A Patient Risk Model of Chemotherapy-Induced Febrile Neutropenia: Lessons Learned From the ANC Study Group

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Abstract

Neutropenia and its complications, including febrile neutropenia (FN), represent major toxicities associated with cancer chemotherapy, resulting in considerable morbidity, mortality, and costs. The myeloid growth factors such as granulocyte colony-stimulating factor (G-CSF) have been shown to reduce the risk of neutropenia complications while enabling safe and effective chemotherapy dose intensity. Concerns about the high costs of these agents along with limited physician adherence to clinical practice guidelines, resulting in both overuse and underuse, has stimulated interest in models for individual patient risk assessment to guide appropriate use of G-CSF. In a model developed and validated by the ANC Study Group, half of patients were classified as high risk and half as low risk based on patient-, disease-, and treatment-related factors. This model has been further validated in an independent patient population. Physician-assessed risk of FN, as well as the decision to use prophylactic CSF, has been shown to correlate poorly with the FN risk estimated by the model. Additional modeling efforts in both adults and children receiving cancer treatment have been reported. Identification of patients at a high individual risk for FN and its consequences may offer the potential for optimal chemotherapy delivery and patient outcomes. Likewise, identification of patients at low risk for neutropenic events may reduce costs when such supportive care is not warranted. This article reviews and summarizes FN modeling studies and the opportunities for personalizing supportive care in patients receiving chemotherapy.

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Neutropenia and its complications represent the major dose-limiting toxicities associated with systemic cancer chemotherapy and is associated with considerable morbidity, mortality, and cost.¹ Neutropenic events may result in dose reductions or treatment delays, and subsequently compromise disease control and overall survival.^{2–6} The myeloid growth factors (MGFs), including granulocyte colony-stimulating factor (G-CSF), have been shown to decrease the risk of neutropenic complications, facilitating the safe delivery of planned chemotherapy dose intensity on schedule. Guidelines from NCCN and ASCO on the use of MGFs have recently been updated.^{7,8} When selecting patients for primary prophylaxis with G-CSF, current guidelines recognize

the need to consider a range of risk factors for the occurrence and consequences of febrile neutropenia (FN), defined as body temperature $>38.5^{\circ}\text{C}$ or 2 consecutive measurements $>38^{\circ}\text{C}$ with an absolute neutrophil count $<0.5 \times 10^9/\text{L}$.

Risk Factors for FN and Its Consequences

The risk of FN in patients receiving systemic chemotherapy has generally been based on the rates of FN in patients eligible for randomized controlled clinical trials (RCTs).⁹ A risk of FN of $>20\%$ has been established as a threshold for the routine use of primary G-CSF prophylaxis in guidelines from NCCN, ASCO, and EORTC based on results from RCTs.^{7,8,10,11} However, the rates of

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chemotherapy-induced FN reported in RCTs vary considerably for commonly used chemotherapy regimens.^{12,13} The risk of FN found in observational or “real-world” patient populations is often greater than that reported in patients eligible for RCTs.¹⁴ Variation in chemotherapy treatment intensity and intent as well as additional risk factors, including patient characteristics and comorbidities, have been identified for chemotherapy-induced FN.^{15–18} Current guidelines distinguish between risk factors that increase the likelihood of FN and those that increase the risk of serious medical consequences or death in those who develop FN, which may be important even among patients considered at low or intermediate risk for developing FN (Table 1).^{7,8,11,19}

Myeloid Growth Factors

Potential Benefits

MGFs have been developed and approved for reducing the risk of FN and subsequent neutropenic complications.^{20,21} FN can be a potentially life-threatening complication of chemotherapy either directly,

leading to infectious complications and death, or indirectly, prompting a reduction in chemotherapy intensity or duration and thereby resulting in greater risk of disease recurrence and cancer-related mortality. A recent analysis of patients receiving systemic chemotherapy in a large US health claims database estimated a 35% increase in early mortality and overall a 15% increased risk of all-cause mortality among patients experiencing FN.²² Although no RCT has been powered to address the issue of disease-free or overall survival,²³ a systematic review and meta-analysis of 17 RCTs of primary prophylaxis with G-CSF, including approximately 3,500 patients with solid tumors or lymphoma, confirmed a significant reduction in the risk of FN, as seen in each individual trial.²⁴ Importantly, in this pooled analysis, significant reductions in the risk of infection-related mortality and early all-cause mortality were observed. In a more recent systematic review of RCTs in patients receiving systemic chemotherapy and randomized to G-CSF support with an average follow-up of 5 years, nearly a 10% reduction in the relative risk for all-cause mortality with G-CSF support was observed.^{25,26} A significant association was also observed between reduced mortality and increases in relative chemotherapy dose intensity in patients treated with G-CSF. As noted earlier, G-CSF is routinely administered in support of dose-dense chemotherapy regimens as well as to enable full-dose chemotherapy on schedule in the curative setting. Greater reductions in mortality were observed among trials with longer follow-up, when treatment was clearly for curative intent, and in which survival was the primary study outcome.²⁶

Potential Harms

At the same time, MGFs are associated with established and hypothetical risks as well as considerable costs.²⁷ Transient bone pain, occasionally severe, represents the most common symptom reported by patients receiving G-CSF. Of greater concern has been the potential for an increased risk for developing acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) in patients treated with MGFs. In an analysis of data from the SEER-Medicare linked files, Hershman et al²⁸ observed a doubling of the risk of subsequent AML or MDS from 0.7% to 1.8% with CSF support among older women diagnosed with early-stage breast cancer from 1991 to 1999 who

Table 1. Patient Risk Factors for FN and Its Consequences	
Risk Factors for FN	Risk Factors for Poor Clinical Outcomes From FN
Age ≥65 y	Sepsis syndrome
Advanced disease	Age >65 y
Previous chemotherapy or RT	Severe neutropenia (ANC <100/mcL)
Preexisting neutropenia or bone marrow involvement with tumor	Neutropenia expected to be >10 days in duration
Infection	Pneumonia
Open wounds or recent surgery	Invasive fungal infection
Poor performance or nutritional status	Other clinically documented infections
Poor renal function	Hospitalization at time of fever
Liver dysfunction, most notably elevated bilirubin	Prior episode of FN
Cardiovascular disease	
HIV infection	
Multiple comorbid conditions	

Abbreviations: ANC, absolute neutrophil count; FN, febrile neutropenia; RT, radiation therapy.
Modified from Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2015;33:3199–3212; with permission.

received MGFs with their adjuvant chemotherapy. In the previously mentioned meta-analysis of comparative studies with at least 2 years of follow-up, approximately 25 RCTs involving >12,000 patients reported on rates of AML/MDS or all secondary malignancies.²⁵ AML or MDS was observed in 0.36% of controls and 0.79% with G-CSF, with nearly a doubling of the relative risk. Due to the enhancement of delivered dose intensity with known leukemogenic chemotherapies with G-CSF support, a direct cause-and-effect relationship with G-CSF could not be established. In addition, the observed overall reduction in all-cause mortality was nearly 10-fold greater than the estimated potential risk of AML/MDS across these studies.

Costs

Despite the lack of definitive evidence for serious long-term toxicities associated with G-CSF support of chemotherapy, the associated cost remains of considerable concern and may contribute significantly to the large financial burden associated with modern cancer therapy, resulting in great financial hardship and even bankruptcy and representing a barrier to access to optimal treatment.^{29,30} Despite the recent introduction of biosimilars, G-CSF remains one of the most expensive agents used in cancer management.^{31,32} Numerous cost-effectiveness studies have been undertaken during the past 20 years as the costs of G-CSF and of hospitalization for treating FN have increased dramatically.³³ Most studies have demonstrated reasonable cost-effectiveness for G-CSF prophylaxis when used according to guideline recommendations in patients at high risk for FN.

Appropriate Use of MGFs

Several studies have shown that the risk of an initial episode of FN is greatest during the first cycle of treatment when patients are generally receiving the full dose intensity.^{34–36} The appropriate balance depends largely on the ability of G-CSF to reduce the risk of hospitalization for FN and resulting complications, and the length of hospitalization.^{37,38} However, the ability of G-CSF to decrease the need for dose reductions and treatment delays, potentially improving overall relative dose intensity, treatment effect, and disease control, must also be considered.^{26,39–41} Nevertheless, concerns about underuse and over-

use of MGFs has led to risk-based recommendations from clinical practice guidelines and initiatives such as Choosing Wisely to foster more appropriate, evidence-based, and cost-effective use of these agents.^{7,8,10,11} Although these recommendations suggest that oncologists consider patient-specific characteristics when prescribing G-CSF, a mechanism to quantify individual patient risk is lacking. As a result, the decision whether to use G-CSF is based on the chemotherapy regimen. However, many investigators have demonstrated that the risk of FN in selected patients in RCTs may differ significantly from patients in a real-world setting where age, socioeconomic conditions, or major medical comorbidities may significantly increase a patient's risk of developing FN or experiencing serious adverse consequences, including death.

Personalized Supportive Care

Personalization of supportive care strategies, such as the appropriate and targeted use of the MGFs in a fashion similar to the personalization of targeted cancer therapies, offers considerable potential for more effective, safe, and cost-effective cancer care along with improved survival and quality of life.¹⁹ Due to the number of identified risk factors for FN and its consequences that have been identified, uncertainty remains about their relative importance and contribution to the overall FN risk. As a result, there has been an increasing interest in the development and validation of multivariable risk models for chemotherapy-associated neutropenia and its consequences. A number of modeling efforts have been designed to predict the risk of serious complications, including death, in patients with established FN.^{42–44} Model performance has often been limited, challenging broad use of these models. Clinical practice guidelines uniformly discuss the importance of identifying patient- and treatment-specific risk factors and the need for further research on the risk of FN in the general cancer population.^{7,8}

Risk Models for FN and Its Consequences The Lyman Risk Model

Attention has recently shifted to creating risk models for FN development in ambulatory patients receiving chemotherapy to guide the appropriate use

of MGFs.^{45,46} The ANC Study Group conducted a prospective cohort study of >3,000 patients treated at oncology practices throughout the United States to explicitly evaluate the incidence of and risk factors for neutropenic events in patients receiving systemic chemotherapy.⁴⁵ Consecutive eligible patients with solid tumors or malignant lymphoma initiating a new chemotherapy regimen were enrolled. Risk factors considered included age, sex, ethnicity, employment and educational status, performance status, body surface area, cancer type, disease stage, history of prior cancer and treatment, concomitant medications, baseline hematology and chemistry results, and planned chemotherapy drugs, dose, and schedule. The primary outcome of the study was severe neutropenia or FN in cycle 1 due to the dominant risk of events in the first cycle and their major impact on subsequent risk and treatment decisions.^{2,3,36} Secondary outcomes included the cumulative risk of neutropenic events including FN, and dose reductions, treatment delays, and delivered chemotherapy dose intensity during the period of observation. Factors significantly associated with neutropenic complications in multivariable analysis included a history of previous chemotherapy as well as baseline leukopenia, hepatic or renal dysfunction, planned chemotherapy relative dose intensity, and the use of prophylactic MGF (see supplemental eAppendix 1, available with this article at JNCCN.org). Using the median predicted risk of neutropenic events, 34% of high-risk patients experienced cycle 1 events compared with 4% in low-risk patients. Figure 1 displays the cumulative risk of FN over repeated cycles of chemotherapy for high- and low-risk patients. Kaplan-Meier estimates of the cumulative FN risk was approximately 20% in high-risk patients compared with 5% in low-risk patients.

External Validation Studies

An external validation of the Lyman risk model was recently reported based on automated retrospective extraction of electronic health record (EHR) data on a cohort of adult patients with newly diagnosed breast, colorectal, lung, lymphoid, or ovarian cancer who received the first cycle of a cytotoxic chemotherapy regimen from 2008 to 2013 at a single cancer clinic.⁴⁷ After chart review validation of EHR treatment data, neutropenia risk stratification was conducted and risk model performance was assessed (Ta-

Figure 1. Kaplan-Meier plot displaying the cumulative proportion of patients experiencing ≥ 1 episodes of FN over time in the days following chemotherapy initiation for both high-risk and low-risk patients based on the risk model.

Abbreviations: FN, febrile neutropenia; HR, hazard ratio.

From Lyman GH, Kuderer NM, Crawford J, et al. Predicting individual risk of neutropenic complications in patients receiving cancer chemotherapy. *Cancer* 2011;117:1925; with permission.

ble 2). The risk prediction tool classified 126 patients (57%) as being low risk for FN, 44 (20%) as intermediate risk, and 51 (23%) as high risk. Model discrimination was considered adequate and comparable to the original model (Figure 2). In a secondary analysis, actual G-CSF prophylaxis was examined according to level of hypothetical risk based on the Lyman risk model but assuming no G-CSF prophylaxis was administered (Figure 3). The authors concluded that the individualized neutropenia risk prediction model performed well in this retrospective external cohort. In this secondary analysis, it was observed that most patients given G-CSF prophylaxis were high risk, based on the model. However, 37% of those predicted to be high risk did not receive G-CSF prophylaxis (Figure 3). The authors estimate that if the model risk-based recommendations had been followed, the overall FN risk of 13% would have been reduced to 8% or even less. Additional external validation of the risk model is currently being pursued in different settings and patient populations. Additional validation has recently been demonstrated using data from a large integrated health system,⁴⁸ and further efforts are underway based on prospective clinical trials.⁴⁹

Comparison With Physician Risk Assessment

A prospective cohort study recently evaluated the correlation between the FN risk in patients with

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Table 2. Neutropenia Event^a Rates Among Patients Receiving Cycle One Chemotherapy Treatment With Any Regimen

Predicted Risk		Observed Events, n				P Value for Difference in Event Rates
Range	Mean	With an Event, n	Without an Event, n	Total Patients, n	Event Rate	
0%–9.9%	5.8%	7	119	126	5.5%	.99
10%–19.9%	13.3%	5	39	44	11.4%	.95
≥20%	37.6%	17	34	51	33.3%	.93
Overall	14.6%	29	192	221	13.1%	

^aSevere or febrile neutropenia.

Modified from Pawloski PA, Thomas AJ, Kane S, et al. Predicting neutropenia risk in patients with cancer using electronic data. *J Am Med Inform Assoc* 2017;24:e129–135; with permission.

nonmyeloid malignancies receiving chemotherapy estimated by physicians versus the risk predicted by the Lyman validated multivariate risk model.⁵⁰ Before patient enrollment, physician and site characteristics were recorded, and 124 community oncologists self-reported the FN risk at which they typically consider primary G-CSF prophylaxis. For each of 944 eligible patients, the treating physician electronically recorded their estimated FN risk, orders for G-CSF primary prophylaxis, and patient characteristics for model predictions. Primary outcomes were the correlations between physician-assessed and model-predicted FN risks and between physi-

cian-assessed FN risk and G-CSF orders. The median physician-assessed and model-assessed FN risks were 20%, and 18%, respectively, with a weak correlation of 0.249 (Figure 4). A moderate correlation between physician-assessed FN risk and subsequent orders for primary G-CSF prophylaxis was observed (0.313). This limited correlation is explained by the classification of different patients as either high risk or not by the physician and the risk model. Among patients with a physician-assessed FN risk ≥20%, 14% did not receive G-CSF orders. At the same time, prophylac-

Figure 2. Area under the receiver operating characteristic curve demonstrating model fit for the neutropenia risk prediction model (area under the curve, 0.7475).

From Pawloski PA, Thomas AJ, Kane S, et al. Predicting neutropenia risk in patients with cancer using electronic data. *J Am Med Inform Assoc* 2017;24:e133; with permission.

Figure 3. A secondary analysis examined actual G-CSF prophylaxis by level of hypothetical risk estimated using the model and assuming no G-CSF prophylaxis was administered.

Abbreviations: G-CSF, granulocyte colony-stimulating factor; med, medium.

From Pawloski PA, Thomas AJ, Kane S, et al. Predicting neutropenia risk in patients with cancer using electronic data. *J Am Med Inform Assoc* 2017;24:e133; with permission.

Figure 4. Correlation between physician-assessed and model-predicted febrile neutropenia (FN) risk over all chemotherapy cycles. The line indicates the estimated mean function, and the shaded area indicates the 95% pointwise confidence interval. Physician-assessed FN risk estimates varied considerably around the model-predicted risk estimates and did not increase linearly with increasing model-predicted estimates >30%. From Lyman GH, Dale DC, Legg JC, et al. Assessing patients' risk of febrile neutropenia: is there a correlation between physician-assessed risk and model-predicted risk? *Cancer Med* 2015;4:1158; with permission.

tic G-CSF was ordered in 21% of patients considered not high risk by the treating physician. The authors concluded that further research and education on FN risk factors and appropriate G-CSF use are needed.⁵⁰

Additional Modeling Efforts

A number of additional modeling efforts have been reported for the risk of FN as well as the consequences of FN in patients receiving chemotherapy. Several studies have developed models tailored to specific cancer types in adults, such as breast and ovarian cancer and lymphoma, or to children receiving cancer chemotherapy.^{3,15,35,51–58} Although most models consider a range of agents, others are tailored to specific chemotherapeutic agents or regimens.^{34,35,53} Because the risk of FN is greatest in the first cycle of chemotherapy when most patients are receiving planned dose intensity, most models are based on commonly available clinical, treatment, or laboratory parameters available at the start of treatment. Nevertheless, some investigators have developed risk models incorporating genetic risk factors,^{55,59} whereas others have developed risk models for future FN risk conditional on outcomes during the first cycle of treatment.⁶⁰ Unfortunately, none of these were able to consider the delivered chemotherapy dose intensity, which appears to have

a substantial effect on the risk and consequences of FN. Finally, as noted previously, several early modeling efforts in both children and adults were developed to predict serious adverse outcomes, including death, in patients with established FN.⁴³ One of the earliest and most broadly studied risk models was developed under the Multinational Association of Supportive Care in Cancer (MASCC).^{42,61–63} Despite early popularity and continued interest, the limitations of the MASCC model have been highlighted elsewhere.⁴⁴

Conclusions

Primary G-CSF prophylaxis starting in the first cycle of chemotherapy has been shown to reduce the risk of serious and potentially life-threatening complications of cancer treatment while allowing for the safe and adequate delivery of effective chemotherapy dose intensity. However, concerns about overtreatment and undertreatment, limited physician adherence to guidelines, and the high costs associated with MGFs have encouraged the development and validation of risk models for more individual risk assessment to guide the use of G-CSF support. In the model presented by Lyman et al,⁵⁰ approximately one-half of patients considered to be intermediate risk were

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classified as high risk based on the risk model that incorporated other patient-, disease-, and treatment-related factors, whereas the remainder experienced an average risk of 5%. This model has been retrospectively validated both internally and externally in an independent patient population. In addition, a priori physician-assessed risk of FN and the decision to use prophylactic CSF correlated poorly with the FN risk estimated by the risk model.⁵² Additional modeling efforts in adults and children receiving cancer treatment to determine the risk of FN and serious adverse consequences in those with FN have

been reported and deserve further study. Clearly, the identification of patients at a personal high risk for FN and its complications offers the potential for optimal chemotherapy delivery and patient outcomes. Alternatively, identification of patients at low risk for neutropenic complications can potentially offer cost savings when more aggressive supportive care is not warranted. Nevertheless, further research is needed to establish and validate optimal FN risk prediction tools as well as provide for model integration into electronic chemotherapy order entry systems.

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