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Granulocyte colony-stimulating factors (G-CSF) and COVID-19: a double-edged sword?

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Dear Editor,
Neutropenia is the most common side effect after the administration of myelosuppressive drugs in cancer patients [1]. Febrile neutropenia (FN) and the related complications represent a real issue in the clinical practice, still associate with an increase in hospital admissions and higher probability of death [2].
Prophylaxis, with the administration of granulocyte colony-stimulating factor (G-CSF), represents an excellent option in the field of the modern supportive care of cancer patients. All the international guidelines suggest the prophylactic administration of G-CSF in patients candidate to receive a cancer chemotherapy regimen with an high (≥20%) risk of myelosuppression as well as in patients with some risk factors (i.e. previous anticancer treatments, comorbidities, advanced age) and candidate to receive chemotherapy regimens with any risk of myelosuppression [3]. The therapeutic use of a G-CSF (both the short-acting and long-acting formulation) after the onset of a febrile neutropenia is still controversial and strictly related to the oncologist experience and practice [4]. The recent authorization of the biosimilar formulation of long-acting G-CSF represents an important innovation in terms of both better adherence to the guidelines for its clinical use and overall treatment cost [5].
At the end of 2019, a novel coronavirus was identified in Wuhan, a city in China, causing a pandemic. The infection-related, named coronavirus disease 2019 (COVID-19), could develop a severe acute respiratory-syndrome and lead to death, especially for patients requiring hospitalization [6]. The initials literature data seems to suggest that one of the primary mechanisms, through this infection appears severe, belongs to an over-response by the immune system and hyperactivation of coagulation cascade [7]. These factors, in association with the virus replication, lead to respiratory distress and respiratory failure. However, the pathophysiology of the sometimes dramatic clinical outcome of this infection is still not clear, and it is under investigation.
Given that cancer patients could have a primary dysfunction of the immune system, this category is considered potentially at high risk for this new infection, and more likely to experience several complications so that recommendations were recently published to guide the various aspects of cancer care in this setting [8-10]. In particular, some international guidelines have extended the recommendations to the prophylactic G-CSF administration to all patients receiving cancer chemotherapy regimens considered at lower risk of FN (10-20%), in order to reduce the risk of COVID-19 infection during the treatment course [11].
However, recently a case-series was published, describing a potential relation between the prevention and treatment of febrile neutropenia in cancer patients and the worsening of COVID-19 outcome, ascribing a determinant role to the administration of G-CSF, leading the rise of neutrophils count rapidly and a contextual respiratory deterioration [12]. Moreover, it is not the first time that the G-CSF receptor seems to be involved in the increase of neutrophils count during pneumonia [13].

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On the other hands, some different experiences suggest that the G-CSF administration is able to counteract the lymphocytopenia (an adverse prognostic factor of COVID-19) during the disease and could improve the outcome of the infection [14, 15].
These points are fascinating and they should be studied in deep, considering the high number of cancer patients that receive G-CSF routinely in clinical practice. The way how a rapid rising of neutrophils could determine a worsening of the respiratory distress syndrome during Covid-19 is suggestive and could lead to taking further considerations and recommendations about the best strategy to manage G-CSF administration in neutropenic cancer patients.
Could it be crucial testing for COVID-19 those cancer patients affected by FN, before the administration of G-CSF, to avoid the risk of a worsening of the COVID-19 related complications?
Could it be the long-acting formulation of G-CSF, characterized by a different mechanism of action that leads to a slower rising of neutrophils count, a valid alternative to the administration of daily G-CSFs in this setting?
The answers to these questions will become more and more important if a relationship between the use of G-CSF and COVID-19 outcome will be clinically confirmed, especially considering that this infection has achieved the characteristics of a pandemic and the time necessary for an effective vaccination (that will be particularly important for specific subpopulations such as cancer patients) has not yet been established. More data in this field urgently need to be brought to optimize the therapeutic approach to cancer patients.

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