

Impact of Covid-19 in Cancer Patients Treated with Immunotherapy: A Review

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ABSTRACT

COVID-19 pandemic has been a devastating disease worldwide. Although an important number of young healthy people have been affected, elderly, comorbid and immunosuppressed patients have been especially compromised. Cancer patients usually share several of these features, being considered high risk population.

Limited reliable information about cancer patients and COVID-19 are available, especially concerning to the risk that oncological therapies could involve. Immunotherapy is a novel therapy extensively used in oncology. Even though it is not a myelosuppressive treatment, its safety use in this context is unknown. Immunotherapy boosts immune system, mainly cytotoxic T cell response. This suggests that could have a favourable role in viral elimination. However, concerns about a detrimental influence have been discussed in oncological community. Most severe COVID-19 patients usually develop an acute respiratory distress syndrome (ARDS) secondary to a cytokine-release syndrome (CRS). Therefore, exacerbation of an inappropriate and excessive immune response secondary to these therapies is feared. Currently there are not evidence which confirms neither of these hypotheses. Further studies are needed to improve prognosis in these patients.

Keywords: COVID-19; Cancer; Immunotherapy

COVID-19 GLOBAL EPIDEMIOLOGY AND EVIDENCE IN CANCER PATIENTS

A novel acute respiratory disease was described for the first time in Wuhan, China, in December 2019. This virus was called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the syndrome generated, coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO). Soon after the first description of the disease in China, the SARS-CoV-2 spread globally and, on 12th March 2020, the WHO announced COVID-19 outbreak a pandemic [1,2].

Nowadays, COVID-19 is a global health concern, with 12322395 cases registered and 556335 deaths around the world according to WHO reports on 11th July 2020 [3].

Several factors have been described linked to an increase morbidity and mortality. Elderly age, chronic pulmonary disease, cardiovascular disease, diabetes, immunosuppression, and cancer are the most relevant [2].

Information about cancer patients are insufficient and heterogeneous. The largest analysis of patients infected by SARS-

CoV-2 in Wuhan included only 18 patients with a history of cancer. In this analysis, patients with cancer presented higher risk of severe events compared with patients without cancer [4]. Mortality rate in these patients has been reported around 25%-28%, higher than in the global population but, again based on analysis with low number of cancer patients included [5,6]. However, despite all these bias, most recent and wide data from European studies showed similar results. The retrospective multicenter observational study named On Covid analysed data from 204 cancer patients and showed a mortality rate of 29% [7]. It is relevant to highlight that cancer patients are frequently not admitted in Intensive Care Units (ICUs) because of their oncologic prognosis and comorbidities, especially in a pandemic situation with less resources than those necessary. This could increase differences in mortality rate in cancer patients compared with global population [8,9].

Despite this increasing knowledge about cancer patients, a comprehensive analysis of this group of patients is necessary to optimize their oncology care. Cancer patients are a heterogeneous population. Type of tumour, tumour stage,

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performance status, age, comorbidities, therapies, etc; all of them are going to influence the susceptibility of the patient to SARS-CoV-2 infection, as well as its severity. In this regard, limited information is available. Previously mentioned reports do not go in detail about it [5,6]. The On Covid study confirmed that older age and the presence of two or more comorbidities (hypertension, diabetes, dementia, cardiovascular disease, chronic kidney disease, chronic pulmonary disease or liver disease) were predictors of patient mortality independently of tumour stage or therapy [7]. Although information about oncology therapy was collected, there was small representativity of others therapies different of chemotherapy, making difficult to extract conclusions [7]. An ambitious Spanish study in this line has been recently reported. A total of 63 patients were analysed, looking for predictive factors of poor outcome [8]. Previous episode of venous thromboembolism disease, bilateral pneumonia on baseline X-ray evaluation, severe neutropenia and pulmonary tumour involvement were independently identified as predictive factors for increased risk of death [9].

IMMUNOTHERAPY AND COVID-19 AVAILABLE DATA

Most information available regarding the evolution of COVID-19 disease in cancer patients on immunotherapy come from small series [10,11] and case reports [12–14].

The United Kingdom Coronavirus Cancer Monitoring Project (UKCCMP) included a total of 800 cancer patients diagnosed of COVID-19, of which a 6% were on immunotherapy. Although is a lower number of patients to establish conclusions, compared with patients on other therapies, patients on immunotherapy were not at any additional risk of death after adjustment for age, gender and comorbidities (OR 0,59; 95% CI 0,27-1,27; p 0,177) [10].

A retrospective study in lung cancer patients with COVID-19 included a total of 41 patients treated with PD-1 blockade. Authors concluded that there was no significant difference in severity regardless of PD-1 blockade exposure when analysis is adjusted for smoking history. In addition, within those patients who received PD-1 blockade, there were no differences in COVID-19 severity based on proximity of exposure to this therapy. Interestingly, peak IL-6 level was not different too [11].

Finally, the Spanish Multidisciplinary Melanoma Group carried out a national registry of melanoma patients infected by SARS-CoV-2 and interesting results from an interim analysis has been published about patients on immunotherapy. A total of 50 patients were included, whose 22 were on treatment with anti-PD-1 antibodies. Mortality rate was not higher in immunotherapy group compared with global of patients included [15].

COVID-19

The most common symptoms are asthenia, myalgias, fever, dry cough, chest tightness and dyspnoea. However, a broader spectrum of symptoms has been described related to this illness: diarrhoea, vomiting, skin lesions, anosmia, ageusia, even neurological symptoms [16].

Laboratory test most frequently shows lymphopenia, raised aspartate aminotransferase, and elevated D-dimer [16].

Spectrum is also broad regarding the severity: from asymptomatic cases to critical ill patients. Although some risk factors have been described, some young healthy people have presented severe disease. Further information about this are necessary.

Initials reports about viral load dynamics of SARS-CoV-2 suggested that viral load peaks during the first 3-5 days of illness and declines thereafter [17,18]. However, clinicians observed that, patients with COVID-19 who became severely illness, often worse 7-10 days after illness onset. And the main cause of death in these patients was an acute respiratory distress syndrome (ARDS) and a multiorgan failure related with a cytokine storm [19]. These observations lead to the theory of the immune system mediating sudden clinical deterioration.

More recent studies showed that the clinical spectrum as well as the viral load pattern of SARS-CoV-2 are more complex and heterogeneous. In general, it seems that patients with mild symptoms are able to clearance the virus early, whereas severe patients have higher viral loads and for a long time [20,21]. So, viral load is directly correlated with the severity of the disease too.

Summarizing, severe cases are related with a potent but ineffective immune response, enable to eliminate the virus.

In this regard, T cells play a relevant role in viral clearance, specially CD8 cytotoxic T cells. And PD-1/PD-L1 axis participated in this role. While the role of this pathway in chronic virus infections is well described, little is known about their function in the acute phase of a viral infection. Preclinical studies with murine models showed that PD-1 in upregulated on naïve virus-specific CD8 T cells before they clonally expand negatively regulating their terminal differentiation into effector CD8 T cells. Blockade of the PD-1 pathway at this point increased effector functions of CD8 T cells and accelerated virus elimination [22]. In chronic viral infections, persistent stimulation by the virus induce negative costimulatory molecules and T cells become exhausted and gradually lose their effector functions [19,22].

This relationship was already found in other viral acute lower respiratory infections. Studies in animal models of human metapneumovirus and influenza A virus demonstrated that PD-1 pathway is rapidly activated, leading to CD8 T cells impairment. Inhibition of the PD-1/PD-L1 binding with monoclonal antibodies prevented this impairment and reduced viral titres, importantly, without exacerbating lung histological damage [23].

Based on the theory of the T-cell exhaustion during COVID-19 and the potential relationship between this and the severity of the disease, Diao et al conducted a retrospective unicentric investigation in patients admitted because of COVID-19 in Wuhan. They described lower levels of total T cell counts as well as CD4 and CD8 T cell counts, and the levels were even more lowers in those patients admitted in ICUs. On the contrary, the cytokines TNF-alpha, IL-6 and IL-10 showed high levels in

patients, especially in ICU patients. Finally, authors described higher levels of exhaustion markers in CD4 and CD8 T cells, mainly PD-1 and TIM-3, in patients versus healthy controls. These markers expressions change with the evolution of the disease and is again higher in more severe patients [24].

IMMUNOTHERAPY AND COVID-19: HOPE OR FEAR?

Chemotherapy has been classically linked to immunosuppression and predisposition to more frequent and severe infections. However, immunotherapy is not a myelosuppressive treatment, on the contrary, it boosts immunity and restore cellular immunocompetence.

Even so, immunotherapy has demonstrated being a double-edged sword: the same mechanism that benefit the patient is able to kill him. Immune-related toxicities are less frequent than chemotherapy toxicities but potentially mortal. The underlying mechanism is the release of the break to immune system and the recognition of self-antigens as foreign ones. This way, a boosted immunity attacks different organs, leading to thyroiditis, hypophysitis, hepatitis, colitis, etc. The most of these adverse events usually improves after a course of corticoid therapy, but a small percentage will need more intense immunosuppressive treatment. Some of these potential toxicities have a high mortality rate, as encephalitis, myocarditis or pneumonitis, and require early and powerful immunosuppression to deal with them [25,26].

Pneumonitis generally appears in less than 5%, 1%-2% grades 3-4, according to the main pivotal trials of the different anti-PD-1/PD-L1 antibodies [27]. Despite its low frequency, in COVID-19 pandemic context, pneumonitis has been a fear issue. On one hand, differential diagnosis between pneumonia secondary to SARS-CoV-2 infection and immune-related pneumonitis can be difficult. Both entities share clinical and radiological findings: dyspnoea, dry cough, bilateral interstitial infiltrates on X-ray or computerized tomography. In addition, information from microbiological test is limited too: CRP for SARS-CoV-2 detection in nasopharyngeal swab has a sensitivity between 63 and 78% [28], and invasive procedures as bronchoscopy were generally avoided because the potential generation of aerosols. On the other hand, while rapid initiation of high dose corticoid is the best approach for immune-related pneumonitis, corticoid use has been controversial in COVID-19 disease for a long time, being initially inadvisable although last reports recommend dexamethasone for severe ill patients [29-32].

Potential clinical overlapping between both syndromes are not the only concern about the use of immunotherapy in the context of COVID-19 pandemic. As mentioned above, a delicate balance is necessary to achieve an effective viral response without excessive tissue damage. Immune system overstimulation by immunotherapy can disrupt this balance towards an excessive inflammation. CRS has been described especially in the context of CAR-T cell therapy, but also with immune-checkpoint blockade antibodies [33]. Clinical features are similar to the ARDS that affects to critically ill COVID-19 patients, including high levels of IL-6. In fact, treatment with Tocilizumab, an anti-IL6 monoclonal antibody approved for the

CRS caused by immunotherapy, has been used empirically in COVID-19 patients and clinical trials are testing its efficacy in this context [19,29].

Nevertheless, immunotherapy can be not so detrimental, but useful in COVID-19 disease. Immune-checkpoint inhibitor antibodies boost mostly CD8 T cell response and can reverse T cells exhaustion state, contributing with viral elimination. Several trials have tested their efficacy and safety in virus-associated cancers and promising trials are evaluating these drugs in the treatment of chronic infections as Human Immunodeficiency Virus (HIV) or Hepatitis B Virus (HBV) [34,35].

In this regard, a phase II trial has been designed evaluating the safety and effectivity of pembrolizumab, an anti-PD-1 monoclonal antibody, and tocilizumab, in patients with COVID-19 pneumonia who are unresponsive to standard care (COPERNICO study, NCT04335305).

CONCLUSION

Cancer patients constitutes globally a risk population for morbidity and mortality in COVID-19 pandemic. Several factors are involved, patient age and comorbidities, the stage and dissemination of the disease, the kind of therapy they are on, even though the recurrent hospital appointments they could need. Our priority should be to minimize the risk, but we can forget about the disease progressing without therapy. Counterbalance benefits and risk is essential but complex. Further studies in oncological populations are needed specially concerning to novel therapies as immunotherapy. The more and more reliable information we have, the better decisions we can take.

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