How Can Oncology Nurses and Advanced Practice Providers Reduce the Burden of Chemotherapy-Induced Febrile Neutropenia in the US?

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Background: Neutropenia and febrile neutropenia (FN) are serious complications of myelosuppressive chemotherapy and present a considerable burden to patients with cancer. Febrile neutropenia is associated with increased risks of infection and hospitalization, a particular concern during the coronavirus disease 2019 (COVID-19) pandemic. Oncology nurses and advanced practice providers (APPs; including nurse practitioners, physician assistants, advanced practice nurses, and pharmacists) play a vital role in the management of patients with cancer and the prevention of infections. **Objectives:** The objectives of this article are to summarize the burden of chemotherapy-related neutropenia and FN in patients with cancer in the US and to evaluate the role of oncology nurses and APPs in preventing and managing FN. **Methods:** This article provides a narrative review of US studies reporting on the burden of FN, FN during COVID-19, adherence to guidelines for the use of prophylactic granulocyte colony-stimulating factors (G-CSFs), the involvement of oncology nurses in FN prevention, management, and patient quality of life, and inappropriate and/or incomplete G-CSF treatment. **Findings:** Despite advances in supportive care for patients with cancer receiving myelosuppressive chemotherapy, neutropenia and FN present a considerable burden to patients, particularly during the COVID-19 pandemic. Oncology nurses and APPs play a vital role in the appropriate and timely delivery of supportive care, which can improve patient outcomes and minimize treatment costs.

Febrile neutropenia (FN) is defined as a temperature ≥ 38.3°C (≥ 100.9°F) orally or ≥ 38°C (≥ 100.4°F) over 1 hour with an absolute neutrophil count (ANC) of < 500 neutrophils/mL, or a predicted decline to ≤ 500 neutrophils/mL within 48 hours (National Comprehensive Cancer Network [NCCN], 2022). The incidence of FN in patients with cancer in the US is estimated at 60,294 cases annually and is observed in approximately 8 cases per 1,000 patients receiving chemotherapy (Rasmy et al., 2016). The incidence of FN varies depending on cancer type, with female sex, older age (≥ 65 years), concurrent radiotherapy, and/or receiving regimens with ≥ 3 agents associated with increased risk (Schelenz et al., 2012; Nordvig et al., 2018; NCCN, 2022).

Administration of recombinant granulocyte colony-stimulating factors (G-CSFs) stimulates neutrophil production and maturation, thus reducing the risk of FN following chemotherapy (Arvedson et al., 2015). The American Society of Clinical Oncology (ASCO; 2023) and the NCCN recommend the use of prophylactic G-CSFs in cancer patients receiving chemotherapy with a high associated risk of developing FN (> 20%). In response to the coronavirus disease 2019 (COVID-19) pandemic, the NCCN, ASCO, and European Society for Medical Oncology (ESMO) published interim guidance regarding the management of cancer patients (Curigliano et al., 2020; Griffiths et al., 2020). To minimize the risks of COVID-19 infection and associated complications, the use of prophylactic G-CSFs was expanded to include patients with > 10% FN risk. These guidelines are still relevant and applicable as the COVID-19 pandemic becomes endemic over time.

Chemotherapy-induced neutropenia (CIN) and FN are serious complications of chemotherapy and present a considerable burden to patients with cancer due to increased infection and hospitalization risk, and the potential need for chemotherapy dose reductions or delays (Aapro et al., 2017; Nordvig et al., 2018). Oncology nurses and advanced practice providers (APPs) play a vital role in the management of patients with neutropenia, especially in the prevention of infections, diagnosis and screening, prescribing medications when needed, and education of patients (Johnson et al., 2007; Rigdon, 2010; Reynolds & McCoy, 2016; Bruinooge et al., 2018; Knobloch et al., 2021).

This review aims to summarize the burden of CIN and FN in patients with cancer in the US during the COVID-19 pandemic and to evaluate the role of oncology nurses and APPs in improving the prevention and management of FN, thereby improving patient outcomes.

METHODS

This article reviews publications of US studies/clinical experiences that report FN burden, FN management during COVID-19 (March 2020 to July 2022), adherence to G-CSF supportive therapy guidelines, oncology nurse and APP involvement in FN prevention or management, and inappropriate and/or incomplete G-CSF treatment.

A PubMed literature search was conducted in July 2022 using the search strings in Table 1. Eligible studies related to the burden and management of FN and the role of oncology nurses or APPs were included if they reported data relevant to the research questions. Additional references were identified by searching the bibliographies of retrieved articles.

RESULTS

The literature searches yielded a total of 196 articles. After reviewing titles and abstracts, 76 articles were considered eligible for inclusion.

Burden of Neutropenia and FN

Neutropenia is one of the most common adverse events (AEs) associated with chemotherapy. The development of grade 3 to 4 neutropenia or FN can lead to chemotherapy delays or dose reductions, impacting patient outcomes (Aapro et al., 2011; Boccia et al., 2022; Blayney & Schwartzberg, 2022; Campbell et al., 2022). The type of treatment can impact CIN incidence, with treatment-dependent variations observed (Falchook et al., 2019; Chen et al., 2020; Sharma et al., 2021). Despite less toxic therapies and advances in the management of chemotherapy-induced myelosuppression, the real-world impact of AEs such as CIN remains substantial (Epstein et al., 2020; Crawford et al., 2021; Epstein et al., 2022).

The management of CIN and FN represents a significant economic burden, particularly when

Table 1. Search Strings

((neutropenia) OR (febrile neutropenia)) AND ((burden) OR (unmet need) OR (COVID-19)) AND (chemotherapy) AND (United States of America)
((neutropenia) OR (febrile neutropenia)) AND (chemotherapy) AND ((G-CSF) OR (pegfilgrastim) OR (filgrastim) OR (short-acting G-CSF) OR (long-acting G-CSF) OR (long-acting filgrastim) OR (short-acting filgrastim)) AND ((appropriate) OR (inappropriate) OR (compliance) OR (adherence) OR (under-prophylaxis) OR (under-prescribing) OR (under-use) OR (over-prophylaxis) OR (over-prescribing) OR (over-use)) AND (United States of America)
((neutropenia) OR (febrile neutropenia)) AND (((nurse) OR (nursing) OR (nurses)) AND ((oncology) OR (cancer))) AND ((prevention) OR (treatment) OR (management) OR (quality of life)) AND (United States of America)
((G-CSF) OR (pegfilgrastim) OR (filgrastim)) AND (administration) AND ((patient) OR (physician) OR (nurse)) AND (preference)

Note. Filters: English language and published in the last 10 years. COVID-19 = coronavirus disease 2019; G-CSF = granulocyte colony-stimulating factor.

hospitalization is required. Analyses examining the economic burden of AEs including CIN and FN in the US reported that managing multiple AEs is associated with greater health-care costs (Goyal et al., 2021a, 2021b). The costs of CIN are substantial, and of all AEs, CIN is reported to be associated with the highest treatment costs (Bilir et al., 2016). Another study evaluating the CIN burden among elderly (≥ 66 years of age) patients found that individual FN episodes required costly care (mean cost per episode: $11,959–$15,006; Li et al., 2020).

Neutropenia and COVID-19 Outcomes

The COVID-19 pandemic remains a challenge in the management of CIN and FN. Patients with cancer have a higher risk of developing COVID-19–associated complications than those without cancer (Patel & Saif, 2020; Yarza et al., 2020; Aapro et al., 2021; Cooksley et al., 2021; Li et al., 2021). As such, the supportive care landscape has transformed to minimize patients' risk of infection and the need for hospital visits (Aapro et al., 2021; Cooksley et al., 2021).

Preliminary results suggest baseline neutropenia correlates with poorer COVID-19 outcomes (Jee et al., 2020; Yarza et al., 2020; Jee et al., 2021). In a prospective observational study of 63 patients with cancer and COVID-19, a cancer diagnosis was associated with worse outcomes for mortality and severe respiratory failure. Pulmonary tumor involvement, severe CIN, and bilateral COVID-19–related pneumonia were deemed independent mortality risk factors (Yarza et al., 2020).

Interestingly, receiving anticancer therapy was not deemed an independent risk factor, except for treatment with anti-CD20 monoclonal antibodies, which was a risk factor for increased duration of hospitalization and death from COVID-19 (Lamure et al., 2021). The mechanism of action of CD20 monoclonal antibodies is that they bind to the CD20 cell surface protein of B cells and induce apoptosis, impairing the antiviral humoral response following infection, leading to prolonged viral replication (Andersen et al., 2022).

A retrospective observational study of patients with cancer and COVID-19 (N = 309) at Memorial Sloan Kettering Cancer Center also demonstrated that receiving chemotherapy was not independently associated with worse COVID-19 outcomes. However, baseline neutropenia (14–90 days pre–COVID-19 test positivity) was associated with increased COVID-19 severity (Jee et al., 2020). A subsequent study at the same center (N = 820) also found chemotherapy was not independently associated with worse COVID-19 outcomes (Jee et al., 2021). However, worse outcomes were observed in patients with neutropenia 7 to 60 days before COVID-19 infection. Interestingly, patients who recorded neutropenia before diagnosis and subsequently showed recovery (ANC ≥ 1,000/μL) still had worse outcomes. Patients with recovery from neutropenia 60 to 180 days before COVID-19 diagnosis and those with mild neutropenia did not have worse outcomes (Jee et al., 2021). A more recent retrospective observational study suggested that neutropenia is not an independent risk factor for worsened outcomes in COVID-19 (Zhang et al., 2022). This study reported that G-CSF therapy was associated with an increased risk of hospitalization in COVID-19

and, among hospitalized patients, statistically increased incidence rates for oxygen supplementation and death (Zhang et al., 2022).

It is worth noting the limitations of the studies discussed. For example, our understanding of risk factors for COVID-19 has evolved over time, meaning that some potential confounders may not have been accurately accounted for. Data from large, randomized, prospective clinical trials are needed to elucidate the complex interactions between anticancer therapy, patient characteristics, cancer type, and COVID-19.

Treatment Guidelines for G-CSF Supportive Therapy During the COVID-19 Pandemic

The importance of managing CIN and FN was heightened by the COVID-19 pandemic. Emerging data suggest neutropenia increases the susceptibility to worse COVID-19 outcomes (Jee et al., 2020; Yarza et al., 2020; Jee et al., 2021). Expanding the use of G-CSFs may reduce AE-associated health-care visits and viral exposure (Aapro et al., 2021; Cooksley et al., 2021; Li et al., 2021). Methods for administering G-CSF are an important consideration in the context of the pandemic, and measures such as same-day administration after chemotherapy or use of an on-body injector may be considered for reducing hospital or clinic visits (Humphreys et al., 2022).

Updated guidance on G-CSF treatment during COVID-19 was developed by ASCO, ESMO, and NCCN (Curigliano, et al., 2020; Griffiths et al., 2020). The expansion of G-CSF prophylaxis to include patients receiving chemotherapy regimens with an intermediate or high FN risk was recommended. American Society of Clinical Oncology recommendations continue to acknowledge the significance of COVID-19, stating that it may be reasonable for patients with > 10% risk of FN to receive growth factor prophylaxis (see Table 2; ASCO, 2023). Similarly, the current ESMO guidance on supportive care states "Consider expanding the indication of G-CSF after chemotherapy to lower the risk of FN" (Curigliano et al., 2020; ESMO, 2023). Unlike ASCO and ESMO, NCCN recommendations no longer make mention of COVID-19 and have returned to the routine use of G-CSFs for patients with high FN risk (> 20%) or intermediate FN risk (10%–20%) if ≥ 1 risk factor is present (NCCN, 2022).

The cost effectiveness of expanding G-CSF usage during the COVID-19 pandemic has been investigated. A study compared the cost effectiveness of primary vs. secondary prophylaxis with a biosimilar, filgrastim-sndz (Zarxio), in patients with intermediate FN risk receiving curative chemotherapy during the COVID-19 pandemic (Li et al., 2021). Primary prophylaxis was a cost-

Table 2. Summarized Treatment Guidelines for the Use of G-CSFs in Patients With Cancer

ASCO	ESMO	NCCN
• Potential use of G-CSFs in patients at a lower level of FN risk (e.g., > 10%) to reduce the risk of FN and emergency care; ANC monitoring and regular contact advised • For patients with potential FN, evaluation of status should occur by phone/telemedicine to determine if the patient should be evaluated in the clinic or sent to the emergency department • Acute care for known FN should be administered according to standard guidelines, regardless of the patient's COVID-19 status	• Expansion of the indication for G-CSF after ChT to lower the risk of FN should be considered; however, it is noted that this may require additional clinic visits » The theoretical concern of acute respiratory failure due to G-CSF–induced leukocyte recovery in patients with pulmonary infections due to COVID-19 infection does not outweigh the benefit • In patients with solid tumors not treated for cure, regimens unlikely to induce FN should be considered » There should be considerable evidence to support using regimens with higher neutropenia risk	• Prophylactic G-CSF is recommended for patients receiving ChT regimens with a high risk of FN (> 20%), and for those receiving an intermediate-risk regimen (10%–20%) and having ≥ 1 patient-specific risk factor for FN • For patients receiving ChT regimens with a low risk of FN (< 10%), prophylactic G-CSF may be appropriate if the patient is receiving therapy with curative intent and is at significant patient-specific risk of developing FN • Patients with FN after ChT who have not received prophylactic G-CSFs should be initiated on prophylactic G-CSFs if the same treatment dose and schedule is planned for the next ChT cycle

Note. ASCO = American Society of Clinical Oncology; ChT = chemotherapy; COVID-19 = coronavirus disease 2019; ESMO = European Society for Medical Oncology; FN = febrile neutropenia; G-CSF = granulocyte colony–stimulating factor; NCCN = National Comprehensive Cancer Network. Information from NCCN (2022); ASCO (2023); ESMO (2023).

effective treatment, providing an additional 0.10 to 0.14 life years and 0.07 to 0.13 quality-adjusted life years (QALYs), with incremental cost effectiveness ranging from $5,660 to $20,806 (US dollars) per FN event avoided, $5,123 to $31,077 per life year gained, and $7,213 to $35,363 per QALY gained (Li et al., 2021). The authors concluded that expanding G-CSF use may reduce unnecessary clinic visits for patients with cancer at risk of complications because of COVID-19 and should be considered indefinitely (Li et al., 2021).

Adherence to G-CSF Supportive Therapy Guidelines

Granulocyte colony-stimulating factor supportive therapy is not always prescribed in accordance with treatment guidelines, with reports of underuse, overuse, and mistiming (Wright et al., 2013; Barnes et al., 2014; Elting et al., 2016; Sureda et al., 2019; Weycker et al., 2019; Averin et al., 2021; Crawford et al., 2021; Schenfeld et al., 2022). A retrospective study of 1,457 patients with cancer demonstrated that 51.5% of patients for whom G-CSF prophylaxis is NCCN recommended did not receive it in treatment cycle 1 (Averin et al., 2021; NCCN, 2022). Similarly, a retrospective study of almost 65,000 Medicare patients aged ≥ 66 years receiving chemotherapy with high or intermediate risk of FN reported primary prophylaxis of 53% with G-CSF during cycle 1 (Schenfeld et al., 2022). Health care claims repository data demonstrated that in cycle 1, 33% of 50,778 patients on commercial plans and 28% of 71,037 patients on Medicare, all of whom were receiving intermediate- or high-risk regimens, did not receive pegfilgrastim (Neulasta) prophylaxis (Weycker et al., 2019).

A review of G-CSF US prescribing patterns reported underuse of G-CSFs in patients at high risk and overuse in patients at low risk of FN. Factors associated with inappropriate G-CSF use included the health-care setting, physician experience, patient characteristics, cancer type, disease severity, and chemotherapy regimen (Barnes et al., 2014).

The Role of Oncology Nurses and APPs in the Prevention and Management of Neutropenia and FN

Advanced practice providers, including nurse practitioners, physician assistants, advanced practice nurses, and pharmacists, are integral to the multidisciplinary oncology care team and have greatly contributed to the improved care and outcomes of patients. Advanced practice providers are qualified to provide a number of services, including, but not limited to, screening and prevention services; ordering, performing and interpreting diagnostic tests; performing clinical procedures and prescribing medications; developing treatment plans and managing symptoms; and providing education and counseling to both families and patients. Many of these services are conducted in collaboration with physicians and other health-care providers to determine treatment decisions (Reynolds & McCoy, 2016; Bruinooge et al., 2018). Incorporating APPs into oncology patient care has been shown to reduce length of patient hospital stay, with patient experience measures remaining stable or improving (Broman et al., 2021).

Oncology nurses and APPs are crucial for the identification of patients most susceptible to CIN and are ideally positioned to initiate strategies to improve guideline adherence and patient care (Table 3). Increased interaction between these health-care providers (oncology nurses and APPs) and patients can decrease the risk of chemotherapy dose reductions. The randomized FORTIS study demonstrated that a telephone intervention strategy delivered by oncology nurses to alleviate AEs could reduce the risk of chemotherapy dose reduction in patients receiving pegfilgrastim prophylaxis. Patients who received the telephone intervention had a decreased risk of dose reductions, grade 3 to 4 CIN, and FN (Ysebaert et al., 2019). This is pertinent as dose reductions were associated with decreased survival (Ysebaert et al., 2019).

Nurses (whether oncology nurses or APPs) are well positioned to implement FN risk assessments prior to the administration of chemotherapy, as well as implement evidence-based guidelines to reduce or manage complications (Wilson & Gardner 2007; Bruinooge et al., 2018). Multiple risk-stratifying tools to guide treatment strategies for FN are available (Sosa et al., 2017; Wijeratne et al., 2021). The Assessment, Information, and Management (AIM) Higher Initiative was conducted in 15 US community oncology practices and focused on improving the management of five chemotherapy-

Table 3. Examples of How Oncology Nurses and Advanced Practice Providers Can Reduce the Burden of Chemotherapy-Induced Neutropenia

Rationale	Tools
Implementing risk assessments prior to the administration of chemotherapy to determine which patients are at greater risk of CIN and identify patients who may benefit from G-CSF supportive therapy	Standardized risk-assessment tool
Educating patients to ensure they are aware of treatment-associated risks, such as CIN	Standardized patient-education materials
Understanding and, when possible, acting on patient preferences for pegfilgrastim administration	Expand the range of assessment time points. Conduct proactive telephone assessments
Improving the understanding of patients' perspectives and satisfaction with different G-CSF treatment options	SEQ-G-CSF
Ensuring timely management of FN, including improving the timeliness of antibiotic delivery	Introduce a neutropenic fever alert in the emergency department

Note. APP = advanced practice provider; CIN = chemotherapy-induced neutropenia; FN = febrile neutropenia; G-CSF = granulocyte colony–stimulating factor; SEQ-G-CSF = Satisfaction and Experience Questionnaire for Granulocyte Colony-Stimulating Factor. Information from Johnson et al. (2007); Moore et al. (2008); Dang et al. (2018); Ysebaert et al. (2019); Yucel et al. (2021).

related toxicities, including CIN (Johnson et al., 2007; Moore et al., 2008). Within AIM, "nurse champions" were designated and received centralized training. Each champion analyzed their practice and developed a quality improvement plan that was implemented through clinic-wide collaboration. Procedures that improved FN care included a standardized pretreatment risk-assessment tool, increased assessment of patients receiving chemotherapy, a standardized documentation tool for patient-reported symptoms, delivery of patient education, and clinic-wide guidelines for symptom management (Moore et al., 2008).

Oncology nurses and APPs provide vital patient education (Rigdon, 2010; Reynolds & McCoy, 2016; Bruinooge et al., 2018). Some, but not all, older patients receiving chemotherapy may have learning difficulties and require additional education on self-care to decrease risks (Rigdon, 2010). Hawley and colleagues (2011) developed patient and caregiver educational materials on self-care strategies to reduce the risk of neutropenic complications.

In addition, nurses can improve the understanding of patient perspectives and potentially increase patient G-CSF adherence. One nurse-led initiative to improve the understanding of patients' satisfaction with G-CSF treatments is the Satisfaction and Experience Questionnaire for G-CSF (SEQ-G-CSF; Yucel et al., 2021). Three nurses in collaboration with 40 patients with cancer participated in a patient satisfaction and tolerability of chemotherapy and G-CSF focus group to develop the SEQ-G-CSF. This is the first patient-reported outcomes instrument designed to assess patient satisfaction and experience with G-CSF prophylaxis options (Yucel et al., 2021).

As the volume of patients treated with chemotherapy in outpatient settings increases, so does the need for prompt treatment of CIN and, therefore, emergency room (ER) evaluation. Optimized procedures in the ER can reduce the time to antibiotic administration, increase the proportion of patients with neutropenic fever identified as an oncology emergency, and increase the numbers of patients admitted to oncology units (Dang et al., 2018). Specifically, a "neutropenic fever alert" includes an overhead paging system to announce an alert, followed by deployment of a multidisciplinary neutropenic fever response team (e.g., ER physician, ER charge nurse, ER clinical pharmacist, laboratory staff, and an oncology service line nurse practitioner). The implementation of this alert at the University of Miami improved real-time communication and enabled the delivery of antibiotics within 60 minutes (Dang et al., 2018). Routing patients from the ER to the outpatient cancer center for rapid diagnosis and treatment can be advantageous given the familiarity of staff with patients and their treatments, as well as the

ability of staff to quickly identify neutropenic symptoms. Developing a multidisciplinary Neutropenic Fever Team process made up of different cancer center staff (physician assistants, pharmacists, charge nurses, infusion nurses, and nurse practitioners) has been proposed as a way to enable the rapid rerouting of patients and initiation of antibiotics within the hour (Hawley et al., 2011).

Patient Preference of G-CSF Administration

Long-acting G-CSF formulations, such as pegfilgrastim, are often preferred by patients and health-care providers as they offer more convenience than the daily administration of filgrastim (Johnson et al., 2014; Xie et al., 2018). In an online questionnaire, patients expressed a preference for G-CSF regimens with greater convenience, lower out-of-pocket costs, lower risk of chemotherapy disruption, and lower risk of infection (Johnson et al., 2014). Currently available G-CSFs are listed in Table 4.

The travel burden associated with G-CSF therapy following chemotherapy has been associated with suboptimal use of G-CSF prophylaxis. Given the burden of daily clinic visits, almost three quarters of patients were able to self-administer filgrastim at home, with over 90% willing to continue home administration (Otremba et al., 2018). This is pertinent in pandemic situations such as COVID-19, when hospital visits may increase viral exposure risk. A study of Medicare claims data for elderly patients with cancer and high FN risk reported that patients were 26% to 52% more likely to receive no G-CSF if they had travelled for > 80 minutes, compared with patients travelling for < 20 minutes. The travel burden was higher for patients receiving short-acting vs. long-acting G-CSFs (Stephens et al., 2019).

Pegfilgrastim is indicated for administration on the day following chemotherapy. This schedule, which is recommended by the NCCN Guidelines (NCCN, 2022), contributes to the travel burden of G-CSF therapy. Therefore, administration of G-CSF on the same day as chemotherapy has been considered (Marion et al., 2016; Kitchen & Mosier, 2022). Several studies have reported no significant differences in FN incidence between same-day and next-day pegfilgrastim administration (Eckstrom et al., 2019; Matera et al., 2021; Kitchen & Mosier, 2022). However, these studies are limited by small patient numbers, retrospective data collection, and restricted follow-up. Larger prospective trials with longer follow-up are required to comprehensively evaluate this topic.

Administration route is a key element in the shared decision-making process, and alternative administration methods available for pegfilgrastim may affect the travel burden and impact treatment adherence (Hauber et al., 2018; Metz et al., 2021). A study investigating patients' perceptions of administration devices, including an on-body injector designed to deliver pegfilgrastim 24 hours after chemotherapy, revealed patients generally prefer the administration method they are most familiar with (Hauber et al., 2018). A database study evaluated the impact of the on-body injector on patient treatment workload (related to outpatient encounters, commuting, and admissions). Patients receiving pegfilgrastim via a pre-filled syringe in the clinic spent approximately 40 minutes longer in appointments and had one additional day in clinic per cycle compared with those with an on-body injector. The authors suggested that, for convenience, patients who live further away from the clinic should be fitted with an on-body injector (Cheng & Levy, 2019). The CONVENIENCE study noted a slight patient preference for the on-body injector over the pre-filled syringe (43.2% vs. 36.0%) owing to the time saving that the device offered. The on-body injector was also shown to improve guideline adherence by delivering pegfilgrastim within the recommended time frame (Metz et al., 2021). However, factors such as insurance coverage, reimbursement, and hospital formulary inclusion impact the choices of G-CSF delivery options (Griffith et al., 2014; Hawkins et al., 2020).

DISCUSSION

Neutropenia and FN are frequent complications of myelosuppressive chemotherapy and remain potentially life threatening despite advances in their management (Barnes et al., 2014; Elting et al., 2016; Sureda et al., 2019; Weycker et al., 2019; Averin et al., 2021). Increasing the availability of supportive clinical interventions such as G-CSF biosimilars facilitates the prevention of FN (Humphreys et al., 2022). However, risk assessments

Table 4. FDA-Approved Granuloycte Colony-Stimulating Factor Products

Name	Indications	Dosing	Administration method
Neupogen (filgrastim) Nivestym (filgrastim-aafi) Releuko (filgrastim-ayow) Zarxio (filgrastim-sndz)	• Decrease the incidence of infection, as manifested by FN, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever • Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with AML	• Recommended starting dose is 5 µg/kg/day • Consider dose escalation in increments of 5 µg/kg for each chemotherapy cycle, according to the duration and severity of the ANC nadir[a] • Should be administered at least 24 hours after cytotoxic chemotherapy and not within the 24-hour period prior to chemotherapy. To ensure a sustained therapeutic response, administer daily for up to 2 weeks or until the ANC has reached 10,000/mm^3 following the expected CIN nadir[b]	Subcutaneous injection, short intravenous infusion (15–30 minutes), or continuous intravenous infusion
	• Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., FN, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation	• 10 µg/kg/day • Administer first dose at least 24 hours after cytotoxic chemotherapy and at least 24 hours after bone marrow infusion • Monitor CBCs and platelet counts frequently following marrow transplantation, and during the period of neutrophil recovery, titrate daily dosage against the neutrophil response	Intravenous infusion no longer than 24 hours
	• Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis[c]	• 10 µg/kg/day[c] • Administer for at least 4 days before first leukapheresis procedure and continue until last leukapheresis • The optimal duration of administration and leukapheresis schedule have not been established, but administration for 6 to 7 days with leukaphereses on days 5, 6, and 7 was found to be “safe and effective” • Monitor ANCs after 4 days, and discontinue if the WBC count rises to greater than 100,000/mm^3	Subcutaneous injection[c]

Note. Information correct as of February 3, 2023. AML = acute myeloid leukemia; ANC = absolute neutrophil count; CBC = complete blood count; CIN = chemotherapy-induced neutropenia; FDA = US Food & Drug Administration; FN = febrile neutropenia; G-CSF = granulocyte colony-stimulating factor; Gy = Gray; WBC = white blood cell. Information from Teva (2019); Amgen Inc. (2021, 2023); Mylan (2021); Pfizer (2021, 2023); Sandoz (2021); Amneal Pharmaceuticals (2023); Coherus BioSciences (2022); Fresenius Kabi (2022); Kashiv BioSciences (2022); Sandoz (2022).

[a]Recommend stopping treatment if the ANC increases beyond 10,000/mm^3.

[b]The duration of therapy needed to attenuate CIN may be dependent on the myelosuppressive potential of the chemotherapy regimen employed.

[c]Neupogen, Nivestym, and Zarxio only.

[d]Neupogen only.

[e]Neulasta only.

[f]Use of the on-body injector for Neulasta is not recommended for patients with hematopoietic subsyndrome of acute radiation syndrome and has not been studied in pediatric patients.

Table 4. FDA-Approved Granuloycte Colony-Stimulating Factor Products (cont.)

Name	Indications	Dosing	Administration method
Neupogen (filgrastim) Nivestym (filgrastim-aafi) Releuko (filgrastim-ayow) Zarxio (filgrastim-sndz (cont.)	• Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia	• Congenital neutropenia: recommended starting dose is 6 µg/kg twice daily • Cyclic or idiopathic neutropenia: recommended starting dose is 5 µg/kg/day • Prior to starting G-CSF, diagnosis of severe chronic neutropenia should be confirmed by evaluating serial CBCs with differential and platelet counts, and evaluating bone marrow morphology and karyotype • Chronic daily administration is required to maintain clinical benefit. Individualize the dosage based on the patient's clinical course as well as ANC • Monitor CBCs for dosage adjustments	Subcutaneous injection
	• Increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome)[d]	• 10 µg/kg/day[d] • Administer as soon as possible after suspected or confirmed exposure to radiation doses > 2 Gy • Obtain a baseline CBC and then serial CBCs approximately every third day until the ANC remains greater than 1,000/mm^3 for three consecutive CBCs. Do not delay administration if a CBC is not readily available • Continue administration until the ANC remains > 1,000/mm^3 for three consecutive CBCs or exceeds 10,000/mm^3 after a radiation-induced nadir	Subcutaneous injection[d]
Granix (tbo-filgrastim)	• Decrease the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of FN	• 5 µg/kg/day • First dose should be administered no earlier than 24 hours following myelosuppressive chemotherapy and do not administer within 24 hours prior to chemotherapy • Daily dosing should continue until the expected neutrophil nadir is passed and the ANC has recovered to the normal range. Monitor CBC prior to chemotherapy and twice per week until recovery	Subcutaneous injection

Note. Information correct as of February 3, 2023. AML = acute myeloid leukemia; ANC = absolute neutrophil count; CBC = complete blood count; CIN = chemotherapy-induced neutropenia; FDA = US Food & Drug Administration; FN = febrile neutropenia; G-CSF = granulocyte colony-stimulating factor; Gy = Gray; WBC = white blood cell. Information from Teva (2019); Amgen Inc. (2021, 2023); Mylan (2021); Pfizer (2021, 2023); Sandoz (2021); Amneal Pharmaceuticals (2023); Coherus BioSciences (2022); Fresenius Kabi (2022); Kashiv BioSciences (2022); Sandoz (2022).

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Table 4. FDA-Approved Granuloycte Colony-Stimulating Factor Products (cont.)

Name	Indications	Dosing	Administration method
Neulasta (pegfilgrastim) Fulphila (pegfilgrastim-jmdb) Udenyca (pegfilgrastim-cbqv) Nyvepria (pegfilgrastim-apgf) Ziextenzo (pegfilgrastim-bmez) Fylnetra (pegfilgrastim-pbbk) Stimufend (pegfilgrastim-fpgk)	• Decrease the incidence of infection, as manifested by FN, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of FN • Increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic subsyndrome of acute radiation syndrome)[e]	• 6 mg once per chemotherapy cycle • Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy • Use weight-based dosing for pediatric patients weighing < 45 kg • For patients acutely exposed to myelosuppressive doses of radiation, two doses, 6 mg each, should be administered 1 week apart[e] • First dose should be administered as soon as possible after suspected or confirmed exposure to myelosuppressive doses of radiation, and a second dose 1 week after[e]	Subcutaneous injection via a single-dose prefilled syringe Neulasta can also be administered subcutaneously via a single-dose prefilled syringe with the on-body injector[e,f] With the on-body injector, treatment is delivered over approximately 45 minutes, approximately 27 hours after application of the device to the patient's skin[e]

Note. Information correct as of February 3, 2023. AML = acute myeloid leukemia; ANC = absolute neutrophil count; CBC = complete blood count; CIN = chemotherapy-induced neutropenia; FDA = US Food & Drug Administration; FN = febrile neutropenia; G-CSF = granulocyte colony-stimulating factor; Gy = Gray; WBC = white blood cell. Information from Teva (2019); Amgen Inc. (2021, 2023); Mylan (2021); Pfizer (2021, 2023); Sandoz (2021); Amneal Pharmaceuticals (2023); Coherus BioSciences (2022); Fresenius Kabi (2022); Kashiv BioSciences (2022); Sandoz (2022).
[a]Recommend stopping treatment if the ANC increases beyond 10,000/mm^3.
[b]The duration of therapy needed to attenuate CIN may be dependent on the myelosuppressive potential of the chemotherapy regimen employed.
[c]Neupogen, Nivestym, and Zarxio only.
[d]Neupogen only.
[e]Neulasta only.
[f]Use of the on-body injector for Neulasta is not recommended for patients with hematopoietic subsyndrome of acute radiation syndrome and has not been studied in pediatric patients.

are required to ensure that patients receive such interventions (Gupta et al., 2019). Moreover, there is evidence that G-CSF therapies are often not used in accordance with the NCCN Guidelines, as reviewed by Crawford and colleagues (2021).

The supportive care landscape has evolved throughout the COVID-19 pandemic (Aapro et al., 2021; Cooksley et al., 2021). Interim supportive care guidelines recommended G-CSF prophylaxis in patients with an intermediate as well as high risk of FN, in the hope of reducing the risks of COVID-19 exposure and the associated complications (Curigliano et al., 2020; Griffiths et al., 2020). Effective prevention and management of CIN are particularly important during the COVID-19 pandemic, as patients with neutropenia may be more susceptible to worse COVID-19 outcomes (Jee et al., 2020; Yarza et al., 2020; Jee et al., 2021). However, one study has suggested that G-CSF therapy and not neutropenia is a risk factor for worsened outcomes (Zhang et al., 2022). Further research is required to reduce the uncertainty in this area.

The implementation of nurse-led initiatives can improve treatment guideline adherence and ultimately improve patient outcomes by minimizing the occurrence of CIN and FN (Lukes et al., 2019; Ysebaert et al., 2019). Although oncologists undertake the primary treatment of

patients with cancer, oncology nurses and APPs play key roles in guideline implementation to improve patient outcomes (Bruinooge et al., 2018). Oncology nurses and APPs assess patients for CIN or FN risk and ensure timely management. They may also improve processes to facilitate efficiency and assist in overcoming barriers to the appropriate administration of G-CSFs, thus ensuring the timely delivery of dose-dense chemotherapy regimens (Lukes et al., 2019; Ysebaert et al., 2019). These measures can reduce the incidence of FN and hospitalizations. Moreover, nurses and other APPs may develop and disseminate effective educational initiatives to patients and caregivers, including education around the use of G-CSF products, which improves outcomes by increasing patient adherence and minimizing the risks of CIN and FN (Hawley et al., 2011).

Prevention of FN with G-CSF supportive therapy is preferred to reactive treatment with antibiotics. Minimizing patient hospitalization increases the likelihood that chemotherapy regimens are delivered on schedule. Studies investigating patient G-CSF preference have shown that the route of administration and delivery device are important for patient satisfaction (Hauber et al., 2018; Metz et al., 2021). In addition, long-acting G-CSF formulations are generally preferred over daily administration owing to greater convenience and reduced clinic visits (Xie et al., 2018). Oncology nurses provide support and advice to patients regarding pegfilgrastim delivery device options (Hauber et al., 2018; Metz et al., 2021) and can identify if devices such as on-body injectors are clinically appropriate. However, it should be noted that factors such as insurance coverage, reimbursement, and institutional formulary may dictate supportive therapy and administration device options (Griffith et al., 2014; Hawkins et al., 2020).

This review has some limitations. The application of limits on the PubMed searches conducted may have excluded relevant articles. In addition, publications assessing the relationship between COVID-19, cancer treatment, and neutropenia were limited and data were still emerging at the time of the literature search. However, the identified publications provide important and consistent information relevant to patient care.

CONCLUSION

Neutropenia and FN represent a significant burden to patients with cancer receiving myelosuppressive chemotherapy. Oncology nurses and APPs play a vital role in ensuring supportive care for CIN is administered appropriately and promptly. Nurse-led initiatives focusing on improvements in adherence to treatment guidelines, CIN/FN risk assessment, and patient/caregiver education may help improve patient outcomes. The role of oncology nurses and APPs in supportive care for CIN has always been of the highest importance, and this has been highlighted throughout the COVID-19 pandemic. Health-care professionals should continue efforts to ensure patients receive optimal care for CIN. ●

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Disclosure

Ms. Orbaugh is on the speakers bureaus for AstraZeneca, Bristol-Myers Squibb, Coherus, Dova, Gilead, MorphoSys, Pfizer, Regeneron, Rigel, and Sanofi. Dr. Cuellar served on an advisory board or speakers bureau for Celgene and Merck. Dr. Kennedy Sheldon served on an advisory board for Pfizer.

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