Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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ANNALS OF ONCOLOGY driving innovation in oncology

EDITORIAL

Personalized cancer supportive care in COVID-19 era

Myelosuppression continues to represent a major cause of dose-limiting toxicity associated with cytotoxic cancer therapy. Fever in patients with severe neutropenia (febrile neutropenia; FN) represents a presumption of infection associated with considerable morbidity and mortality.[1] FN risk increases proportionally with the severity and duration of neutropenia, and serious medical complications and mortality increase with the number of major medical comorbidities and infectious complications.[2,3] While initiation of empiric broad-spectrum antibiotics has greatly reduced the previous high death rate associated with FN, in hospitalized patients it remains unacceptably high.[3,4] FN in patients receiving cancer chemotherapy may also result in treatment delays, dose reductions or early stopping, leading to a reduction of relative dose intensity.[5,6] Although a number of risk factors for FN have been identified and validated in multivariable models, a patient's risk of FN is generally based on highly selected patients entered into pivotal randomized, controlled trials (RCTs) establishing the efficacy and safety of the regimen.[7–9] The risk for neutropenic complications has consistently been shown to be greatest during the first cycle of chemotherapy when most patients are still receiving the full dose and schedule.[8] RCTs of primary prophylaxis with recombinant granulocyte colony-stimulating factors (G-CSF) initiated in the first cycle within 24—72 h of chemotherapy and continued until neutrophil recovery by days 7—14 have consistently demonstrated a significant reduction in the risk of FN.[10] Clinical practice guidelines from multiple professional organizations recommend routine primary prophylaxis with G-CSF in patients at 20% or greater risk of FN, and consideration of their use with lower risk regimens when utilized in patients with one or more risk factors for FN.[11–13] Despite the paucity of data supporting G-CSF dose and duration outside of that used in pivotal RCTs and incorporated into the regulatory labels and guideline recommendations, clinicians have considerable discretion in judging individual patient need and the appropriate schedule of G-CSF prophylaxis in patients receiving cancer chemotherapy.[9,14] We clearly must continue to encourage controlled clinical trials to confirm the safety and efficacy of off-label G-CSF prophylaxis schedules outside of current recommendations.

One such trial is reported in this issue of the *Annals of Oncology* by investigators from Canada. Clemons et al[15] conducted an open label, multicenter, randomized, non-inferiority trial comparing 5 versus 7—10 days of primary G-CSF prophylaxis in 466 patients with early-stage breast cancer receiving adjuvant or neoadjuvant chemotherapy. The primary outcome was a composite of either FN or treatment-related hospitalization, while secondary outcomes included chemotherapy dose reductions, delays, or discontinuation. The proportion of patients with at least one composite outcome was 11.8% for the 5-day schedule compared with 15.0% for 7/10-day control arm. In the primary analysis, the authors conclude that for patients eligible for and selected for this trial, the difference in risk per cycle was consistent with non-inferiority of a 5-day schedule compared with 7/10 days. While acknowledging the challenges imposed by the mid-trial protocol change from three-arm to two-arm and the imbalance in the initial 7-day and 10-day arms, the authors conclude that 5 days of primary G-CSF prophylaxis should be considered the standard of care. Unfortunately, the potential for selection bias of younger, healthier patients for this trial calls into question such a broad assertion. While the conclusion supporting less intensive supportive care may be valid for younger healthy people, it may not hold for older and more vulnerable individuals. The authors do not report the frequency of important comorbidities or other FN risk factors other than age and treatment regimen. Imbalances in such risk factors between treatment groups may occur purely due to chance, despite randomization. The authors acknowledge the imbalance in the decline in events from the intention-to-treat analysis to the per-protocol analysis between the 7/10-day arm (13%) and the 5-day arm (40%). Of note, the G-CSF schedule was observed to increase more often in the 5-day arm and decrease more often in the 7/10-day arm. Finally, the observed number of events in both arms was considerably lower than anticipated, reducing study statistical power which, when combined with the likely selection bias and protocol deviations discussed earlier, limits the claim for non-inferiority for the 5-day intervention across a broad patient population. While the authors attribute these limitations to the pragmatic nature of the trial capturing real world experience, they beg for further controlled trials before claiming a new standard of care.

Nevertheless, it is reasonable to assume that some patients receiving cancer chemotherapy do not require a full 7—10 days of prophylactic G-CSF. At the same time, it would be unreasonable to assume that no patients benefit from the recommended G-CSF schedule. In fact, in the context of the current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic and risk for coronavirus disease 2019 (COVID-19) illness, there has been considerable discussion of extending the recommendations for prophylactic G-CSF to patients receiving cancer chemotherapy considered at lower risk for FN. Early

reports from China and now from the USA have suggested that patients with cancer are over-represented and more likely to experience severe complications including mortality.[16–19] While cancer therapy can sometimes be safely delayed or modified, many patients still require known effective systemic therapy associated with an increased risk of FN and immune suppression putting them at increased risk for COVID-19 and serious complications. Aggressive supportive care strategies, including prophylactic G-CSF, have become an important part of the discussion for enabling patients to continue cancer therapy, while reducing the risk of FN and exposure in the emergency room or hospital when the health system is stressed. In an effort to reduce FN risk in patients receiving chemotherapy and reduce exposure to risk through the health care system, the National Comprehensive Cancer Network (NCCN) has posted interim recommendations on the use of hematopoietic growth factors including G-CSF[13] (https://www.nccn.org/covid-19). In the context of increased risk for COVID-19 associated with excess exposure to the heath care setting resulting from the development of FN, prophylactic G-CSF recommendations have been extended to all patients receiving chemotherapy regimens at intermediate risk of FN (10%–20%) as well as patients receiving low-risk regimens whose age or comorbidities place them at inherently higher risk for FN and its complications. An important caveat to this recommendation is for patients with COVID-19 and symptoms or signs of acute respiratory distress syndrome (ARDS). As G-CSFs have been suspected of increasing production of inflammatory cytokines, the potential for causing further harm requires extreme caution in patients with active COVID-19.[20]

G-CSF has become part of routine care for patients receiving cancer chemotherapy associated with a high risk for FN. The costs and toxicities associated with G-CSF prophylaxis in this setting deserve careful and systematic study to better identify patients in need of the recommended schedule to enable safe delivery of potentially curative chemotherapy and those who may benefit from more abbreviated schedules, potentially reducing cost and side-effects. Despite the limitations of the RCT reported in this issue of *Annals of Oncology*, Clemons et al.[15] are to be lauded for taking on this important but difficult challenge. At the same time, in the current global COVID-19 crisis, care must be taken in patients requiring cancer therapy to reduce the risk of serious complications such as FN and minimize patient exposure and resource utilization that can further place both themselves and the health care system at risk.

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