Cancer Reports and Reviews

Mini Review ISSN: 2513-9290

Treating Severe COVID-19 in Cancer Patients

Fatih M Uckun*

Worldwide Clinical Trials, Wayne, PA 19087, USA

Abstract

The high fatality rate of COVID-19 pneumonia, especially in imuno-compromised high risk patient populations, like those with hematologic malignancies or solid tumors who are receiving or have recently received immune-suppressive chemotherapy, has triggered a global search for effective therapies that can stop or reverse the inflammatory process that causes the acute respiratory distress syndrome (ARDS) and multi-organ failure after development of the pulmonary inflammation. This article summarizes the available risk mitigation strategies based on the insights and lessons learned from clinical trials in cancer patients in which a similar fulminant and systemic inflammatory process, known as the cytokine release syndrome (CRS) has been encountered.

After infection with SARS-CoV-2, up to one third of COVID-19 patients develop an acute pulmonary inflammation with a fulminant progression to acute respiratory distress syndrome (ARDS) with a high fatality rate in high risk patient populations despite best available supportive care [1-3]. Older patients with lung cancer, esophageal cancer and breast cancer who had co-morbidities were reported to have a particularly high risk. Most importantly, cancer patients showed a rapid deterioration of their pulmonary condition after SARS-CoV-2 infection and a third have died. It is to be anticipated that patients with acute leukemias and high-grade lymphomas undergoing therapy that can not be delayed, representing the most vulnerable patient population, will have a particularly fulminant form of COVID-19 pneumonia with a likely fatal outcome. In these patients, the "burst release" of proinflammatory cytokines in massive amounts and in succession causes a severe form of systemic capillary leak syndrome with pulmonary edema, pericardial effusion, and cardiac failure, that can culminate in hypoxic injury and dysfunction of multiple organs, ultimately causing an irreversible and fatal multi-organ failure [1-3]. This hyperacute immune-pathology is reminiscent of the cytokine release syndrome (CRS) observed in cancer patients treated with immunotherapeutic modalities such as CAR-T cells (e.g. tisagenlecleucel) or bispecific T-cell engagers (e.g. blinatumomab) that may hyperactivate elements of both the innate and acquired immune system [4-8]. Although an intensive research effort is underway globally to identify effective antiviral drugs or drug combinations against SARS-CoV-2, it is unlikely that such treatments could effectively reverse or ameliorate the pulmonary and systemic inflammation in COVID-19 patients with evolving or established ARDS. Therefore, there is an urgent and unmet medical need for treatments that can effectively reduce the risk of ARDS or its mortality rate in cancer patients with COVID-19 pneumonia.

A major immuno-modulatory cytokine that contributes to the severity and systemic complications of CRS is interleukin-6 (IL-6) [4-8]. Consequently, blocking IL6 signaling with the anti-IL6 receptor (R) antibodies tocilizumab or siltuximab was highly effective in reversal of CRS caused by treatment of B-lineage leukemia/lymphoma patients with tisagenlecleucel or blinatumomab [7,8]. Importantly, a similar anti-IL6 antibody showed promising clinical activity in COVID-19 pneumonia patients with CRS which lead to its approval in China for severe forms of COVID-19. Anti-IL6 receptor antibodies tocilizumab and sarilumab are currently being evaluated for their efficacy in COVID-19 patients in both open-label as well as randomized clinical trials. Severe cases of CRS can be associated with hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS), which involves, besides IL6, also interferon gamma (IFN-γ) and granulocyte-macrophage colony stimulating factor (GM-CSF). Such cases may benefit from treatment with high dose steroids as well as precision medicines such as emapalumab, an FDA-approved monoclonal antibody that binds and neutralizes IFN-γ and lenzilumab, an investigational monoclonal antibody that binds and neutralizes GM-CSF [3,9]. Besides the cytokine storm, activation of complement signalling pathway [10,11] also contributes to the inflammation associated with the pathophysiology of ARDS in severe cases of COVID-19 [3]. In the SOLID-C19 Expanded Access study (ClinicalTrials.gov Identifier: NCT04288713), the complement inhibitor eculizumab, an FDA and EMA-approved humanized monoclonal antibody that binds to the complement component C5, is being used in an attempt to reduce the mortality in COVID-19 patients.

The insights and lessons learned from clinical trials of CRS-causing therapies for oncology patients are now being leveraged in an effort to reduce the mortality rate in hospitalized patients with severe forms of COVID-19 pneumonia. Innovatove clinical trials that leverage the aforementioned anti-inflammatory treatment modalities available for reversing CRS as well as promising antiviral agents with specific activity against SARS-CoV-2 have the potential to facilitate a rapid identification of much needed effective treatment algorithms that can reduce the mortality of COVID-19 pneumonia in high-risk cancer patients. In parallel, it is critical to use stringent fit-for-purpose infection control

Correspondence to: Fatih M. Uckun, MD, PhD, Vice President and Clinical Strategy Lead, Oncology and Hematology, Wordwide Clinical Trials, 480 E. Swedesford Road Suite 200, Wayne, PA 19087, USA. E-mail: fatih.uckun@worldwide.com

Key words: *2019-nCoV, pneumonia, ARDS, cytokine release syndrome, COVID-19, systemic capillary leak*

Received: March 29, 2020; **Accepted:** April 13, 2020; **Published:** April 20, 2020

policies in cancer treatment facilities and set priorities in the treatment plans of cancer patients so as to maximize the benefit of the anti-cancer therapies while minimizing the risk of developing and dying of fatal COVID-19 [12,13].

Conflict of interest

The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

Author contribution

FMU conceived the review, analysed the contents of relevant publications and wrote the manuscript. No medical writer or editor was involved.

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, et al. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 395: 497-506.
2. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, et al. (2020) Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. *JAMA* 3.
3. Zumla A, Hui DS, Azhar EI, Memish ZA, Maeurer M (2020) Reducing mortality from 2019-nCoV: host-directed therapies should be an option. *Lancet* 395: e35-e36.
4. Maude SL, Barrett D, Teachey DT, Grupp SA (2014) Managing cytokine release syndrome associated with novel T cell-engaging therapies. *Cancer J* 20: 119-122.
5. Davila ML, Riviere I, Wang X, Bartido S, Park J, et al. (2014) Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. *Sci Transl Med* 6: 224ra25.
6. Teachey DT, Rheingold SR, Maude SL, Zugmaier G, Barrett DM, et al. (2013) Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. *Blood* 121: 5154-5157.
7. Khadka RH, Sakemura R, Kenderian SS, Johnson AJ (2019) Management of cytokine release syndrome: an update on emerging antigen-specific T cell engaging immunotherapies. *Immunotherapy* 11: 10.
8. Garcia Borrega J, Gödel P, Rüger MA, Onur ÖA, Shimabukuro-Vornhagen A, et al. (2019) In the Eye of the Storm: Immune-mediated Toxicities Associated With CAR-T Cell Therapy. *HemaSphere* 3: 2.
9. Teachey DT, Rheingold SR, Maude SL (2013) Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine directed therapy. *Blood* 121: 5154-5157
10. Gralinski LE, Sheahan TP, Morrison TE, Menachery VD, Jensen K, et al. (2018) Complement activation contributes to severe acute respiratory syndrome coronavirus pathogenesis. *mBio* 9: 01753-01718.
11. Wang R, Xiao H, Guo R, Li Y, Shen B (2015) The role of C5a in acute lung injury induced by highly pathogenic viral infections. *Emerging Microbes & Infections* 4: 1-7.
12. Hanna TP, Evans GA, Booth CM (2020) Cancer, COVID-19 and the precautionary principle: prioritizing treatment during a global pandemic. *Nat Rev Clin Oncol*
13. Liang W (2020) Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *The Lancet Oncology* 21: 335-337.