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Original Article

Caveats, Nuances and Benefits of the Clinical Use of granulocyte Colony-Stimulating Factors in Cancer Patients with Coronavirus Disease 2019

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ABSTRACT

The rapid escalation of the Coronavirus Disease 2019 (COVID-19) pandemic has prompted the reformulation of a number of clinical protocols for cancer management, to reduce the hospital admissions and dampen the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Multiple clinical guidelines have emphasized the need to reinforce the supportive care delivery during the pandemic, including the recommendations to expand the use of granulocyte colony stimulating factors (CSFs) in the prophylaxis and treatment of febrile neutropenia. However, the role of CSFs in the pathogenesis of COVID-19 has not been fully elucidated and concerns have been raised for its extensive use in the pandemic era. The role of granulocyte CSFs in COVID-19 has been reviewed, along with clinical data on the pharmacological manipulation of CSFs in cancer patients and COVID-19. CSFs seem to provide a protective role in the initial phases of SARS-CoV-2 infection, enhancing the antiviral immune- response. However, in patients experiencing a hyperinflammatory phenotype of COVID-19, CSFs effects appear detrimental. In addition, clinical studies seem to suggest that the use of CSFs in the earlier stage of COVID-19 has a favorable safety profile. In opposition, CSFs used in cancer patients with febrile neutropenia may worsen the COVID-19 course and accelerate the progression to a more severe phenotype. A number of clinical trials is ongoing, with either agonists or antagonists of the CSFs, thus expected to inform on the opportunity to revise the clinical recommendations on CSFs in cancer patients. To date, no major disruptions of the clinical cancer care should be pursued, enhancing a value- based approach in the priority-setting for oncological treatments during the COVID-19 pandemic, including the best supportive care.

Keywords: SARS-CoV-2 Pandemic, COVID-19, Supportive care, Colony stimulating factors, Cancer, Impact on cancer treatment.

INTRODUCTION

The rapid escalation of the SARS-CoV-2 related disease (COVID-19) pandemic in 2020 has challenged the health systems and service delivery capacities of all the countries in the world. With more than 55 million persons affected and 1.3 million patients died, as of November 2020, COVID-19 pandemic has been defined as the most challenging global health problem of the last decades, having conditioned any aspect of the social, politic and health related contextures.[1,2]

In response to the need to prioritize the efforts to tackle the pandemic health demands while assuring the delivery of essential health services, like cancer care, the scientific societies have provided a number of adaptations of the clinical protocols for cancer management, to reduce the hospital admissions and dampen the risk of SARS-CoV-2 infection. The formulation of clinical recommendations has been essentially based on expert inputs, aiming to assure the safest conditions for patients receiving cancer treatments.[3] In the efforts to harmonize the value- based clinical decisions making, the European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO) and other key cancer Organizations have developed frameworks and adapted recommendations for cancer management.[4-10] The essential principles of beneficence and non-maleficence have been pursued to assure the delivery of established cancer treatments, and enforce the supportive care capacity; this includes the appropriate prevention and management of chemotherapy- related neutropenia.[11-13] The use of colony-stimulating factors for Granulocytes (G-CSF) such as filgrastim and its biosimilar and subsequent compounds (e.g., pegylated formulations) and in a less extent of the Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) analogues like sargramostim, has been emphasized in multiple COVID-19-adapted clinical guidelines as

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instrumental to assure the safest treatment delivery.[14] However, data on the safe use of CSFs in patients with cancer and COVID-19 have not been reviewed before. The aim of this work is to describe the role of CSFs and related compounds in the pathogenesis of COVID-19 and report the clinical safety data on the use in patients with cancer and COVID-19, to understand the rationale behind the adapted clinical guidelines recommendations and portray the *nuances*, possible *caveats* and suggested *benefits* in this setting.

RESEARCH METHODOLOGY

The lead authors (DT, GC) developed a research strategy run on PubMed, Google Scholar and Scopus, using the research terms "COVID-19", "SARS-CoV-2", "cancer", "neutropenia" – variously combined with the Boolean operators (timeline: January – November 2020; no language restriction; first run: 5th November 2020; re-check: 25th of November). The abstracts submitted to the ASCO and ESMO 2020 meetings were manually searched, to identify adjunctive references. The principal clinical guidelines for the clinical use of CSFs were consulted, including the proposed adaptations for cancer management during COVID-19 pandemic.[4-10] The bibliography lists of the most relevant papers were consulted for snowballing. Three authors (GC, FG, DT) selected the pertinent eligible from the scoping research, and extracted the papers discussing CSFs use, COVID-19 and cancer. The major findings of the papers were then synthetized in an Excel Table, shared to all the authors to give inputs. Eventually, to study the landscape of the current clinical trials, we consulted the WHO International Clinical Trials Registry Platform at https://apps.who.int/trialsearch.

The functions of CSFs in the immune response and the role in the pathogenesis of COVID-19

G-CSF, GM-CSF, and the macrophage colony-stimulating factor (M-CSF/ CSF1) are three cytokines with pleiotropic effects on the immune- regulation. CSFs are circulating glycoproteins,[15] harboring strategic functions in the steady state and in inflammatory responses, by governing the differentiation and maturation of granulocytes and monocytes – via autocrine, paracrine and endocrine loops.[16] In the immune response dynamics, the inflammation is lighted by macrophages, which are reciprocally stimulated by T-cell-derived cytokines and various antigenic stimuli. The activated macrophages can produce pro-inflammatory cytokines, including the interleukin (IL)-1 and the tumor necrosis factor (TNF), which amplify the pro-inflammatory signaling to the neighboring non-immunocompetent cells (e.g., endothelial or epithelial cell), which can in return be activated to produce CSFs. CSFs activity is mediated through membrane receptors. Each receptor shows variable features and structures: M-CSF receptor is a homo-dimeric class III tyrosine kinase receptor; GM-CSF receptor is represented by an unique α-chain and a common β-chain; G-CSF receptor is a type I cytokine receptor. The interaction between the receptors and its ligand activates different transduction pathways, such as JAK/STAT, Ras/MAP and PI3K/Akt.[17] G-CSF receptor is highly expressed in the bone marrow and on the neutrophils. In the bone marrow, G-CSF receptor mediates the proliferation and differentiation of precursor cells into mature granulocytes. It is demonstrated that G-CSF treatment alters the equilibrium of chemokines in the bone marrow, by both increasing chemokines expression like CXCL2 from the endothelium and decreasing CXCL12 expression from osteoblast lineage cells, resulting in a rapid release of neutrophils into the blood stream.[18] Also, G-CSF stimulates the survival, proliferation, differentiation, and effector functions of mature circulating neutrophils, thus enhancing the phagocytosis, bactericidal activity, antibody-dependent cellular toxicity, and cytokine production. While the functions of G-CSF have been traditionally restricted to the innate immune system, CSFs can influence also the adaptive immune responses.[19,20] Therefore, the role of CSFs is positioned at the crossroads of a myriad of biological functions. This may explain the controversial role of CSFs in the pathogenesis of infectious diseases, including COVID-19.

Patients with COVID-19 present profound dysfunctions of the immune system.[21] In the complex dynamics of immune dysregulations observed in this disease, both hyper immune activation and immunosuppression have been recalled as mechanisms of pathogenesis, affecting the overall outcome.[22,23] The previous experiences with viral infections such as influenza have suggested a role of G-CSF in the determination of an immune-depressing alveolar *milieu*, facilitating secondary bacterial infections, ultimately compromising the overall prognosis.[24,25] GM-CSF has been showed to play a role in the pathophysiology of acute respiratory distress syndrome (ARDS) by inducing the production of pro-inflammatory cytokines such as interleuin-6 (IL-6),[26] that is a proposed hallmark of severe COVID-19. The upregulation of both GM-CSF and G-CSF and the raise of circulating CD4+ and CD8+ T lymphocytes expressing GM-CSF receptors have been reported as adverse prognostic factors in COVID-19, in comparison to healthy subjects.[27,28] The current disease modelling suggests a double-edge role of CSFs in COVID-19: in the initial phase of SARS-CoV-2 infection, the CSFs mediated response is physiological and potentially can enhance the immune- clearance of the virus, *in medias stat* of the innate and adaptive responses.[29] However, GM-CSF can accelerate the progression to a hyperinflammatory status in more advanced stages, becoming a key mediator of the adverse pathogenesis.[28]

The clinical use of CSFs in the prophylaxis and management of neutropenia induced by antineoplastic treatments

The most frequent dose-limiting toxicity of antineoplastic chemotherapy in patients with cancer is hematological; among all, neutropenia is positioned as the main adverse effect resulting in dose delays and reductions.[30,31] Patients experiencing neutropenia with fever are more exposed to infectious complications, including fatal outcomes in frailer patients, with more toxic regimens and/or in a deep immune-suppressed status.[31] Moreover, moderate to severe neutropenia is a common contraindication to administrate cytotoxic chemotherapy, undermining the possibility to maintain adequate relative dose intensity (RDI) and dose- density of the treatments. Dose reductions, reduced RDI and dose delays of chemotherapy have been all associated with a worse prognosis, especially in the early setting of treatment for some tumor types (e.g., adjuvant and neoadjuvant treatment of breast cancer).[32,33] In particular, the findings from multiple studies have concluded that a RDI inferior to 85% is associated with reduced benefit of anticancer treatments and poorer survival.[34] The human recombinant G-CSF is currently used as a pharmacological agent to prevent and treat chemotherapy- related neutropenia, representing a valuable weapon to tackle the dose modifications implicated by this adverse effect.[35] There are four pharmacological preparations of recombinant human G-CSF currently available: filgrastim (not-glycosylated) and lenograstim (glycosylated) are short acting; pegfilgrastim (pegylated) and lipegfilgrastim (glycopegylated) have a longer plasmatic half-life. There are two main strategies commonly considered for the prevention of chemotherapy- associated neutropenia: the primary and secondary prophylaxis, instituted *de novo* in patients starting a new treatment or *in itinere*, if experiencing neutropenia under treatment, respectively. The international guidelines for the supportive care suggest that primary G-CSF prophylaxis should be always considered when the risk of febrile neutropenia is higher than 20%.[36] When the calculated risk of neutropenia is intermediate (10-20%), the guidelines suggest to identify competitive risk factors of severe complications Table 1. No indication of routinely primary prophylaxis is set for regimens with a low potential to induce febrile neutropenia (<10%). Secondary prophylaxis is recommended in patients experiencing febrile neutropenia, and for whom dose reductions or delays can be detrimental, as significantly affecting the benefits of the treatments. Both in secondary and in

primary prophylaxis, filgrastim or lenograstim should be started from 24 to 72 hours after the administration of chemotherapy;[37,38] G-CSF analogues with short half-life should be continued daily until the absolute neutrophil count is more than 1000/L, after the nadir. When pegylated analogues are preferred, a single injection is enough, once per cycle, at 24 - 72 hours after chemotherapy administration. The therapeutic use of G-CSF for patients with febrile neutropenia has the primary purpose to reduce the neutropenic time and hospital stay. A recent metanalysis suggested no significant improvement in overall survival for patients with chemotherapy- related febrile neutropenia treated with filgrastim,[39] arguing against a systematic use in all patients with febrile neutropenia. Therefore, G-CSF should be considered in selected cases of patients with treatment- induced febrile neutropenia and not in all comers.[40-44]

The clinical use of CSFs in patients with cancer and COVID-19

Clinical data on the Safety of CSFs in patients with COVID-19. G-CSF is administrated routinely in patients with cancer for prophylaxis or management of neutropenia. In September 2020, an expert panel from the US *National Comprehensive Cancer Network* (NCCN) has developed guidance for the use of granulocyte stimulating factors during the COVID-19 pandemic (Table 2). The panel agreed on the value to provide G-CSF primary prophylaxis for regimens deemed to pose high risk of neutropenia, as in the standard clinical practice, and extended the indication in patients at intermediate risk and selected patients at low risk of febrile neutropenia.[45] The primary aim of these changes were to reduce the hospital admission of patients, limit frequent visits to outpatient centers and, in case of febrile neutropenia, shorten the time to neutrophil recovery. While the safety of stimulating factors in patients with cancer is well established, the use in patients with COVID-19 seems still controversial.[46] It is unclear if the use of G-CSF can either increase the risk of SARS-CoV-2 infection, accelerate the progression to symptomatic disease or induce a more severe phenotype.[47] Overall, based on the proposed role of G-CSF in stimulating the inflammatory response in the lungs, by attracting neutrophils and macrophages, concerns have been raised.[48] Actually, the accumulation of neutrophils in the lung is a hallmark of ARDS, including COVID-19-related ARDS; also, the use of filgrastim and related compounds has been implicated in the pathogenesis of some iatrogenic ARDS.[49] G-CSF is presently viewed as a double-edged sword, and the pharmacological use of CSFs may result in opposite effects, based on the COVID-19 stage, severity, and disease phenotype; indeed, the modifying effect of cancer- related immune- dysregulations may be another factor to account. That is why the NCCN panel expressed a caveat for patients with pulmonary infections, especially in case of certain or suspected SARS-CoV-2 infection.[45] Similarly, some

Table 1: Clinical indications for the use of colony stimulating factors, based on the principal guidelines for supportive care in oncology.

	NCCN [40]	ESMO [41]	ASCO [42]	EORTC [43]	AIOM [44]
Definition of FN	T*>38.3°C and ANC <500 or ANC <1000 with a predicted decline to <500 in 48 h	T# >38.3°C and ANC <500 or expected to fall below 500	NR	T>38°C^ or clinical signs of sepsis and ANC<500 or <1000 predicted to fall below 500 within 48 h	T‡ >38°C and ANC <500 or ANC <1000 predicted to fall below 500 within 48 h
Indications for Primary G-CSF prophylaxis	FN risk>20% FN risk 10-20% and ≥1 risk factor ** Previous FN	FN risk>20% FN risk 10%–20% in selected patients ##	FN risk>20% (*estimation of the risk based on disease and treatment-related factors and not only the chemotherapy regimen*)	FN risk>20% FN risk 10-20% in selected patients^^	FN risk >20% FN risk 10%–20% based on a multifactorial risk assessment ⌗
Indications for secondary G-CSF prophylaxis	Dose- limiting neutropenic event (if no prior use of G-CSF)	Dose- limiting neutropenia resulting in a non-desirable dose-reduction or delay of ChT (e.g., curative setting)	Dose- limiting neutropenia resulting in a non-desirable dose-reduction or delay of ChT (e.g., compromise of treatment outcome)	Previous neutropenia	Dose- limiting neutropenia resulting in a non-desirable dose-reduction in the curative setting
Therapeutic use of G-CSF	Based on risk-factor assessment	NR	Based on risk-factor assessment	FN in special situations ^^^	Based on a multifactorial risk assessment

ANC is expressed as cells per microliter. Therapeutic use of G-CSF is intended only for patients with cancer experiencing treatment- related FN.
ANC: Absolute neutrophil count; FN: Febrile neutropenia; ChT: Chemotherapy; T: Temperature; h: hours; NR: Not reported; G-CSF: Granulocyte colony stimulating factor (i;e;: filgrastim: biosimilars: subsequent compounds); NCCN: National comprehensive cancer network; ESMO: European society for medical oncology; ASCO: American society of clinical oncology; EORTC: European organisation for research and treatment of cancer; AIOM: Italian association of medical oncology.
*Intended as oral temperature, assessed either as a single temperature, or over 1 hour. # Oral temperature of >38.3°C or two consecutive readings of >38.0°C for 2 hours. ^Fever is defined as a rise in axillary temperature to >38.5 °C sustained for at least one hour. ‡T>38°C for more than 1 h, or temperature >38°C for 3 consecutive measurement when ANC <500 or <1000 predicted to fall below 500 within 48 h. ** the recommendation for the intermediate risk is based on a multi-factorial assessment, based on the identification of specific risk factors associated with poor clinical outcomes or complications resulting from febrile neutropenia or infection: sepsis syndrome, age >65 years, profound neutropenia (i.e., ANC<100), neutropenia expected to last >10 days, pneumonia, invasive fungal infection, clinically- documented infections, hospitalization at the time of fever (i.e., possible resistant pathogens), prior episode of febrile neutropenia, previous ChT and/or radiation therapy, HIV status. ##patient's age and any coexisting morbidities or reduced bone marrow reserve (e.g., extensive radiotherapy or HIV-infection with neutropenia). ^^particular attention should be given to the assessment of patient characteristics that may increase the overall risk of FN. ⌗ the multiple factors to be considered include patient-, disease and treatment- related considerations. ^^^patients who are not responding to appropriate antibiotic management and who are developing life-threatening infectious complications, such as severe sepsis or septic shock.

Table 2: Proposed extended indications for the clinical use of G-CSF during COVID-19 pandemic.

	Primary prophylaxis	Secondary prophylaxis	Therapeutic use
COVID9 adapted **NCCN** [45]	FN risk≥10% FN<10% and intrinsically higher risk for FN due to poor bone marrow reserve	No change in the recommendations	All patients with FN

NCCN: National comprehensive cancer network; FN: Febrile neutropenia

authors have argued against the systematic use of G-CFS as primary prophylaxis for patients receiving conventional chemotherapy during the pandemic, for a hypothetical though unconfirmed risk of increasing pro-inflammatory cytokines involved in ARDS, such as IL-6.[50] Presently, none of these concerns is evidence- based and conclusive studies in humans are largely missing.[51] In the absence of controlled studies, the occurrence of an adverse outcome in cancer patients with febrile neutropenia treated with C-GSF is controversial to interpret, including in patients with co- occurring COVID-19, as both represent events with an intrinsic prognostic significance, in a *de facto* frailer population.[52] Therefore, the very poor outcomes reported in the small studies in literature should be viewed as non-conclusive, given the high risk of complications, especially for patients with advanced cancer, deep neutropenia and multiple co-morbidities.[53]

Few clinical studies have been reported on G-CSF in cancer patients with COVID-19. The first study was a small series (n=3) of patients admitted for chemotherapy- related neutropenia and treated with G-CSF.[54] The authors reported the case of one 65-year old man with two malignancies, a metastatic prostate cancer and a relapsed acute myeloid leukemia, who had experienced a fatal outcome after few days from the administration of filgrastim for febrile neutropenia. Then, they reported the case of one patient with a diffuse large B-cell lymphoma and another one with an invasive ductal breast carcinoma, treated with G-CSF, who had not experienced an adverse outcome. The investigators argued a possible role of G-CSF in accelerating the progress of COVID-19 to more severe phenotypes, and performed an analysis of blood biomarkers, speculating on the prognostic and predictive significance of an increased absolute neutrophil- to-lymphocyte count ratio. More recently, a research group from the Memorial Sloan Kettering Cancer Center NYC in USA has explored the effect of neutropenia and filgrastim in cancer patients with COVID-19 infection.[55] The authors enrolled 304 patients in a retrospective observational cohort, showing no independent association between neutropenia during COVID-19 course and severe respiratory failure or COVID-19-related mortality (HR: 0.71, 95% Cl: 0.34-1.50, P value: 0.367). However, patients receiving filgrastim seemed more likely to require oxygen supplementation and experience a fatal outcome (HR: 2.97, 95% CI: 1.06-8.28, P value: 0.038). The adverse prognostic effect appeared magnified in those patients who had experienced brisk responses to the G-CSF administration (i.e., increase in absolute neutrophil count at day +1 post-G-CSF administration above the 50th percentile; HR: 5.18, 95% CI: 1.61-16.64, P value: 0.006). The authors argued that a subset of patients treated with G-CSF may experience an overwhelming infiltration of inflammatory myeloid cells into the lungs, that is enhanced by filgrastim, resulting in a possible detrimental effect on the overall survival. Therefore, a special precaution in the use of filgrastim should be taken for some cancer patients hospitalized with severe COVID-19.

CSF- blockade as a pharmacological strategy to manage COVID-19 patients. The need to build and rapidly scale-up the treatment armamentarium in a priority area of health with high unmet needs has prompted the development of various clinical trials, based on a multitude of pre-clinical assumptions.[56,57] One attempt to control the hyper-inflammatory syndrome in COVID-19 has been pursued with the use anti-cytokine molecules. A number of clinical trials has utilized anti-CSF molecules, with the primary aim to tackle the macrophage-orchestrated immune dysregulations observed in severe COVID-19.[26,58,59] The GM-CSF axis seems mostly involved in the initiation and perpetuation of the pathological inflammatory process more than the G-CSF related signaling, that has been assigned a protective role. Accordingly, clinical trials with G-CSF mimicking molecules have been developed in the earlier stages of COVID-19 while anti-GM-CSF are being implemented in more severe diseases.

The first clinical study published with CSF in COVID-19 was an open-label randomized trial (ChiCTR2000030007), performed in China. The investigators used a recombinant human granulocyte colony-stimulating factor (rhG-CSF) at the dose of at 5 μg/kg three times per day, against a control group receiving the usual care.[60] The primary endpoint of the study was the time from randomization to improvement of at least 1 point on a 7-category disease severity score. The scale graded the clinical severity of the COVID-19, from 1 (i.e., non-hospitalized patient with normal activities) to 6 (i.e., hospitalized patient requiring extracorporeal membrane oxygenation, invasive ventilation, or both) and death (score 7). The study did not enroll patients with cancer. Two- hundred patients with COVID-19, related pneumonia and an absolute lymphocyte count ≤800/μL were enrolled 1:1 in the trial. The incorporation of rhG-CSF did not improve the outcome, as the time to clinical improvement was similar between the two groups (hazard ratio, 1.28; 95% CI, 0.95-1.71; P = 0.06). Patients who had received rhG-CSF were less likely to progress to ARDS, sepsis, or septic shock (absolute risk reduction −13%; 95%CI, −21.4% to −5.4%) or to die (HR, 0.19; 95%CI, 0.04-0.88), suggesting a non-detrimental effect of this molecule on the pathogenesis of COVID-19. Interestingly, patients with baseline lymphocytic count ≤ 400/μL seemed to derive the greatest benefit. The study excluded patients with a higher likelihood of experiencing a hyper-inflammatory syndrome and in general patients with severe COVID-19 (exclusion criterion number 2, per protocol: critical illness requiring invasive ventilation, shock or other organ failure that requires admission to intensive care unit); therefore, the safety of CSFs in patients with ARDS and severe disease course cannot be extrapolated from this study.

The first study published with a monoclonal antibody neutralizing GM-CSF was an Italian open label cohort of COVID-19 patients treated with mavrilimumab, which targets GM-CSF receptor-α.[61] The study enrolled 13 patients with severe COVID-19 pneumonia (acute lung injury or ARDS) and systemic hyperinflammation (i.e., elevation of serum inflammation markers C-reactive protein >100 mg/L; ferritin >900 μg/L). The trial did not show an improved 28-day mortality of the patients treated with mavrilimumab versus a control group in the usual care arm; however, mavrilimumab was associated with a higher proportion of patients experiencing clinical improvement, in a shorter time (mean time to improvement 8 days [IQR 5 to 11] vs 19 days [11 to >28], p=0.0001). A second clinical trial has used a direct GM-CSF inhibitor, the neutralizing monoclonal antibody lenzilumab, in hospitalized patients with COVID-19 pneumonia and various risk factors for poor outcomes.[62] The study enrolled 12 patients; the use of lenzilumab appeared to be safe and well tolerated, resulting in a clinical improvement of the general conditions in 11/12 (92%) patients, along with a better respiratory performance. A subsequent case-control analysis was developed for this cohort, suggesting an improved clinical outcome for the patients treated with lenzilumab versus patients in the usual care, in term of time to clinical improvement (median of 5 days versus 11 days; P= 0.006) and respiratory performance.[63] Both the analyses from these two clinical trials using anti-GM-CSF (mavrilimumab, lenzilumab) are to be considered ad interim, aiming to orient the research priorities, inform timely on the safety profile and disengage from futile or risky treatments. The role and value of anti-GM-CSF molecules is under investigation in numerous clinical trials, using new drugs like otilimab (NCT04376684/ OSCAR), gimsilumab (NCT04351243/ BREATHE), TMJ2/TJ003234 (NCT04341116) and namilumab (UK-based CATALYST clinical trial program). The studies with G-CSF mimetics and anti-GM-CSF molecules will clarify whether CSFs may play a valuable role in the treatment of patients with COVID-19, possibly informing on the opportunity to withhold CSFs in cancer patients with febrile neutropenia in scenarios at higher disease severity and/or elevated community transmissibility of SARS-CoV-2. The systematic exclusion of patients with cancer in the clinical trials for COVID-19 is mostly unjustified, as these patients have a higher risk of SARS-CoV-2 infection and an increased probability to experience an adverse disease course, thus representing a population with a high unmet need in the pandemic era (Table 3).

Table 3: Ongoing clinical trials assessing the value of agonist or antagonist molecules of the granulocyte colony stimulating factors for the management of COVID-19.

Intervention	Activity	Trial ID	Primary sponsor	Target size (patients)	Phase	Primary outcome	Countries
rhG-CSF	agonist	ChiCTR2000030007	The First Affiliated Hospital of Guangzhou Medical University	200	0	Clinical symptoms improvement	China
Sargramostim	agonist	NCT04411680	Partner Therapeutics, Inc.	60	II	Change in oxygenation parameters	United States
Multiple agents; includes Namilumab	antagonist	EUCTR2020-001684-89-GB (CATALYST)	University of Birmingham	168	II	Change in oxygenation parameters	United Kingdom
Otilimab	antagonist	EUCTR2020-001759-42-GB	GlaxoSmithKline Research & Development	800	II	Safety and tolerability	Multiple countries
Molgramostim (rHuGM-CSF)	agonist	EUCTR2020-001654-21-DE	Justus-Liebig-University Gießen	238	II	Cumulative proportion of patients who require mechanical ventilation during a 15-day period following randomization	Germany
Gimsilumab	antagonist	NCT04351243 (BREATHE)	Kinevant Sciences GmbH	227	II	Incidence of mortality	United States
Sargramostim	agonist	NCT04400929	Singapore General Hospital	30	II	Change in oxygenation parameters	Singapore
Molgramostim nebuliser solution	agonist	NCT04569877 (GI-COVID)	University of Giessen	238	II	Requirement of mechanical ventilation	Germany
TJ003234	antagonist	NCT04341116	I-Mab Biopharma Co. Ltd.	384	II/III	Proportion of subjects recovered	United States
Sargramostim	agonist	EUCTR2020-001254-22-BE (SARPAC)	University Hospital Ghent	80	IV	Change in oxygenation parameters	Belgium
Sargramostim	agonist	NCT04326920	University Hospital, Ghent	80	IV	Change in oxygenation parameters	Belgium; Italy
rhG-CSF	agonist	IRCT20200502047268N1	Semnan University of Medical Sciences	10	NR	Blood lymphocytes change	Islamic Republic of Iran

Interventional clinical trials were searched and extracted from the WHO International Clinical Trials Registry Platform (last access 25 Nov 2020) at https://apps.who.int/trialsearch/Default.aspx. G(M)-CSF: Granulocyte(macrophage) colony stimulating factor; rH and rHu: Recombinant human; ID: Identification code.

CONCLUSIONS

The clinical use of CSFs in patients with cancer is essential to prevent and treat febrile neutropenia. The role of G-CSF and GM-CSF in the pathogenesis of COVID-19 has been partially described: in the early phase of the viral infection, these mediators seem to contribute to the clearance of SARS-CoV-2; however, in the hyper-inflammatory status, their role may be detrimental and accelerate the progression to ARDS. Preliminary clinical observations have resulted in some caveats in the extended clinical use of CSFs in patients with cancer, especially if presenting with pulmonary infections. In addition, data from clinical trials seem to report a possible role of the G-CSF analogues in the earlier stage of COVID-19, and of the anti-GM-CSF molecules to tackle the hyperinflammatory status of severe COVID-19. While none of the caveats for the clinical use of CSFs in established indications is conclusive, it is critical to pursue a value- based treatment- decision making during the COVID-19 pandemic, and not dissuade from delivering essential treatments, especially when the precautionary assumptions are largely speculative. Clinical trials will clarify the beneficial, noxious, or irrelevant role of CSFs in patients with COVID-19, and how they can modulate the risk of infection or the disease course in SARS-CoV-2 infected cancer patients. This must pass through the inclusion of cancer patients in the clinical trials for COVID-19. In the meantime, there is no need to alter dramatically the standard clinical practices, unless robust evidence will emerge, prompting a change of the recommendations. Cancer care is a priority care during COVID-19 pandemic, and the established cancer treatments are healthcare priority, including the most valuable supportive and palliative care interventions.

DECLARATIONS

Author's contribution: The paper has been developed with the substantial contribution of all the authors. GC and DT conceptualized and designed the study; FG and DT worked on the acquisition, analysis and interpretation of the data, under the supervision of GC; all the authors contributed to the drafting of the paper, critical revision and provided inputs for the improvement of the contents. A final copy of the manuscript has been shared, reviewed, and approved by all the authors.

Statement of conflict of interest: GC has received honoraria from Pfizer, Novartis, Lilly, Roche; fees for expert testimony and medical education from Pfizer; and has participated in advisory boards for Pfizer, Roche, Lilly, Novartis, Seattle Genetics, Celltrion. All the other authors declare no competing conflicts of interest.

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