The Effect of Neutropenia and Filgrastim (G-CSF) on Cancer Patients With Coronavirus Disease 2019 (COVID-19) Infection

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Background. Neutropenia is commonly encountered in cancer patients. Recombinant human granulocyte colony-stimulating factor (G-CSF, filgrastim), a cytokine that initiates proliferation and differentiation of mature granulocytes, is widely given to oncology patients to counteract neutropenia, reducing susceptibility to infection. However, the clinical impact of neutropenia and G-CSF use in cancer patients with coronavirus disease 2019 (COVID-19) remains unknown.

Methods. An observational cohort of 379 actively treated cancer patients with COVID-19 was assembled to investigate links between concurrent neutropenia and G-CSF administration on COVID-19-associated respiratory failure and death. These factors were encoded as time-dependent predictors in an extended Cox model, controlling for age and underlying cancer diagnosis. To determine whether the degree of granulocyte response to G-CSF affected outcomes, the degree of response to G-CSF, based on rise in absolute neutrophil count (ANC) 24 hours after growth factor administration, was also incorporated into a similar Cox model.

Results. In the setting of active COVID-19 infection, outpatient receipt of G-CSF led to an increased number of hospitalizations (hazard ratio [HR]: 3.54, 95% confidence interval [CI]: 1.25–10.0, P value: .017). Furthermore, among inpatients, 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 value: .024). This effect was predominantly seen in patients that exhibited a high response to G-CSF based on their ANC increase post-G-CSF administration (HR: 7.78, 95% CI: 2.05–27.9, P value: .004).

Conclusions. The potential risks versus benefits of G-CSF administration should be considered in neutropenic cancer patients with COVID-19, because G-CSF administration may lead to worsening clinical and respiratory status.

Keywords. COVID-19; granulocyte colony stimulating factor; cancer; neutropenia.

Neutropenia is a common side-effect of many anti-cancer therapies due to their effects on rapidly dividing hematopoietic cells. Recombinant human granulocyte colony stimulating factor (G-CSF, filgrastim) is often given to cancer patients for ongoing or impending neutropenia. During the ongoing coronavirus disease 2019 (COVID-19) pandemic, there has been uncertainty about the effect of commonly used medications, such as G-CSF, on clinical outcomes. The stimulatory effects of G-CSF on cytokine and neutrophil production [1], the association of G-CSF with acute lung injury (ALI) or adult respiratory distress syndrome (ARDS) [2, 3], and observations of COVID-19-associated cytokine storm in severely ill patients, have raised concerns about the safety profile of G-CSF in COVID-19 patients. Moreover, autopsies of COVID-19 patients have shown neutrophil extravasation in the alveolar spaces of lungs [4–6], raising concerns that G-CSF administration and the resulting neutrophil expansion could lead to exaggerated neutrophil responses, worsening respiratory function in COVID-19 patients.

Our group published a case series describing the rapid clinical deterioration of 3 COVID-19 patients soon after receiving G-CSF [7]. Herein we sought to determine the clinical effects of G-CSF in a larger cohort of cancer patients with COVID-19 illness, in order to investigate whether receipt of G-CSF in cancer patients with COVID-19 illness would increase risk of adverse outcomes.
In the primary analysis, we applied an extended Cox proportional hazards model using age (binned into ≤49, 50–59, 60–69, and ≥70 years old categories), receipt of cytotoxic (vs non-cytotoxic) chemotherapy within 30 days prior, and cancer type. We considered the top 5 cancer types in terms of prevalence and aggregated all other types into a sixth group. The first occurrence of neutropenia and the first administration of G-CSF (filgrastim or pegfilgrastim) following SARS-CoV-2 positivity were introduced as binary time-dependent covariates in the model, as these variables change over the follow-up period [14]. G-CSF events were encoded 1 day following actual administration to capture the timing of its expected effect (furthermore, the earliest evidence of ANC recovery we had was a day after G-CSF administration). Start time was defined as the date of COVID-19 diagnosis for each patient.

To determine whether G-CSF administration in the outpatient setting increased the risk of hospitalization, we applied the aforementioned extended Cox model to 379 analyzed patients with the endpoint defined as the date of admission/hospitalization.

The primary inpatient analysis was performed on the 130 hospitalized patients using a composite endpoint defined as the first occurrence of respiratory failure (defined above) or death following COVID-19 diagnosis. For the second analysis, to determine whether the degree of G-CSF response affected clinical outcomes, we categorized G-CSF recipients into high- and low-response groups, defined by the degree of ANC elevation (see Study Population), and introduced these as mutually exclusive binary time-dependent covariates.

All outpatient and inpatient patient events were right-censored (time-to-event) to 30 days, respectively, as events outside of this time window were considered unlikely to be related to COVID-19. All analyses were performed in R version 3.6.2 with the survival (version 3.1–11) [15].

**RESULTS**

To determine the relationship between G-CSF administration and clinical outcomes due to COVID-19, we assembled a cohort of 379 cancer patients at MSKCC who tested positive for COVID-19 and received cancer directed therapy within 30 days of their COVID-19 diagnosis between 11 March 2020 and 16 November 2020. These cases comprised a variety of cancer types, including breast cancer (n = 90; 24%), colorectal cancer (n = 41, 11%), lung cancer (n = 37, 10%), lymphoma (n = 30, 7%), prostate cancer (n = 27; 7%), and other cancers (n = 144, 41%). Of all patients with different cancer types, 227/379 (60%) of patients received cytotoxic chemotherapy within 30 days of their COVID-19 diagnosis. New symptoms at the time of testing are also shown: fever, cough, shortness of breath, and diarrhea (Table 1). No patients in our cohort required supplemental oxygen at home. The anticancer agents patients received within 30 days of their COVID-19 diagnosis and the COVID-19 therapies to treat them are shown in Supplementary Tables 1 and 2, respectively. Of the 379 outpatients enrolled in this study, 28 received either
In total, 130 of the 379 patients were hospitalized (34.3%) and confirmed by review of each patient's medical record; it was determined that they were admitted to the hospital for the management of COVID-19 symptoms. Using an extended Cox model with G-CSF encoded as a time-dependent covariate, G-CSF administration was significantly associated with increased risk of hospitalization in patients with COVID-19 infection (hazard ratio [HR]: 3.54, 95% confidence interval [CI]: 1.25–10.0, \( P \text{ value}: .017\), Table 2, Supplementary Figure 1). Even among patients who were asymptomatic from COVID-19 infection, this association remained significant (HR: 18.31; 95% CI: 2.51–96.8, \( P \text{ value}: .008\), Supplementary Table 3).

Next, we considered whether inpatient administration of G-CSF was associated with respiratory compromise or death (ie, the primary composite endpoint) among cancer patients (Supplementary Figure 1). Even among patients who were asymptomatic from COVID-19 infection, this association remained significant (HR: 18.31; 95% CI: 2.51–96.8, \( P \text{ value}: .008\), Supplementary Table 3).
Outpatient and inpatient swimmer plots showing time-to-endpoint (hospitalization for outpatients and respiratory failure/death for inpatients) for each patient are shown in Supplementary Figures 3 and 4. Many outpatients and inpatients appeared to reach endpoint if G-CSF was given soon after COVID-19 diagnosis (day 0).

Ten of the 16 patients with serial CBCs that were neutropenic and received G-CSF had a pre- and post-chest radiograph, and 6/10 (60%) demonstrated radiologic worsening within 7 days of receiving G-CSF (Supplementary Table 4); 3 patients that developed radiographic deterioration post-G-CSF use are shown in Supplementary Figure 5 that correlated with an increase in oxygen requirements.

To determine whether the neutrophil-inducing properties of G-CSF may relate to the poor outcomes associated with G-CSF in COVID-19 infection, we further considered the neutrophil concentrations in peripheral blood prior to and immediately after G-CSF administration. As expected, ANC and ANC/ALC (ratio of absolute neutrophil count to absolute lymphocyte count) values increased after G-CSF administration. Changes in ANC values were primarily limited to the day after G-CSF administration (Figure 2A and 2C), whereas ALC values remained relatively constant (Figure 2B). We stratified the 16 inpatients that received G-CSF with serial CBCs based on their response to ANC, computed as the log fold-change between ANC values 1 day after the day of G-CSF administration (Figure 3A).

Using response categories (“high” and “low”), we modified the extended Cox model shown in Figure 1 to categorize G-CSF events as high and low response; 9 patients and 7 patients were deemed to have a high and low response, respectively. There was a pronounced difference in the clinical outcomes of patients with low and high response to G-CSF. Although low response to G-CSF was not significantly associated with the primary composite endpoint (HR: 4.04, 95% CI: 0.80–16.7, P value: .086), high response to G-CSF was significantly associated with poorer outcomes (HR: 7.78, 95% CI: 2.05–27.9, P value: .004; Figure 3B).

The difference between high- and low-response categories was statistically significant (HR: 7.78, 95% CI: 2.05–27.9, P value: .004; Figure 3B).
### Figure 1
Forest plot showing the effect (HR) of (G-CSF) on the composite endpoint of the first occurrence of “respiratory failure” (defined in Methods) or death. HRs were computed with an extended Cox model, using binned ages and cancer type as time-independent covariates and neutropenia and G-CSF as time-dependent covariates. Abbreviations: CI, confidence interval; G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio.

### Table 1
|                          | Hazard ratio (95% CI) | P-value |
|--------------------------|-----------------------|---------|
| G-CSF                    | 3.58 (1.18 – 10.2)    | .024 *  |
| Neutropenia              | 0.95 (0.39 – 2.1)     | .907    |
| Age                      |                       |         |
| ≤49 (N=24)               |                       |         |
| 50–59 (N=54)             | 2.01 (0.67 – 6.9)     | .218    |
| 60–69 (N=40)             | 2.92 (1.08 – 9.4)     | .035 *  |
| ≥70 (N=42)               | 3.91 (1.48 – 12.4)    | .005 ** |
| Cancer                   |                       |         |
| Breast (N=59)            |                       |         |
| Colorectal (N=11)        | 3.16 (1.07 – 9.1)     | .038 *  |
| Lung (N=20)              | 2.81 (1.14 – 7.4)     | .024 *  |
| Lymphoma (N=14)          | 3.40 (1.19 – 9.9)     | .023 *  |
| Prostate (N=10)          | 1.65 (0.47 – 5.3)     | .415    |
| Other (N=49)             | 1.09 (0.46 – 2.8)     | .846    |
| Cytotoxic chemotherapy   |                       |         |
| Given within 30 days (N=84)| 1.12 (0.68 – 2.2) | .722    |

### Figure 2
Lab values of ANC (K/mcL) (A), ALC (K/mcL) (B), and their ratio, ANC/ALC (C) within a 4 day window for patients that received G-CSF around the time of G-CSF administration. Day 0 corresponds to the date of G-CSF administration. Black dashed line in each panel corresponds to the average lab value per day for all patients. Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; G-CSF, granulocyte colony-stimulating factor.
not solely explained by steroid use (n = 5/9 of high- and n = 4/7 of low-response patients received steroids).

**DISCUSSION**

The COVID-19 pandemic has complicated the delivery of effective cancer care, given the need to balance the competing risks of death from untreated cancer versus death or serious complications from COVID-19 infection [11, 16–20]. Although there have been some attempts to study the safety of administering chemotherapy to COVID-19 positive patients [11], this remains a complicated matter. In this study, we evaluated the potential impact of G-CSF use in cancer patients in the setting of neutropenia with concurrent COVID-19 infection. We observed a higher risk of hospitalization, as well as respiratory failure and death in patients that received G-CSF, particularly among patients that had a robust neutrophil response. Our observations on the inpatient side also suggest that neutropenia during COVID-19 illness itself was not an independent risk factor for adverse outcomes in COVID-19 illness.

There has recently been accumulating evidence of rapid clinical deterioration in some patients with COVID-19 due to the hyperactive immune response driving COVID-19 progression, causing extensive infiltration of myeloid cells into the lungs (particularly monocytes, macrophages, and neutrophils) [4, 21–23], leading to a cytokine storm. Zuo et al used cell-free DNA as a marker to detect neutrophil extracellular trap (NET) remnants in the blood, showing that these were strongly correlated with absolute neutrophil counts, which predict worse outcomes [6]. Lung injury is one consequence of the cytokine storm that can progress into its more severe form, ARDS [24]. Considering that neutrophil influx in the lung is a hallmark feature of ARDS [25], and that ARDS has already been reported as a potential complication of G-CSF use [2, 3], administering G-CSF to all cancer patients with COVID-19 may have detrimental clinical consequences. Similar concerns exist for patients who receive chimeric antigen receptor T (CAR-T) cell therapy [26], where G-CSF administration is generally avoided to prevent immune system overactivation, given the increased risk of cytokine storm in these patients.

To best estimate the effects of neutropenia and G-CSF on respiratory function and death, we encoded G-CSF as a time-dependent covariate, while controlling for neutropenia as another time-dependent covariate. We also compared the clinical outcomes of patients that had different levels of response to G-CSF, finding that robust G-CSF neutrophil response was associated with substantially higher hazard (HR: 7.78, 95% CI: 2.05–27.9, P value: .004) for respiratory decompensation, compared to a cytokine storm. Zuo et al used cell-free DNA as a marker to detect neutrophil extracellular trap (NET) remnants in the blood, showing that these were strongly correlated with absolute neutrophil counts, which predict worse outcomes [6]. Lung injury is one consequence of the cytokine storm that can progress into its more severe form, ARDS [24]. Considering that neutrophil influx in the lung is a hallmark feature of ARDS [25], and that ARDS has already been reported as a potential complication of G-CSF use [2, 3], administering G-CSF to all cancer patients with COVID-19 may have detrimental clinical consequences. Similar concerns exist for patients who receive chimeric antigen receptor T (CAR-T) cell therapy [26], where G-CSF administration is generally avoided to prevent immune system overactivation, given the increased risk of cytokine storm in these patients.

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to those that had less robust levels of response to G-CSF (HR: 4.04, 95% CI: 80–16.7, P value: .086). We also show that there is a substantial increase in the neutrophil to lymphocyte ratio (ANC/ALC) after G-CSF administration, previously shown to be an independent risk factor for mortality in hospitalized patients with COVID-19 [27]. Together, these results imply that the detrimental effects of G-CSF in newly COVID-19 positive cancer patients are primarily driven by patients with robust increases in ANC following G-CSF administration. Interestingly, neutropenia alone was not statistically associated with worse outcomes. Although our analysis solely considering neutropenic patients did not show a statistically significant effect of G-CSF on clinical outcomes, this is not unexpected given the small size of that cohort (n = 39).

To our knowledge, this is the first study describing the course of COVID-19 infection in selected cancer patients who received G-CSF for neutropenia. A randomized control study of G-CSF in non-cancer patients with lymphopenia was performed and found no difference in their primary endpoint (time to clinical improvement) [28, 29]. They did note a smaller number of patients progressing to critical illness in the G-CSF group, but no significant differences in the duration of hospitalization or supplemental O2 use were observed. However, the study cohort was limited (n = 200) and primarily composed of young patients with few or no medical comorbidities, who likely have good baseline pulmonary function and tend to have the best clinical outcomes with COVID-19, regardless of intervention.

This study has its limitations. First, the study ultimately included a modest number of patients that received G-CSF (n = 50). Some of our patients received pegfilgrastim instead of filgrastim, although we note that our results did not change when restricting to patients that only received filgrastim. In this observational cohort, unaccounted confounding factors are plausible. We also did not consider how inpatients with COVID-19 responded to G-CSF after the observation window (30 days after COVID-19 diagnosis).

This analysis attempted to assess G-CSF over a wide range of cancers; due to limitations in sample size, tumor-specific effects were difficult to ascertain. We also limited our primary analysis to the subset of patients who were hospitalized in order to assess our clinical endpoints of interest (respiratory failure or death). In both the inpatient and outpatient setting, adverse events (ie, hospitalization and severe respiratory failure, respectively) were only observed in patients receiving G-CSF within 10 days of COVID-19 diagnosis. The impact of G-CSF later in a patient’s course requires further study, as does the impact of G-CSF in those cancer patients who are persistently COVID-19 positive [30]. Although our analysis adjusts for the neutrophil count prior to G-CSF administration, we have not incorporated data on concurrent therapies such as chemotherapies or surgery prior to the diagnosis of COVID-19 in these patients.

### Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyrighted and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

**Figure S1:** Schematic diagram showing the experimental design and time-dependent survival modelling. Neutropenia and G-CSF are encoded as time-dependent covariates that are active after the time of occurrence (blue and red lines, respectively).

**Figure S2:** Boxplot showing the severity of neutropenia, as measured by the ANC nadir (K/ml), in patients who did and did not receive G-CSF.

**Figure S3:** Swimmer plot showing each patient’s time to primary outpatient endpoint—in this case, inpatient hospitalization (“X”) after receiving G-CSF (represented by pink line). Each bar represents one patient and bar length represents time to endpoint. Patients were more likely to reach this endpoint if G-CSF was given soon after COVID-19 diagnosis (day 0). Patients that did not meet endpoint had more patient-time to receive G-CSF.

**Figure S4:** Swimmer plot showing each patient’s time to primary inpatient endpoint—in this case, respiratory failure and death (“X”) after receiving G-CSF (represented by pink line). Each bar represents one patient and bar length represents time to endpoint. Patients were more likely to reach this endpoint if G-CSF was given soon after COVID-19 diagnosis (day 0). Patients that did not meet endpoint had more patient-time to receive G-CSF.

**Notes**

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