UJEMI PERSPECTIVES

Pathophysiology of Lung Cancer in the Context of SARS-CoV-2 Variants of Concern

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SUMMARY Many retrospective cohort studies have revealed that patients with cancer are at increased risk of severe complications and mortality from COVID-19 due to a multitude of factors, including advanced age in this cohort, high incidence of underlying comorbidities, and immunosuppression caused by cancer and its treatments. It has been further demonstrated that individuals with lung cancer face a disproportionately higher risk of mortality compared to other cancer types following SARS-CoV-2 infection. However, several questions remain unanswered regarding the understanding of the pathophysiology of lung cancer in the context of COVID-19, as well as the effects of SARS-CoV-2 variants of concern on patient outcomes. This article aims to investigate the following gaps concerning the clinical manifestation of SARS-CoV-2 infection in patients with lung cancer: the molecular characteristics of lung cancer driving the development of severe COVID-19, and the role of COVID-19-induced inflammation in accelerating the development and increasing the severity of lung cancer, particularly with respect to the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1) and Delta (B.1.617.2) variants. Understanding the crosstalk between lung cancer and COVID-19, particularly concerning the early variants of concern, will reveal the unique mechanisms contributing to poor outcomes following SARS-CoV-2 in patients with lung cancer, including the maintenance of a hyperinflammatory state, TMPRSS2 expression patterns, and tumor-associated immune evasion, among others. This work will be valuable in the development of improved antivirals and vaccines against SARS-CoV-2 in the cancer population and will help provide insight into the pathogenesis of current and emerging variants of concern in this at-risk cohort. Additional studies and a high degree of caution are essential in understanding the impacts of newer and emerging variants of concern such as Omicron (B.1.1.529) and its subvariants on patients with lung cancer.

INTRODUCTION

The novel coronavirus disease 19 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in over 451 million total cases and over 6 million deaths as of March 2022 (1). The earlier Variants of Concern (VOCs) of COVID-19- Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1) and Delta (B.1.617.2)- result in higher disease severity than the Omicron (B.1.1.529) variant, with lower lengths of hospital stays and decreased ICU admittance and mortality associated with the early Omicron variant BA.1 (2, 3). Early reports have identified the Omicron BA.2 subvariant to have higher virulence and pathogenicity than BA.1; however, this data is preliminary, and the context of this review will therefore be on the aforementioned earlier VOCs, for which more robust data and established studies on patient cohorts are available (4).

The clinical spectrum of COVID-19 presentation ranges from asymptomatic to severe, critical illness resulting in respiratory failure and/or organ dysfunction requiring intensive care unit (ICU) admission and/or mechanical ventilation (5). Patients with cancer experience disproportionately poor survival outcomes following SARS-CoV-2 infection, with estimated mortality rates of 13-40%, compared to a global mortality rate of approximately 1.3% (1, 6–8). Patients with lung cancer face higher mortality compared to other cancer types, with data

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from the COVID-19 and Cancer Consortium (CCC-19) showing a mortality rate of 26% in patients with lung cancer (6, 8).

Severe COVID-19 is associated with acute respiratory distress syndrome (ARDS), a severe inflammatory reaction in the lungs resulting in higher rates of ICU admission and mortality (9). COVID-19 ARDS is associated with diffuse alveolar damage in the lungs that may progress to multiple organ failure due to blood oxygen saturation of 93% or below (10). ARDS is the major cause of mortality in COVID-19, contributing to a 30-day mortality rate of 41% in a cohort of hospitalized patients with confirmed COVID-19 infection admitted to the ICU (11). Factors that are associated with the development of severe COVID-19 include age >65, male sex, obesity, immunosuppression, diabetes, COPD, smoking history and the presence of other respiratory and cardiovascular comorbidities (9, 12).

PROPOSED RESEARCH QUESTIONS

Studying the presentation of COVID-19 in patients with lung cancer is crucial because it allows us to gain a better understanding of the unique molecular background contributing to the poor survival rates seen in patients with lung cancer who become infected with SARS-CoV-2. It would also help inform the development of more specialized treatments for patients with lung cancer who develop COVID-19. Finally, understanding the presentation of COVID-19 in patients with lung cancer will provide key insights into the important crosstalk between COVID-19 and cancer, an area which warrants further study and exploration.

To address the current gaps in our knowledge, this paper aims to first identify the molecular characteristics of lung cancer driving the development of a more severe COVID-19 presentation. This leads us to then explore the role of COVID-19-induced inflammation in accelerating the development and severity of lung cancer.

PROPOSED PROJECT NARRATIVE

What are the molecular characteristics of lung cancer driving the development of a severe COVID-19 phenotype? The unique molecular background of lung cancer associated with the underlying cancer and its treatment contributes to increased susceptibility to severe COVID-19. Understanding cancer in the context of SARS-CoV-2 infection is crucial in the development of improved anticancer therapies and improved treatment recommendations for patients with lung cancer who become infected with SARS-CoV-2.

There are two distinct types of lung cancer: small cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) (13). For both lung cancer subtypes, metastatic cancer (classified as extensive stage in SCLC and stage IV in NSCLC) is associated with significantly poorer survival outcomes (13, 14). Patients with small, localized lung cancer (stage I) have a 1-year survival rate of 81-85% while the survival rate of those with metastatic cancer (stage IV) drops to 15-19% (15).

One of the most prominent hallmarks of lung cancer in the context of severe COVID-19 is a background of chronic, tumor-promoting inflammation. The underlying genomic instability of cancer leads to aberrant hyperactivation of the JAK/STAT pathway and contributes to inflammation-associated alterations of the alveolar epithelium (16, 17). This is characterized by increased infiltration of inflammatory immune cells and tissue-resident-macrophages, as well as increased serum levels of cytokines such as IL-6 (16). IL-6 is one of the most important players in the crosstalk between COVID-19 and lung cancer and has been shown to trigger the overexpression of proinflammatory cytokines in the tumor microenvironment, increasing the severity of lung injury and promoting tumorigenesis through the induction of the epithelial to mesenchymal transition (EMT) (16, 18, 19).

In addition to the molecular factors driven by the underlying cancer, there are several risk factors associated with the treatment of lung cancer that also contribute to the poor prognosis following SARS-CoV-2 infection in individuals with lung cancer. Patients with lung cancer who have undergone thoracic surgery and/or radiation experience defective pulmonary and alveolar architecture (14). Patients whose lung cancer was treated with surgical resection exhibit a notable pattern of increased expression of both angiotensin-converting enzyme 2

(ACE2) and transmembrane protease serine 2 (TMPRSS2) found along the resection margins in lung tissue (20). Increased expression of ACE2 and TMPRSS2 are associated with higher susceptibility to SARS-CoV-2, given the role of ACE2 as the entry receptor for SARS-CoV-2 and the importance of TMPRSS2 in priming the SARS-CoV-2 spike protein (S protein) used for entry into host cells (21). This reveals a promising mechanism underlying the increased likelihood of developing severe COVID-19 in patients with lung cancer.

What is the role of COVID-19-induced inflammation in accelerating the development and severity of lung cancer? Understanding the role of COVID-19-induced inflammation allows us to learn more about the crosstalk between COVID-19 and lung cancer leading to especially poor outcomes in this patient cohort.

Early SARS-CoV-2 variants of concern- Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1) and Delta (B.1.617.2)- exhibit high tropism for lung tissue, contributing to their pathogenicity by inducing proliferative lung injury via cytokine signaling. SARS-CoV-2 viral replication causes injury to alveolar cells, leading to type II pneumocyte hyperplasia and hyaline membrane formation, characterized by the accumulation of necrotic cells, fibrin and protein in the delicate alveolar walls (10, 22). In cases of severe COVID-19, the progression to ARDS is driven by chronic inflammation associated with both the underlying cancer and COVID-19-induced inflammatory markers such as CXCL10, GM-CSF, IL-2, IL-7, IL-10, TNF- α, IFNγ, and IL-6 (16, 23–25).

Several existing anticancer therapies targeting IL-6 have been shown to be successful in treating COVID-19 in patients with lung cancer. Tocilizumab, an antibody targeting the IL-6 receptor (IL-6R) is routinely used in treating COVID-19-related respiratory failure in patients with cancer (16). An alternative monoclonal antibody, Siltuximab, has also shown promise in targeting IL-6R in patients with cancer and COVID-19 (26).

Another anticancer treatment, Ruxolitinib, is a small molecule inhibitor of JAK1 and JAK2- downstream targets of IL-6- and has been demonstrated to be effective in reducing proinflammatory cytokine secretion associated with COVID-19 (16). Other areas warranting further exploration are the effects of IFN-1 signaling and immune checkpoint signaling on the severity of COVID-19 in the context of lung cancer.

POTENTIAL IMPACT/CONCLUSIONS

The COVID-19 pandemic has resulted in significant burdens on global healthcare systems and will forever be remembered as a period marked by extremely rapid advancements in medicine and technology made possible by the collaboration of clinicians, scientists, and global leaders to control the spread of COVID-19 and protect vulnerable populations through the implementation of vaccine programs and the development of novel antivirals. Given the disproportionately poor outcomes in patients with lung cancer, aggressive vaccination programs are critical in keeping up with new and emerging variants of concern. Additionally, improved antivirals are necessary in treating patients with COVID and lung cancer, who are at increased risk of severe COVID-19 and mortality following infection with SARS-CoV-2 due to factors related to the treatment of lung cancer and the underlying cancer pathophysiology, as well as other comorbidities and risk factors.

Key areas for future research include identifying differences in outcomes between primary tumours originating in the lung compared to metastatic lung tumors originating from other sites in the body. Additionally, more research is needed regarding the impact of newer variants like Omicron or its subvariants on the severity of COVID-19 presentation as well as the progression of lung cancer in the context of differences in tissue tropism of newer VOCs. Emerging data suggests that the BA.2 variant of omicron is a highly concerning VOC warranting further study (4). As this data continues to emerge, we will gain a better understanding of the unique crosstalk between COVID-19 and cancer. This research will help deepen the understanding of lung cancer and cancer progression in general, the evolution of SARS-CoV-2 and risk factors contributing to severe COVID-19, and ultimately lead to the development of improved antivirals and anticancer therapies for patients in this at-risk cohort.

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