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European Journal of Cancer 134 (2020) 6–8

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Letter to the Editor

# Risk of coronavirus disease 2019 in patients treated for cancer: An immune response–based hypothesis

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Received 5 May 2020; accepted 11 May 2020
Available online 18 May 2020

Despite a considerable increase of new coronavirus (Severe acute respiratory syndrome (SARS)-CoV-2) related publications, there are still few data to quantify the risk of infection in patients under treatment for cancer. Reports from the epicentre of the viral epidemic show in patients with cancer a risk of infection and a mortality rate of about 2% and 4%, respectively [1–3]. (Table 1).

Mildly different was the Italian report on a subsample of 2351 patients with COVID-19 who died in hospital with pre-existing conditions, where 383 (16.3%) patients had had active cancer in the past 5 year [4]. Although the mortality of patients with cancer was higher than that reported in the Chinese studies, a direct comparison is not allowed for the lack of detailed information about anticancer treatment adopted and type of cancer. Moreover, as reported by Onder *et al.*, [5] a plausible explanation for the higher Italian case-fatality rate is based on defining COVID-19–related deaths independently from pre-existing diseases that may have caused the death. Therefore, whether this finding is secondary to cancer or a pre-existing comorbidity is unknown.

We appreciated the study of Trapani D *et al.* [6] published in *European Journal of Cancer*, which, to the best of our knowledge, was the first Italian report of patients with cancer experiencing COVID-19. The authors reported data of 9 patients with cancer referred to the European Institute of Oncology in Lombardy Region, epicentre of the outbreak in Italy. In accordance with previously published studies focused on patients with cancer [1–3], the majority of patients were male (78%), with a median age higher than 65 years (range: 42–79) and a median of one comorbidity per patient (range: 0–2). In this report, 8 patients were under active treatment, mostly chemotherapy (50%), followed by experimental immune checkpoint inhibitors (25%) and small molecules (25%) (Table 1). However, none of those patients died or accessed the intensive therapy unit and out of two patients with severe pneumonia which required hospitalization, all the other patients had a mild COVID-19 syndrome and were referred to home-based management.

Although the overall limited sample size, patients with cancer are thought to be more susceptible to the infection due to their immunocompromised status caused by both the malignancy and anticancer

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https://doi.org/10.1016/j.ejca.2020.05.003

Table 1
Summary of published studies including patients with cancer under active treatment.

| References | N. cancer patient (% of Covid-19) | Advanced stage | Lung cancer | Chemotherapy | Immunotherapy | Target therapy | Deaths |
|---|---|---|---|---|---|---|---|
| Liang W *et al.* [1] | 18 (1.0) | 4 | 6 | 2 | 1 | 3 | Not specified |
| Ju Y *et al.* [2] | 12 (0.79) | 8 | 7 | 3 | 0 | 2 | 3 |
| Zhang L *et al.* [3] | 28 (2.2) | 10 | 7 | 3 | 1 | 2 | 8 |
| D Trapani *et al.* [6] | 9 (100) | 5 | 1 | 4 | 2 | 2 | 0 |

treatments. As a matter of fact, COVID-19 is a highly contagious infection to which everyone may be vulnerable [7]. However, not all people exposed to SARS-CoV-2 became infected, and not all infected patients develop severe respiratory illness. Furthermore, not all patients with cancer correspond to patients with advanced cancer, who are supposed to be immunosuppressed.

To thicken the plot, an effectual host immune response, including innate and adaptive immunity, seems crucial to control and resolve the SARS-CoV-2 infection. During the first period of incubation, an effective specific adaptive immune response is required to eliminate the virus and to preclude disease progression to severe stages. Therefore, a non-immunocompromised status and an appropriate genetic background (e.g. HLA) are both important. At this initial stage, strategies to boost immune responses, such as checkpoint inhibitors immunotherapy, could even be more useful than harmful in patients with cancer.

Otherwise, when the adaptive immune response is impaired or dysregulated, virus can propagate and lead to massive destruction of the affected tissues, especially lungs or organs displaying ACE2 hyperexpression [8]. At this advanced stage, the excessive production of proinflammatory cytokines eventually followed by the so called 'cytokine storm' is supposed to play an important role in the development of life-threatening acute respiratory distress syndrome [9]. Paradoxically, at this later stage a good general health may be disadvantageous for patients with cancer and contrariwise a strong immunosuppression could lead to better outcomes. Beyond 'cytokine storm' we should also consider the role of a multifactorial process to justify the rapid evolution of lung and multiorgan injury. We endorse the idea of a microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (Micro-CLOTS) as a new name for severe pulmonary coronavirus disease 2019 (COVID-19). In predisposed individuals, alveolar viral damage is followed by an inflammatory reaction and by microvascular pulmonary thrombosis [10]. This progressive endothelial thromboinflammatory syndrome may also involve the microvascular bed of the brain and other vital organs, leading to multiple organ failure and death. Future steps in the understanding of the disease and in the identification of treatments may benefit from this definition and hypothesized sequence of events.

In this context, immunotherapy, chemotherapy, as well as antiangiogenic targeted agents, could represent bivalent options for patients with cancer, with opposite role in accordance with the different viral infection stages.

A separate analysis is necessary for lung radiotherapy, which in addition to a systemic immunosuppressive effect might result in lung locoregional tissue damage.

Finally, it should be reminded that patients with cancer are often older and frequently affected with comorbidities, such as diabetes and hypertension that, even taken individually, are those most related to COVID-19 infection damage and deaths [7].

Thus, we did not consider all the patients as the same, but by considering patients by patients, including sex, age, comorbidities, tumour characteristics and the ongoing anticancer treatment. In accordance with the current evidence, the limited sample size of patients with cancer, especially for those actively receiving anticancer treatment, and the heterogeneous characteristics of patients included in published studies (up to May 4th, 2020), we think that data on patients with cancer are still inconclusive. We agree with Trapani D. et al. [6] that our goal, as oncologist, is to ensure the best possible support to our patients by taking further more detailed analyses to better understand the role of each anticancer drug in the fight against COVID-19, and which kind of behaviour we should adopt towards our patients rather than believing everything as evidence.

## Conflict of interest statement

All authors have nothing to disclose in relation to this manuscript.

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