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Understanding the Unmet Needs and Burden of Chemotherapy-Induced Neutropenia

Chemotherapy remains the cornerstone of treatment for most cancer types, with approximately 665,000 patients with cancer receiving chemotherapy each year in the United States.[1] Myelosuppressive chemotherapeutic treatments commonly lead to neutropenia in patients undergoing treatment for various types of cancer.[2] Neutropenia is characterized by an abnormally low number of blood neutrophils, the most important being white blood cells (WBCs) that work as a host defense against infections.[3] Absolute neutrophil count (ANC), a measure of the number of blood neutrophils, is between 2500/µL and 6000/µL in healthy individuals.[3] Neutropenia is often defined by an ANC of less than 1500/µL and is graded according to the level of decrease in the ANC (**Table 1**).[4,5] Neutropenia is generally classified by its etiology; the 4 commonly described types are congenital, autoimmune, idiopathic, and chemotherapy-induced neutropenia (CIN).[6,7]

Neutropenia can be described by its duration as chronic or transient.[2] Chronic, or persistent, neutropenia is usually described as neutropenia lasting longer than 3 months. Persistent ANC levels in the severe neutropenic range place patients at increased risk of severe infection-related complications. Transient neutropenia, also known as acute neutropenia, may result from viral infections, whereas transient drug-induced neutropenia can result from the use of a wide variety of medications (eg, chemotherapy agents) and may lead to CIN.[2] As an additional complication, patients undergoing chemotherapy who develop a fever in the presence of neutropenia are described as having febrile neutropenia, which indicates the presence of an ongoing infection.[7]

CHEMOTHERAPY-INDUCED NEUTROPENIA

Neutropenia can develop from a variety of causes, but CIN is a common, serious, life-threatening condition resulting from the myelosuppressive effects of chemotherapy in cancer patients and associated with substantial clinical and economic burdens on patients and health care systems.[2,7,8] Based upon incidence data, approximately 369,000 cases of CIN occurred in the United States in 2018, representing about 55% of the 665,000 patients being treated with chemotherapy.[1] The incidence of CIN is expected to increase to an estimated 462,073 cases by 2030.[1]

Febrile neutropenia

Febrile neutropenia (ie, an oral temperature ≥ 38.5°C in 2 consecutive readings within 2 hours in the setting of severe neutropenia) is considered an oncologic emergency.[7] Rapid treatment of febrile neutropenia is necessary to prevent serious infections and improve patient survival; therefore, patients who develop febrile neutropenia in the setting of CIN require emergency-department visits and immediate hospital admission for assessment and treatment.[7,9] Current guidelines recommend the treatment of febrile neutropenia using intravenous (IV) antibiotics, growth factors, and blood transfusions.[7] However, data suggest that these current treatment regimens provide only a small reduction in infection-related mortality, indicating an unmet need in the management of febrile neutropenia.[7]

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Table 1. Absolute Neutrophil Count Ranges and Associated Grade Designations[4,5]

Grade	Absolute neutrophil count range[a]
1	1500 - 2000
2	1000 - 1499
3	500 - 999
4	< 500
Profound neutropenia	< 100

[a] Per microliter

Risk factors for CIN and febrile neutropenia

A variety of patient- and regimen-specific risk factors are associated with the development of CIN. The type of chemotherapy regimen used impacts the risk of developing CIN, as some agents and regimens are known to be more myelosuppressive than others.[10] In a retrospective cohort study of data from 4 US health systems (Geisinger Health System, Henry Ford Health System, Kaiser Permanente Northwest, and Reliant Medical Group) of 1457 adults with metastatic cancer who received myelosupressive chemotherapy (2009-2017), patients were classified by febrile neutropenia risk level of the chemotherapy regimen that they received.[11] Assignment of risk level was based on published guidelines and expert opinion. The percentage of patients classified as high, intermediate, low, and unclassified risk levels varied by cancer type. These data demonstrated that most breast cancer patients received high-risk chemotherapy (45.8%); most colorectal cancer patients and non-Hodgkin lymphoma patients received intermediate-risk regimens (54.7% and 50.6%, respectively); and most lung cancer patients received low-risk regimens (41.2%). Patients with elevated risk of febrile neutropenia due to chemotherapy regimen can be identified prior to treatment initiation to ensure that they receive the necessary supportive care.[11]

The risk of developing CIN and febrile neutropenia can be impacted by the specific agents used during the chemotherapy regimen as well as the overall dose intensity, as defined by the drug dose delivered per time unit.[10] Other factors that may influence the risk of developing CIN include the type of cancer involved, the presence of a low ANC at baseline, advanced age or disease, poor performance status, bone marrow involvement, and female gender. Myelosuppression increases with age; patients older than 65 years of age are at increased risk of developing CIN. Similarly, patient-specific factors closely associated with age (eg, presence of advanced disease, comorbidities) also increase the risk of developing CIN and febrile neutropenia.[10]

Low platelet count has also been identified as a risk factor for severe CIN and febrile neutropenia.[12] In a retrospective study analyzing data from patients with breast cancer or diffuse large B-cell lymphoma, a low platelet count (< 150,000/µL) was a significant risk factor for severe neutropenia. The odds of severe neutropenia were nearly 6 times greater among patients with low platelet counts when compared with patients with normal platelet counts. Older age, no radiation therapy, and low platelet count were independently predictive of neutropenia, whereas multivariate logistic analysis suggested that low platelet count was the only independent risk factor for the development of febrile neutropenia.[12]

Additional risk factors for the development of febrile neutropenia include specific genetic polymorphisms, which also are associated with an increased risk for the development of leukemia, particularly in patients receiving chemotherapy. Mutations and polymorphisms involving the *MBL2*, *GSTP1*, *UGT1A1*, *TP53*, or *MDM2* genes contribute to the development of leukemia in febrile neutropenia.[5]

UNMET NEEDS IN THE MANAGEMENT OF CIN

One of the most pressing unmet needs when addressing CIN in patients treated with chemotherapy is related to limitations of the current standard of care—use of pegylated granulocyte colony–stimulating factor (PEG G-CSF). Nearly 1.3 million cycles of PEG G-CSF are used each year in the United States, so improvements in this unmet need represent a significant shift in the overall management of CIN.[13] Studies of G-CSF given as primary prophylaxis during chemotherapy have found that the lowest ANC level measured during treatment (ANC nadir) is demonstrated around 7 days following administration of chemotherapy.[14,15] This creates a critical time period involving a "neutropenia vulnerability gap" that places patients at risk for serious consequences of CIN.[14]

To treat neutropenia, G-CSF is used during chemotherapy to accelerate rates of maturation and proliferation of neutrophil precursors in the bone marrow. This cytokine is produced by monocytes, macrophages, fibroblasts, endothelial cells, and bone marrow stromal cells and is known to play a major role in the regulation of granulopoiesis.[16] Some aspects of granulopoiesis, such as neutrophil development and the dynamics of cell proliferation and blood turnover, are well studied. However, the precursor expansion and maturation phases are incompletely understood. Researchers agree that the precursor expansion phase culminates in the cells becoming metamyelocytes; this stage is clearly separated from the maturation phase that follows it, which typically lasts approximately 5 to 6 days before the neutrophils are released into circulation.[17] As such, the use of G-CSF may not result in observable changes to neutrophil counts for up to a week, which may limit its prophylactic efficacy.

One study evaluated the impact of primary prophylaxis with G-CSF on the ANC level profile and incidence of febrile neutropenia among patients receiving docetaxel (Taxotere), doxorubicin, and cyclophosphamide (TAC) for breast cancer.[14] Pegfilgrastim, a pegylated G-CSF, was administered 24 to 48 hours following chemotherapy. Grade 4 neutropenia was observed in 83.3% of the cycles and was reported in all patients during at least 1 cycle. The mean duration of severe (grade 3 or 4) neutropenia was 2.4 ± 1.6 days, whereas grade 4 neutropenia had a mean duration of 1.8 ± 1.2 days. The ANC decreased at day 6 and reached its lowest level at day 7, when the mean ANC was 375.3/µL and the mean depth of ANC nadir was 265.7/µL. Approximately 66% of cycles produced an ANC nadir at day 7, whereas 29.2% of

cycles produced an ANC nadir at day 6. Febrile neutropenia was reported in 16.4% of patients, occurring most frequently during the first chemotherapy cycle.[14]

Other studies of CIN prophylaxis have reported similar results. A phase 3 trial that compared the efficacy of pegfilgrastim with a proposed biosimilar agent (MYL-1401H) for CIN prophylaxis among patients receiving TAC chemotherapy for breast cancer demonstrated an ANC nadir that occurred about 7 days following chemotherapy.[15] The primary end point of this trial was the duration of severe neutropenia during cycle 1, which was defined as an ANC level of less than 500/µL. Secondary end points included the frequency of grade 3 or 4 neutropenia, incidence of febrile neutropenia, and the depth and time to ANC nadir. During cycle 1, 91% of patients who received MYL-1401H experienced neutropenia of grade 3 or greater compared with 82% of those who received pegfilgrastim. Grade 4 neutropenia was reported in 75% and 64% of patients who received MYL-1401H and pegfilgrastim, respectively.[15]

The mean ANC level profiles were similar between the 2 groups, with a mean time to ANC nadir of 6.2 days and 6.3 days for the MYL-1401H and pegfilgrastim groups, respectively.[15] Treatment with MYL-1401H and pegfilgrastim was associated with a median ANC nadir of 210/µL (range, 0-2500/µL) and 270/µL (range, 0-6700/ µL), respectively. Mean time to ANC recovery following ANC nadir was 1.9 days (standard deviation [SD], 0.85) for the MYL-1401H group and 1.7 days (SD, 0.91) for the pegfilgrastim group. Febrile neutropenia was reported in 6% of patients given MYL-1401H and 2% of patients given pegfilgrastim. As with the other study, most febrile neutropenia events occurred during the first cycle.[15]

CLINICAL BURDEN OF CIN

The severity of CIN is varied, and its occurrence is associated with adverse effects that lead to worsened clinical outcomes and increased hospitalizations that create additional burdens to patients.[18] The risk of death in the setting of febrile neutropenia is further increased in patients with comorbidities, older age, and poor performance, health, and nutritional status.[7] A mortality rate of approximately 10% has been reported among patients with CIN who are hospitalized for febrile neutropenia, and the mortality rate has been reported to be as high as 20% for patients with multiple and/or severe comorbidities.[18] As many as 90% of patients who receive high-dose chemotherapy and subsequent G-CSF monotherapy as primary prophylaxis experience grade 3 or 4 neutropenia.[14]

Bone pain

In addition to the clinical burden directly related to CIN, patients are also burdened by the potential adverse events associated with standard treatments.[19] As many as half of patients treated with myelosuppressive chemotherapy who receive G-CSF as primary prophylaxis experience bone pain of any grade of severity. A pooled analysis evaluated clinical trial data from pegfilgrastim studies to identify potential risk factors for bone pain among patients with nonmyeloid malignancies who received myelosuppressive chemotherapy and pegfilgrastim as primary prophylaxis. Using the adverse events reported in the original trials, bone pain was identified and coded according to the *Medical Dictionary for Regulatory Activities, Version 15.1*, and *The Common Terminology Criteria for Adverse Events* was used to record the severity of bone pain. Based on analysis of data from 1949 patients from 22 studies, bone pain of grade 2 or greater severity was reported in 19% of patients during cycle 1, 16% during cycles 2 to 6, and 28% during cycles 1 to 6; bone pain of any grade of severity was reported by 36%, 34%, and 51%, respectively.[19]

Using multivariable logistic regression, history of prior bone pain was identified as a potential risk factor for bone pain of grade 2 or greater severity in this setting.[19] Prior history of osteoporosis or osteopenia was also associated with increased bone pain of grade 2 or greater during cycles 1 through 6, but no association was observed specifically during cycle 1 alone. Compared with patients younger than age 45 years, those aged 65 or older had a lower risk of grade 2 or greater bone pain during cycle 1 (odds ratio [OR], 0.64; 95% CI, 0.42-0.98). Sensitivity analyses confirmed the association between older age and reduced risk for bone pain (OR, 0.88/10-year increase; 95% CI, 0.78-0.99). It is unclear why older patients appear to be at a lower risk for bone pain associated with G-CSF use than are younger patients, but it may be related to bone marrow expansion, which is a likely cause of G-CSF related bone pain. Red marrow is increasingly converted to fatty marrow with aging; therefore, differences in bone and bone marrow architecture (eg, acute bone marrow expansion) may lead to more pain in younger patients.[19]

Risk of infection

Patients with CIN are at increased risk for serious systemic infections and complications related to infection, which may include fungal infections, severe bacteremia resulting in sepsis, respiratory tract infections, cerebrovascular disease, hepatic and renal disorders, and death.[7] Additionally, infection as a consequence of CIN may result in extended hospitalizations. The length of hospital stay in patients with febrile neutropenia can range from a few days to weeks depending upon the severity and duration of neutropenia. In general, neutrophil counts above 500/µL and no evidence of infection are needed before safely discharging patients. For many patients, extended hospital stays with multiple blood transfusions are needed, particularly for older patients and those with hematologic malignancies, due to the slow recovery time of neutrophil counts.[7]

ECONOMIC BURDEN OF CIN

To address CIN and febrile neutropenia, additional evaluations and treatments may be needed, which can substantially increase the annual costs associated with the use of health care resources.[7,8] In a retrospective analysis of data collected between 2016 and 2019, researchers studied the financial burden of treatment on more than 300 patients with small cell lung carcinoma who had chemotherapy-induced grade 3 or 4 myelosuppression in the first-, second-, or third-line treatment settings.[8] The costs of care were determined by calculating the actual treatment costs for inpatient,

outpatient, and emergency department visits following initial diagnosis and treatment with chemotherapy. Neutropenia, present in 45% of patients, was the hematologic adverse event associated with the greatest cost. When compared with patients without grade 3 or 4 hematologic events, patients with grade 3 or 4 neutropenia had an annual incremental associated cost of $63,245 more per patient.[8]

Based on a cost-effectiveness analysis, avoiding febrile neutropenia events with the use of primary prophylaxis in patients with breast cancer, non–small cell lung cancer (NSCLC), and non-Hodgkin lymphoma can result in substantial cost savings when compared with secondary prophylaxis.[20] In this analysis, savings per each avoided febrile neutropenia event was estimated to range between $5660 to $20,806. Additionally, researchers reported savings of $5123 to $31,077 per life year gained and $7213 to $35,563 per quality-adjusted life year gained. Thus, preventing febrile neutropenia events can lead to substantial cost savings by reducing the need for hospitalizations or outpatient care.[20]

CHEMOTHERAPY-INDUCED NEUTROPENIA INFLUENCES TREATMENT DECISION-MAKING

Given the potential for complications, the development of CIN can compromise treatment decisions and affect treatment outcomes for patients with cancer.[18] In the setting of CIN, clinicians often employ 1 or several different types of chemotherapy adjustments, such as decreasing the recommended dose, delaying cycles, downgrading or switching to less toxic but potentially less effective regimens, and/or discontinuing chemotherapy. Severe neutropenia is a strong predictor of reduced chemotherapy dose intensity. Reducing the relative dose intensity of chemotherapy leads to suboptimal patient outcomes, including decreased response and survival rates, as data have demonstrated that chemotherapy dose intensity plays a key role in achieving optimal survival outcomes.[18]

Impact of CIN on chemotherapy dose adjustments

Given its impact on treatment decisions and interference on planned regimens, CIN is associated with poor chemotherapy outcomes.[7] The impact of CIN on chemotherapy dose adjustments, including delays and dose reductions, can differ according to type of cancer being managed.[21]

A retrospective cohort study was conducted to estimate the incidence of chemotherapy dose delays, dose reductions, missing doses, and reduced relative dose intensity among 16,233 patients with 6 different tumor types who received adjuvant or neoadjuvant chemotherapy regimens commonly used in community oncology practices in the United States.[21] The study used a large electronic health record database used by oncology practices across the nation. It included patients who had received at least 1 IV administered myelosuppressive agent given during the first chemotherapy cycle, had no distant metastatic disease prior to treatment initiation, were not treated for another tumor type, and were not participants in any clinical trials during the regimen course. Dose delays and dose reductions were common across regimens (range, 22.9%-88.4% and 22.3%-93.1%, respectively). Additionally, up to 87.6% of patients missed at least 1 dose of a myelosuppressive agent that was considered to be a part of the standard regimen. In this cohort study, among the 10,435 patients with breast cancer, almost 33% of patients had dose reductions of 15% or more based on the planned regimen, and 38.0% experienced dose delays of 7 or more days from the planned schedule.[21]

Dose adjustments and delays varied not only by the type of cancer but also by the chemotherapy regimen given.[21] Among patients with ovarian cancer who received carboplatin and paclitaxel, 67.2% experienced a dose delay of 7 days or more, 77.4% had dose reductions of at least 15%, and 50.0% had a missing dose. Treatment with carboplatin and paclitaxel among patients with NSCLC was associated with dose delays of at least 7 days in almost 64% of patients, dose reductions of at least 15% in 83.6% of patients, and missed doses in 52.4% of patients. For patients with NSCLC treated with cisplatin and vinorelbine, dose delays of at least 7 days were reported in 61.5% of patients, dose reductions of at least 15% occurred in 91.3% of patients, and missed doses were reported in 45.4% of patients. In the case of colorectal cancer, dose delays of 7 days or more occurred in 88.4% of patients treated with folinic acid, 5-fluorouracil, and oxaliplatin as part of the FOLFOX-4 regimen; 82.1% of those given these drugs as part of the modified FOLFOX-6 regimen; and 75.2% of those given a 5-fluorouracil regimen. Among patients treated for this malignancy, dose reductions of at least 15% or more were reported in 84.2%, 79.4%, and 93.1% of patients, respectively, and missed doses were reported in 67.6%, 64.6%, and 87.6% of patients given these regimens, respectively.[21]

Oncologist-reported treatment decisions

Results from a 2020 market research study using a 30-minute quantitative survey completed by 101 medical directors and oncologists in community settings demonstrated that nearly one-third of respondents would decrease the recommended dose of chemotherapy if a patient experienced severe neutropenia (ie, of grade 3 or 4). In addition, 54% of oncologists at academic centers and 36% of those at community settings would delay cycles of chemotherapy in patients with severe neutropenia.[22]

A separate market research study assessed the priorities for treatment decision-making among oncologists.[23] A 45-minute online quantitative survey was conducted among 102 medical oncologists and hematologic oncologists based in the United States who had at least 3 years of practice and who treated more than 30 adult patients per month for cancers (eg, those of the pancreas, breast, colorectal, and NSCLC). Responses were measured on a scale from 1 to 9, with answers of 1 to 3 representing very low priority, of 4 to 6 corresponding to moderate priority, of 7 or 8 representing high priority, and of 9 indicating the highest priority. When asked how much of a priority treating CIN is in the overall treatment plan relative to other complications of chemotherapy (eg, liver or renal toxicity, anemia, or nausea and vomiting), the majority of respondents indicated that CIN represents a high priority or the highest priority (**Figure 1**).[23] Specifically, 76% and 10% reported prophylactic CIN treatment as a high or the highest priority, respectively, whereas 13% indicated that

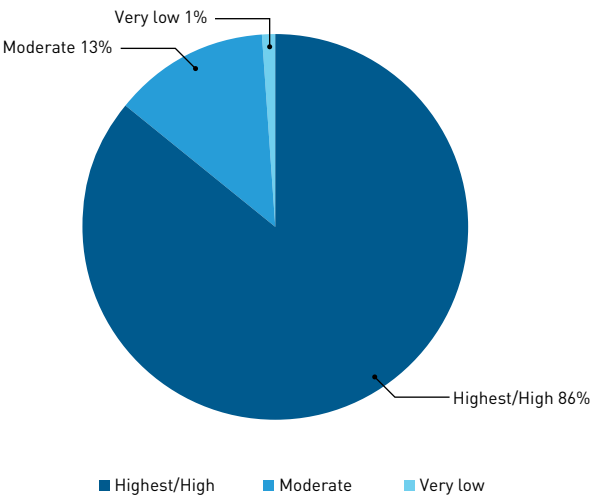
it is a moderate priority, and only 1% indicated that it is a very low priority. Thus, results suggest that, among chemotherapy-related treatment considerations, CIN is considered a significant priority.[23]

CONCLUSIONS AND UNMET NEEDS TO ADDRESS IN CIN FOR MANAGED CARE

During the course of cancer treatment with myelosuppressive regimens, the development of CIN is associated with substantial burdens to patients and the health care system.[7,8] Neutropenia in the setting of chemotherapy-induced myelosuppression impacts the treatment course and increases the need for additional interventions to address serious complications of CIN (eg, systemic infections).[7,8] The increased risk of developing febrile neutropenia is a major concern in patients receiving chemotherapy, since this complication can substantially decrease survival rates.[9]

Most febrile neutropenia events occur during the first chemotherapy cycle. Despite the availability of prophylactic treatment options, CIN and febrile neutropenia remain major chemotherapy dose-limiting toxicities, with studies demonstrating that severe neutropenia is a strong predictor of reduced chemotherapeutic dose intensity.[14,15,18] The critical "neutropenia vulnerability gap" seen 7 days post treatment leaves patients particularly susceptible to the serious consequences of myelosuppression, illustrating the unmet clinical need that exists in the management of CIN.[14,15] ●

Figure 1. Results From a Survey on the Priority of CIN in Chemotherapy-Related Treatment Decisions Among Oncologists[23,a]



CIN, chemotherapy-induced neutropenia.

[a]Response to the level of importance and priority of prophylactic CIN treatment relative to other chemotherapy complications. Oncologists (N = 102) assigned a level of importance on a 1-9 scale where 1 to 3 = very low priority, 4 to 6 = moderate priority, 7 to 8 = high priority, and 9 = highest priority.

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