patients had either stabilised or had demonstrated improved disease symptoms at the interim analysis.15 In an observational study of 2773 hospitalised COVID-19 patients, the in-hospital mortality among 786 patients who received systemic anticoagulation was 22.5% with a median survival of 21 days, compared with 22.8% and 14 days, respectively, in patients who did not receive anticoagulation.16 Eleven of the 31 patients in a retrospective review of patients with COVID-19 had received corticosteroid treatment, and no association was observed between corticosteroid treatment and virus clearance time (hazard ratio [HR], 1.26; 95% confidence interval [CI], 0.58–2.74), hospital length of stay (HR, 0.77; 95% CI, 0.33–1.78) or duration of symptoms (HR, 0.86; 95% CI, 0.40–1.83).17 There are emerging and sometimes conflicting data regarding the use of corticosteroids in patients with COVID-19, including potential adverse effects on viral clearance and replication. Two patients who tested positive for the SARS-CoV-2 infection during the course of treatment with checkpoint inhibitors were reported to have recovered from the viral infection and will resume anticancer therapy.18

Anti-cytokines are among the most common classes of agents being tested for COVID-19. On the one hand, neutrophils and macrophages may secrete IL-6, TNF, IL-17A, granulocyte macrophage colony stimulating factor (CSF), and granulocyte CSF, all of which tip the scales in favour of hyperinflammation; on the other hand, regulatory T cells, natural killer cells, and B cells secrete IL-15, IFN-α, -β, and -γ, IL-12, and 1L-21, which aid viral clearance and hence need to be spared.19 There is, therefore, a need for caution in selecting which precise components of the cytokine system to target therapeutically in patients with COVID-19. For this reason, the National Cancer Institute has recently discouraged the use of JAK inhibitors in patients with COVID-19 since this class of agents has a broad anti-inflammatory action.20

Conclusion

The COVID-19 pandemic has swiftly swept through the world, resulting in huge morbidity and significant mortality. Until an effective vaccine or antiviral specifically against SARS-CoV-2 is developed, there will remain a need for new and effective treatment for patients with severe COVID-19. Repurposed drugs targeting inflammation, immune dysfunction, and coagulopathy, including a variety of anticancer agents, should be evaluated systematically through well-designed and often novel trial platforms. The COVID-19 pandemic is an opportunity for the pharmaceutical and CRO industry, academia, and clinicians across a range of specialties to develop new models for the rapid evaluation of innovative therapeutic approaches.

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M.L., K.S.S., and M.R. conceptualised the manuscript; all authors provided significant inputs; K.S.S. wrote the manuscript; all authors reviewed, edited, and approved the manuscript.

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