Should We Expand the Use of Granulocyte-Colony Stimulating Factors (G-CSF) during the COVID-19 Pandemic?

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Abstract

Cancer patients are considered more susceptible to the SARS-CoV-2 infection. Higher rates of respiratory failure and death were reported in cancer patients and COVID-19, compared with the general population. Among other measures deemed to protect this vulnerable subcategory, both ASCO and ESMO recommended the extension of G-CSF use, to include prophylactic administration in all patients receiving regimens with 10%-20% risk of febrile neutropenia (FN) and also in regimens with risk of FN <10%, if patients were considered with poor bone marrow reserve due to comorbidities or advanced age. However, accumulating data reported in several recent publications suggested a direct involvement of the high neutrophil count, due to G-CSF stimulation, in the development of the adult respiratory distress syndrome (ARDS), the hallmark of the severe COVID-19 disease. In addition, some recent evidences suggest that G-CSF may hamper the efficacy of the mRNA vaccine. This paper reviews the most important data reporting higher rates of respiratory failures and death associated with G-CSF treatment in cancer patients and SARS-CoV-2 infection. Therefore, we consider that the current recommendation of expanding the G-CSF use in cancer patients during the COVID-19 pandemic should be reconsidered. The most important protective measures for cancer patients remain specific vaccination and a rigorous compliance with the general protective measures, whereas the G-CSF should be administrated as traditionally recommended by the current guidelines.

Keywords: COVID-19, G-CSF, cancer, neutropenia

1. Background

The COVID-19 pandemic has profoundly affected the global population and the health care systems across the world. As of November 2021, more than 250 million infected cases and more than 5 million deaths associated with COVID-19 have been reported globally (1). Initially, patients with cancer were considered more vulnerable to SARS-CoV-2 infection due to the coexisting chronic diseases, overall poor health status, and systemic immunosuppressive condition caused by both cancer and anticancer treatments (2). Recent reports confirmed this assumption, with the largest meta-analysis showing an overall case fatality rate due to COVID-19 in cancer patients of 22.4% (3), compared with 7.2 % in patients without cancer (4).

As such, the main oncology societies in United States (ASCO) and Europe (ESMO) had published guidelines on how to mitigate the impact of SARS-CoV-2 pandemic on patients with cancer, stipulating some specific recommendations, including prioritization of cancer treatment according to the goal of therapy, using telemedicine to avoid frequent hospital visits, switch to oral drugs when available, and postponing the medical interventions which, were believed to be non-essential (5-7). In the same context, recommendation was made that patients with active cancer and those on treatment should be prioritized for vaccination and should be immunized when any authorized vaccine is available to them. Individuals with cancer have an appropriate, protective immune response to vaccination without experiencing any more side effects than the general population (8).

2. Rationale for expanding the G-CSF use during the COVID-19 pandemic and the current recommendations.

A special attention was paid on the use prophylactic G-CSF during COVID-19

pandemic. Neutropenia induced by anti-cancer therapies is one of the most common side effects seen in cancer patients, commonly accompanied by a decrease in other hematopoietic lineages, like anemia and/or thrombocytopenia. Soon after the onset of the pandemic, both ASCO and ESMO recommended the extension of G-CSF use, to include prophylactic administration in *all* patients receiving regimens with 10%-20% risk of febrile neutropenia (FN) and also with regimens with *risk of FN <10%*, if patients were considered with poor bone marrow reserve due to comorbidities or advanced age (6, 9). Therefore, the majority of patients receiving chemotherapy would have received G-CSF support whatever the FN risk might be. By acting this way, it was expected to reduce the risk of hematologic complications associated with cancer chemotherapy and thereby to minimize the patient exposure in the clinic for supplementary analysis and treatment, the referral to the emergency department and hospital occupancy in times when these places may be in short supply and/or pose an exposure risk for this vulnerable population. Moreover, for patients presenting with FN after chemotherapy who have not previously received prophylactic treatment with pegylated G-CSFs, the recommendation was that *all patients* be started on G-CSFs to shorten the time to neutrophil recovery (6).

3. The potential detrimental effect of G-CSF on COVID-19 course

Despite this enthusiastic initiative for expanding the G-CSF indications, some indirect alarming data emerged from published series correlating the high leukocyte level with the odds of in-hospital death due to SARS- COV 2 infection (OR = 6.60 (3.02–14.41), $p < 0.0001$, for the white blood cell count level $> 10 \times 10^9/L$) (10). In addition, it has been suggested that the G-CSF may increase pulmonary inflammation and enhance production of inflammatory

cytokines such as interleukin-6 associated with severe COVID-19 (11). Autopsies of COVID-19 patients have shown neutrophil extravasation in the alveolar spaces of lungs, raising concerns that G-CSF administration and the resulting neutrophil expansion could lead to exaggerated neutrophil responses, worsening respiratory function (12).

Former knowledge about the non-COVID-19 “Acute Respiratory Distress Syndrome” (ARDS) recognized the neutrophil influx into the extravascular compartments of the lungs as a primordial characteristic. In ARDS, neutrophils and their toxic mediators can cause tissue injury, including an increase in lung epithelial and endothelial permeability, which, leads to the influx of protein-rich alveolar edema and arterial hypoxemia. Neutrophilia is common in the broncho-alveolar lavage fluid of patients with ARDS and the extent of this correlates with clinical outcome. ARDS is associated with elevated levels of primed neutrophils within the systemic circulation, suggesting that ARDS may be associated with a failure of neutrophil depression, thus providing a potential ‘crosstalk’ mechanism for the remote organ damage that is the predominant cause of mortality and long-term morbidity in patients with ARDS. In fact, mortality from ARDS correlates with the extent of neutrophilia in the lung (13). Very important, the G-CSF is the dominant colony-stimulating factor released from lung cells in response to pro-inflammatory cytokines (14). In addition, neutrophils are important contributors to both venous and arterial thrombus formation and progression. Neutrophil extracellular traps promote vessel occlusion by providing a scaffold for platelets, red blood cells, and procoagulant molecules, enhance coagulation through both the intrinsic and extrinsic pathways. Vascular neutrophilic inflammation and immune thrombosis are characteristics of COVID-19 infection and have been described as being associated with G-CSF treatment (15).

Addressing the impact of G-CSF treatment during the SARS-CoV-1 infection, the paper by Lazarus et al. raises the hypothesis that Granulocyte Macrophages-Colony Stimulating Factor (GM-CSF) may be a better choice for neutrophil count support due to a broader range of biologic activities. The G-CSF receptors are expressed primarily on neutrophils and bone marrow precursor cells whereas the GM-CSF- receptors are, more widely expressed being present on neutrophils, monocytes, eosinophils, dendritic cells, basophils, and, possibly, B cells. Therefore GM-CSF may be responsible for a broader range of biologic activities than G-CSF as well as anti-bacterial, anti-fungal, and anti-viral properties (16). Moreover, some data suggest that GM-CSF may be effective in treating some pulmonary conditions like the acute respiratory distress syndrome (ARDS) (17). The suggestion was that in persons with lung infection and/or ARDS, GM-CSF may be a safer drug than G-CSF (16). On the other hand, an open-label multicenter, randomized clinical performed in China suggests a higher lymphocyte count recovery with G-CSF administration in patients with COVID-19 pneumonia and lymphocyte count < 800 per μ L. Moreover, the number of patients developing critical illness (2% vs 15%) or dying (HR, 0.19; 95% CI 0.04-0.88) was reduced in the G-CSF treated group. However, some important limitation of the study, including the exclusion of patients with comorbidities and an imbalance in the use of antivirals and dexamethasone, may have precluded a reliable conclusion based on the recorded data (18).

Anecdotal case reports were among the first to rise the hypothesis of correlating the COVID-19 related ARDS with G-CSF treatment in cancer patients. Nawar and colleagues reported 3 persons with ARDS in the setting of COVID-19 with rapid deterioration of lung function after receiving G-CSF (19). Taha and colleagues report similar rapid deterioration in someone with COVID-19-related ARDS receiving G-CSF,

concluding: “*This rapid neutropenia recovery and the robust inflammatory response in COVID-19 raise concerns about G-CSF safety in patients with COVID-19*” (20). Moreover, a retrospective study of 83 neutropenic oncological patients who simultaneously had neutropenia and an infection with COVID-19 showed that the respiratory failure and death was associated with the number of days of G-CSF treatment (OR = 1.4, 95% CI [1.1-03.92], $p = 0.01$). The authors concluded that a prolonged G-CSF treatment could be disadvantageous for cancer patients with infections by COVID-19, due to a higher probability of worse outcome (21).

The last updated data related to this issue were recently published in a “*Major Article*” of the *Clinical Infectious Disease* (official publication of the Infectious Diseases Society of America) (22). The authors performed a retrospective analysis of 379 cancer patients at Memorial Sloan Kettering Cancer Center who tested positive for COVID-19 and received cancer directed therapy within 30 days of their COVID-19 diagnosis between March 11 and November 16, 2020. The majority of cancer types were breast cancer (24%), colorectal cancer (11%), lung cancer (10%), lymphoma (7%) and prostate cancer (7%). Two hundred twenty-seven (60%) patients received cytotoxic chemotherapy within 30 days of their COVID-19 diagnosis. Meanwhile, 28 (7.4%) patients received either filgrastim or pegylated filgrastim. Among the 379 patients, 130 (34.3%) were hospitalized for the management of COVID-19 symptoms. The primary composite endpoint was the occurrence of respiratory failure (defined as the requirement for high-flow nasal oxygen, non-rebreather, bi-level positive airway pressure [BIPAP], and mechanical ventilation) or death following COVID-19 diagnosis. Using an extended Cox model with G-CSF encoded as a time-dependent covariate, the researchers found that G-CSF administration was significantly associated

with increased risk of hospitalization in patients with COVID-19 (HR 3.54, 95% CI 1.25-10.0, $p = 0.017$). The association remained significant when considering patients who had asymptomatic COVID-19 (HR 18.31, 95% CI 2.51-96.8, $p = 0.008$). Similarly, among the 130 patients who were hospitalized, G-CSF administration was associated with increased need for high levels of oxygen supplementation and death (HR 3.56, 95% CI 1.19-10.2, $p = 0.024$), while neutropenia was not (HR 0.95, 95% CI 0.39-2.1, $p = 0.907$). Based on the neutrophil count, the patients were stratified into “high” (defined as a >50th percentile increase in ANC, equivalently, a fold change of ≥ 4) or “low” responders to G-CSF. The poorer outcome was predominantly seen in the “high responders” group (HR 7.78, 95% CI 2.05-27.9, $p = 0.004$), whereas a non-significant trend was noted for the “low responders” (HR 4.04, 95% CI 0.80-16.7, $p = 0.086$). Interestingly, in the multivariate model, neutropenia by itself did not portend a worse outcome (HR: 0.95, 95% CI 0.39–2.1, $p = 0.907$). Moreover, the severity of neutropenia (ANC nadir) was not correlated with G-CSF use (Wilcoxon P value 0.55), which, ruled out the possibility of G-CSF being reserved for cases with more severe neutropenia (22).

Besides a possible detrimental impact on the COVID 19 course, the G-CSF treatment may hamper the efficacy of the mRNA vaccine, as suggested by a recently published paper. The authors prospectively analyzed a cohort of 366 cancer patients who completed the two mRNA-BNT162b2 vaccine doses. Some 285 patients were on active treatment within the previous 28 days before the first vaccine dose whereas some 81 patients discontinued such treatment. A multivariate analysis showed no interaction between cytotoxic chemotherapy and antibody response, but ECOG PS2 and G-CSF use were significantly associated with lower IgG titer and lack of seroconversion after either dose of vaccine (for G-CSF

usage HR0.20, $p=0.003$ after first dose and HR0.26, $p=0.01$ after the second dose). In addition, the G-CSF usage was associated with an increased risk of vaccine associated side effects (for fever OR= 3.37, $p=0.022$) (23).

Conclusions

In conclusion, it is reasonable to consider that the recommendation for expanding the use of G-CSF during the COVID-19 pandemic should be reevaluated, as several high quality reports and meta-analysis do not show cancer patients to be at higher risk of developing more severe COVID-19 disease even when receiving anti-cancer therapy (24, 25). Strong evidences suggest that the high neutrophil count related to G-CSF treatment may

worsen the COVID-19 course, including higher risk of respiratory failure and death. In addition, a detrimental impact on mRNA vaccine efficacy and safety was recently suggested. Recommendation for G-CSF administration should remain as traditionally specified by the guidelines: regularly for FN risk > 20%, for FN risk of 10-20% in the presence of other patient related risk factors and refrained in case of FN risk <10%. In case of established FN, G-CSF should be administered only in high-risk cases (26). When it comes to COVID-19 pandemic and cancer patients, we strongly advice in favor of anti SARS-CoV-2 vaccination, including the third booster dose, along with rigorous compliance with the general protective measures (hand washing, mask wearing, social distancing).

Abbreviations:

ARDS – Acute Respiratory Distress Syndrome

COVID-19 – Corona-Virus Disease of 2019

FN – Febrile Neutropenia

G-CSF – Granulocyte-Colony Stimulating Factor

GM-CSF – Granulocyte Macrophages-Colony Stimulating Factor

ASCO – American Society of Clinical Oncology

ESMO – European Society of Medical Oncology

ANC – Absolute Neutrophil Count

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