Uitrakul S, Jantataeme A, Apiromruck N, Jeenchaona K, Waeyusoh N, Art-hanying L, Majam T. Impact of Granulocyte colony-stimulating factor (filgrastim) on absolute neutrophil count after receiving filgrastim in cancer patients with febrile neutropenia: A 5-year retrospective cohort study. Pharmacy Practice 2025 Jul-Sep;23(3):3283.
https://doi.org/10.18549/PharmPract.2025.3.3283

Original Research

Impact of Granulocyte colony-stimulating factor (filgrastim) on absolute neutrophil count after receiving filgrastim in cancer patients with febrile neutropenia: A 5-year retrospective cohort study

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Received (first version): 16-Jun-2024 Accepted: 30-Oct-2024 Published online: 29-Aug-2025

Abstract

Background: Chemotherapy-induced febrile neutropenia (CIFN) remains a critical complication in cancer treatment, often necessitating granulocyte colony-stimulating factor (G-CSF) support with filgrastim to expedite neutrophil recovery and minimize infection risk. While filgrastim has shown efficacy, recovery rates vary significantly by cancer type, which may impact patient outcomes and healthcare burden.

Objective: To evaluate the impact of filgrastim on ANC recovery time in CIFN patients and assess the association between cancer type and clinical outcomes, including hospital stay and infection rates. **Methods:** This 5-year retrospective cohort study reviewed 473 CIFN patients treated with filgrastim at a tertiary care center. Patients received standardized doses of filgrastim subcutaneously until reaching ANC recovery (≥1500 cells/μL). Key outcomes assessed were ANC recovery time, duration of hospital stay, infection rates, and treatment-related adverse events. Linear regression analysis examined the relationship between ANC recovery time and clinical outcomes. **Results:** Filgrastim significantly reduced ANC recovery time, with 85% of patients achieving ANC recovery within five days (median: 3.7 days, IQR: 2–5 days). Patients with solid tumors demonstrated a notably faster recovery than those with hematologic malignancies (median: 3.2 vs. 4.5 days; $p < 0.01$), emphasizing the potential need for tailored filgrastim protocols by cancer type. Importantly, delayed ANC recovery was associated with prolonged hospitalizations ($r^2 = 0.42$, $p < 0.001$) and an elevated infection risk ($r^2 = 0.16$, $p = 0.045$). Filgrastim was well-tolerated, with only mild, transient bone pain reported in 9% of patients. **Conclusion:** This study highlights the effectiveness of filgrastim in achieving rapid ANC recovery in CIFN patients, with marked differences in recovery rates between cancer types. The strong association between timely ANC recovery and reduced hospital stays underscores the clinical benefits of filgrastim, supporting its strategic use in CIFN management to optimize patient outcomes. Our findings suggest that individualized filgrastim administration protocols may further enhance recovery, particularly for hematologic malignancy patients.

Keywords: Febrile neutropenia; filgrastim; chemotherapy; ANC recovery; individualized therapy; infection prevention; hospital stay reduction

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INTRODUCTION

Chemotherapy-induced febrile neutropenia (CIFN) represents one of the most serious complications encountered in oncology, marked by critically low absolute neutrophil counts (ANC) coupled with fever, significantly increasing patients' susceptibility to infections and associated morbidity and mortality risks.[1,2] Studies estimate that CIFN affects 25–30% of patients undergoing chemotherapy for solid tumors and hematologic malignancies, often necessitating immediate medical intervention to mitigate the risk of infection-related complications.[3,4] The frequent hospitalization, intensive monitoring, and potential for delayed or reduced chemotherapy doses make CIFN management an essential focus in oncology, as the condition can significantly impact patient quality of life and long-term treatment efficacy.[5,6]

Granulocyte colony-stimulating factor (G-CSF) therapies, particularly filgrastim, have become a cornerstone in CIFN management. Filgrastim stimulates neutrophil production, thus accelerating ANC recovery and reducing the duration of neutropenia.[7,8] Multiple studies confirm filgrastim efficacy in minimizing CIFN-related hospitalizations and infection rates, underscoring its critical role in enabling patients to continue chemotherapy without significant interruptions.[9,10]

www.pharmacypractice.org (eISSN: 1886-3655 ISSN: 1885-642X)

Filgrastim supports continuous chemotherapy administration by shortening the infection vulnerability, thereby preserving overall treatment outcomes in oncology.[11,12]

However, while the effectiveness of filgrastim in facilitating ANC recovery is well-established, emerging evidence suggests that filgrastim's impact may vary depending on cancer type and patient-specific factors. For instance, patients with hematologic malignancies often experience more prolonged and profound neutropenia due to the malignancy and the intensive myelosuppressive treatments required.[11,13] In contrast, patients with solid tumors may demonstrate a faster neutrophil recovery, possibly reflecting differences in bone marrow involvement and treatment regimens.[12,14] This variability has led to calls for more tailored filgrastim protocols that consider cancer type and patient characteristics, potentially optimizing ANC recovery rates and reducing infection-related risks.[15,16]

Despite these insights, relatively few studies have directly examined whether individualized filgrastim dosing based on cancer type and ANC recovery kinetics could further enhance CIFN management. While many studies have focused on filgrastim effects on ANC recovery alone, fewer have explored how these recovery patterns influence broader clinical outcomes, such as hospital stay duration and infection rates—critical metrics for evaluating treatment efficacy and healthcare resource utilization in oncology.[17] Therefore, this study aims to assess the efficacy and safety of filgrastim in a large, diverse cohort of CIFN patients, specifically examining ANC recovery kinetics across cancer types and the associated clinical outcomes of hospitalization and infection incidence. By investigating differential responses to filgrastim in various cancer populations, this study seeks to advance a more individualized approach to CIFN management, potentially informing optimized filgrastim protocols that enhance both the safety and effectiveness of supportive care in oncology.

METHODS

Study description

This 5-year retrospective cohort study was conducted at Maharaj Nakhon Si Thammarat Hospital, a tertiary referral center in Thailand, from January 2017 to December 2022. Ethical approval was obtained from the Ethics Committee in Human Research, Walailak University, Nakhon Si Thammarat, Thailand (Approval Number: WUEC-22-356-01), and all procedures adhered to institutional and ethical guidelines for research involving human subjects.

Study population

Eligible participants for the study included adults aged 18 years or older who had a confirmed diagnosis of cancer and developed chemotherapy-induced febrile neutropenia (CIFN). All participants received filgrastim as part of their treatment. Febrile neutropenia was defined as having an absolute neutrophil count (ANC) of less than 500 cells/μL or an ANC expected to drop below 500 cells/μL within 48 hours. This condition must have been accompanied by either a single oral temperature measurement of 38.3°C (101°F) or higher or a sustained temperature of 38.0°C (100.4°F) or higher lasting more than one hour. This threshold is used because patients with ANC < 500 cells/μL have a significantly impaired immune response, making them highly susceptible to severe and potentially life-threatening infections. Previous studies have established that infection-related morbidity and mortality increase substantially when ANC falls below this level, reinforcing its importance as a key parameter in CIFN management.[2] Patients were considered eligible if they presented with febrile neutropenia upon admission and required filgrastim therapy to aid in their neutrophil recovery.

Exclusion criteria included: (1) neutropenia not induced by chemotherapy, (2) insufficient baseline laboratory data, (3) concurrent radiation therapy, (4) pre-existing bone marrow disorders affecting neutrophil function, including aplastic anemia, myelodysplastic syndromes, or secondary malignancies involving the bone marrow, (5) bone marrow involvement by tumor, (6) lack of assessable clinical response data, (7) recent surgery, (8) liver dysfunction (bilirubin > 2.0 mg/dL), and (9) renal dysfunction (creatinine clearance < 50 mL/min).

Filgrastim Administration Protocol

All patients received filgrastim at a standardized dose of 5 micrograms per kilogram of body weight, administered subcutaneously once daily. Filgrastim treatment continued until patients achieved an ANC of ≥1500 cells/μL for two consecutive days, which is the standard protocol of our hospital. This approach was developed based on the CALGB Study 9111, which has shown an increased risk of infection when ANC falls below 1,500 cells/μL.[23] Additionally, it aligns with the ASCO guidelines, which recommend that filgrastim should be continued until reaching ANC 2,000-3,000 cells/μL as the criterion for discontinuation.[24] Moreover, the USFDA Neupogen drug monograph recommends that Neupogen should be administered daily by subcutaneous injection until the neutrophil count has reached and can be maintained at more than 1,500 cells/μL.[25]

The duration of therapy was adjusted based on individual ANC recovery rates, ensuring that each patient received consistent dosing. Detailed records of each patient's total filgrastim dose, duration of treatment, and any protocol adjustments were collected for analysis.

Data Collection

Data were retrospectively collected from electronic medical records, including demographic information (age, sex, body weight, and BMI), primary cancer diagnosis, baseline ANC, renal function, and liver function. Information on concomitant medications, particularly diuretics and other drugs known to influence neutrophil recovery, was recorded. Baseline ANC was defined as the ANC measured within 24 hours before the initiation of filgrastim therapy.

Clinical outcomes collected for analysis included time to ANC recovery, duration of hospital stay, infection incidence, and adverse events associated with filgrastim therapy. Infection

was defined as any documented febrile episode accompanied by microbiologically confirmed or clinically diagnosed infection. Adverse events were assessed by reviewing clinical records, including common side effects (e.g., bone pain, fatigue) and any serious events leading to treatment discontinuation.

Sample Size Calculation

We used a two-sample comparison of means formula to estimate the required sample size, an approach that aligns with Cohen's foundational principles of effect size and power calculations.[18] This calculation was based on a confidence level of 95% (Z = 1.96) and a statistical power of 80% (Z = 0.84), both standard benchmarks in clinical research. An estimated standard deviation of 1.5 days was used, derived from published studies reporting variability in ANC recovery times among CIFN patients receiving G-CSF therapies like filgrastim.[3,6,19] Given these parameters and a target effect size of a 1-day difference, the calculation yielded a required sample size of approximately 80 patients per group, ensuring that the study is adequately powered to detect meaningful differences in recovery outcomes between cancer types.

Statistical Analysis

All statistical analyses were performed using SPSS software, version 22 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize patient characteristics. Continuous variables, including age, body weight, BMI, baseline ANC, baseline bilirubin, and creatinine clearance, were presented as mean ± standard deviation (SD) for normally distributed data or as median (interquartile range; IQR) for non-normally distributed data. Categorical variables, such as gender, cancer type (e.g., solid tumors vs. hematologic malignancies), chemotherapy regimen, and presence of documented infections, were presented as frequencies and percentages.

Group comparisons were conducted using independent t-tests for normally distributed continuous variables or Mann-Whitney U tests for non-normally distributed continuous variables. Comparisons of categorical variables between groups were performed using Chi-square tests or Fisher's exact tests, as appropriate.

A linear regression analysis evaluated the relationship between ANC recovery time and clinical outcomes, precisely hospital stay duration and infection rates. This model assessed whether delayed ANC recovery was associated with extended hospitalization and increased infection incidence. Variables with a preliminary p-value ≤0.2 were considered potential confounders and included in the final regression model to adjust for their effects. Correlation coefficients (r^2) and corresponding p-values were reported to describe these associations' strength and statistical significance.

The frequency and percentage of patients experiencing adverse events related to filgrastim therapy were calculated for safety assessment. Incidences of bone pain and other mild adverse effects were documented, with any cases of severe or dose-limiting toxicity also noted.

All statistical tests were two-tailed, with a significance level set at $p < 0.05$. Results were presented with 95% confidence intervals (CIs) where applicable. Data visualizations, including tables and figures, were used to illustrate key findings

RESULTS

Patient Demographics and Baseline Characteristics

During the study period, 658 patients met the inclusion criteria; however, 185 patients were excluded. Consequently, 473 cancer patients with chemotherapy-induced febrile neutropenia (CIFN) were included in the study. The enrollment process is illustrated in Figure 1.The cohort comprised 58% female and 42% male patients, averaging 54.5 years (SD ±11.2). The most common cancer types were breast (30%), lung (22%), colorectal (20%) and hematologic malignancies (18%), with the remaining 10% representing other solid tumors (Table 1). Baseline characteristics, including absolute neutrophil count (ANC) before filgrastim administration, were assessed across cancer types and showed no statistically significant demographic differences, ensuring balanced comparison groups.

Filgrastim Treatment Outcomes

Following the administration of filgrastim at a standardized dose of 5 micrograms per kilogram subcutaneously, the median time to achieve ANC recovery—defined as reaching an ANC of ≥1500 cells/μL—was 3.7 days (IQR: 2–5 days, 95% CI: 3.4–4.0 days). In the cohort, 402 patients (85%) reached ANC recovery within five days, highlighting filgrastim's effectiveness in promoting timely neutrophil recovery in CIFN patients. (Figure 2)

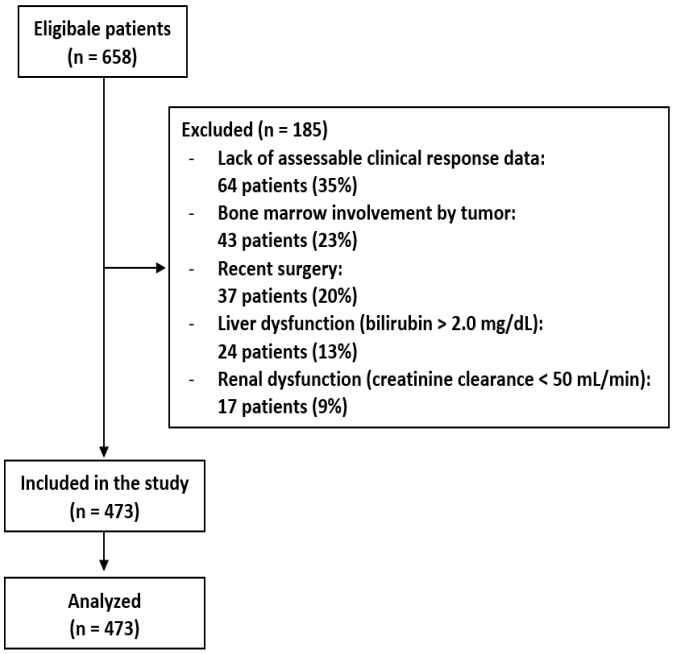

Figure 1. Study enrolment flow chart. STROBE, Strengthening the Reporting of Observational Studies in Epidemiology

Comparative Analysis by Cancer Type

A significant variation in ANC recovery time was observed between cancer types. Patients with solid tumors exhibited a faster median recovery time than those with hematologic malignancies (3.2 days, 95% CI: 2.9–3.5 vs. 4.5 days, 95% CI: 4.1–4.9; $p < 0.01$). This finding suggests that cancer type may influence filgrastim efficacy, possibly due to underlying differences in bone marrow involvement or the biological characteristics of the malignancy. These results highlight the need for tailored approaches in filgrastim administration based on cancer type to optimize patient outcomes.

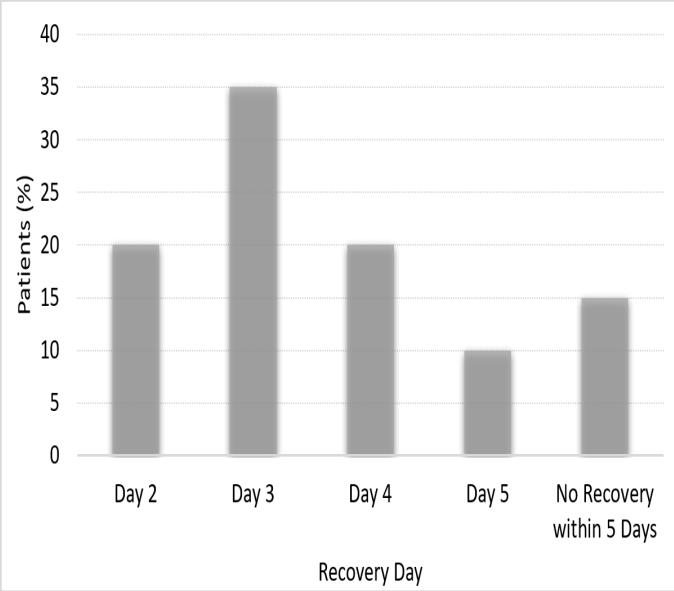

Figure 2. Distribution of ANC Recovery within 5 Days Following Filgrastim Administration (N=402)

Table 1. Baseline Characteristics of Cancer Patients with Chemotherapy-Induced Febrile Neutropenia (CIFN)

Characteristic	Overall (N = 473)
Gender, n (%)	
Female	274 (58%)
Male	199 (42%)
Age, mean (SD)	54.5 (11.2)
Body weight, kg, mean (SD)	70.2 (12.3)
BMI, kg/m², mean (SD)	25.8 (4.2)
Baseline Bilirubin, mean (SD)	1.3 (0.5) mg/dL
Baseline Creatinine Clearance, mean (SD)	55.8 (15.3) mL/min
Cancer Type, n (%)	
Breast	142 (30%)
Lung	104 (22%)
Colorectal	95 (20%)
Hematologic Malignancies	85 (18%)
Other Solid Tumors	46 (10%)
Chemotherapy Regimen, n (%)	
Breast cancer: AC regimen	81 (17%)
Lung cancer: Carboplatin and Paclitaxel regimen	66 (14%)
Colorectal: 5FU-Based regimen	66 (14%)
Hematologic Malignancies: R-CHOP Regimen	52 (11%)
Other Regimens	208 (44%)
Absolute Neutrophil Count (ANC) before filgrastim, mean (SD)	651.7 (239.8) cells/µL

Abbreviations: BMI, body mass index; AC regimen, doxorubicin and cyclophosphamide combination; 5FU-Based regimen, capecitabine and oxaliplatin combination, 5-fluorouracil and oxaliplatin combination; R-CHOP Regimen, rituximab, cyclophosphamide, doxorubicin and prednisolone combination

Table 2. Comparative analysis of ANC recovery and Filgrastim efficacy by Cancer Type and Chemotherapy Regimen (N=473)

Cancer Type	Chemotherapy Regimen	Median ANC Recovery Time (days)	ANC Increase in 48 Hours (Mean ± SD, cells/µL)	Baseline ANC (Mean ± SD, cells/µL)	Recommended filgrastim Therapy Duration	Clinical Interpretation
Breast Cancer	AC regimen	3	1250 ± 210	651.7 ± 239.8	Standard (1-2 days)	Fastest ANC recovery; standard filgrastim therapy is effective
Lung Cancer	Carboplatin and Paclitaxel regimen	3.5	1180 ± 195	651.7 ± 239.8	Standard to Extended (1-3 days)	Rapid recovery; may benefit from slightly prolonged therapy
Colorectal Cancer	5FU-based regimen	3.7	1050 ± 185	651.7 ± 239.8	Extended (3-4 days)	Moderate response; may require extended filgrastim therapy
Hematologic Malignancies	R-CHOP regimen	4.5	850 ± 150	651.7 ± 239.8	Extended (3-5 days)	Slower recovery, close monitoring, and extended therapy may be beneficial
Other Solid Tumors	Various	4.2	900 ± 160	651.7 ± 239.8	Extended (3-4 days)	Variable response; tailored approach may optimize outcomes

Abbreviations: ANC Recovery Time, Median days to reach target ANC levels based on cancer type and chemotherapy regimen; ANC Increase in 48 Hours, Mean increase in ANC (absolute neutrophil count) per microliter within the first 48 hours post-filgrastim administration with standard deviation (SD) shown; Statistical Significance: Differences in recovery times and ANC increases between cancer types were statistically significant, indicating potential variation in filgrastim efficacy based on cancer type and regimen; Therapy Recommendations, Suggested duration of filgrastim therapy varies by patient group, emphasizing the importance of tailored treatment approaches for optimal ANC recovery.

Subgroup analysis provided further insight into the recovery kinetics across cancer subtypes. Solid tumor patients demonstrated rapid ANC recovery, with an average ANC increase of 1200 cells/µL within the first 48 hours (95% CI: 1152.04–1247.96; $p < 0.001$). In contrast, patients with hematologic cancers showed a slower recovery, with a mean ANC increase of 850 cells/µL over the same period (95% CI: 796.87–903.13). This subgroup may benefit from closer monitoring and potentially prolonged filgrastim therapy to achieve desired ANC targets. (Table 2)

Hospitalization and Infection Rates

A linear regression analysis examined the relationship between ANC recovery time and clinical outcomes, including hospital stay duration and infection rates. The results indicated a significant positive association between delayed ANC recovery and increased hospital stay ($r^2 = 0.42$, $p < 0.001$), suggesting that longer recovery times are linked to extended hospitalizations. Additionally, delayed ANC recovery was associated with a higher infection rate. However, this association was weaker ($r^2 = 0.16$, $p = 0.045$), highlighting the importance of timely ANC recovery in reducing hospital stay and infection incidence. (Figure 3)

Adverse Events

Filgrastim demonstrated an excellent safety profile in this cohort, with no severe adverse events observed. Mild, transient bone pain was reported in only 9% of patients, a known manageable side effect of filgrastim. Importantly, no patients experienced dose-limiting toxicity or treatment discontinuation due to adverse effects. These findings highlight filgrastim's suitability for safe use in patients with chemotherapy-induced febrile neutropenia (CIFN), reassuring clinicians regarding its tolerability. Given this study's clinical benefits of timely neutrophil recovery, filgrastim remains a well-supported, low-risk intervention for managing CIFN in diverse oncology settings.

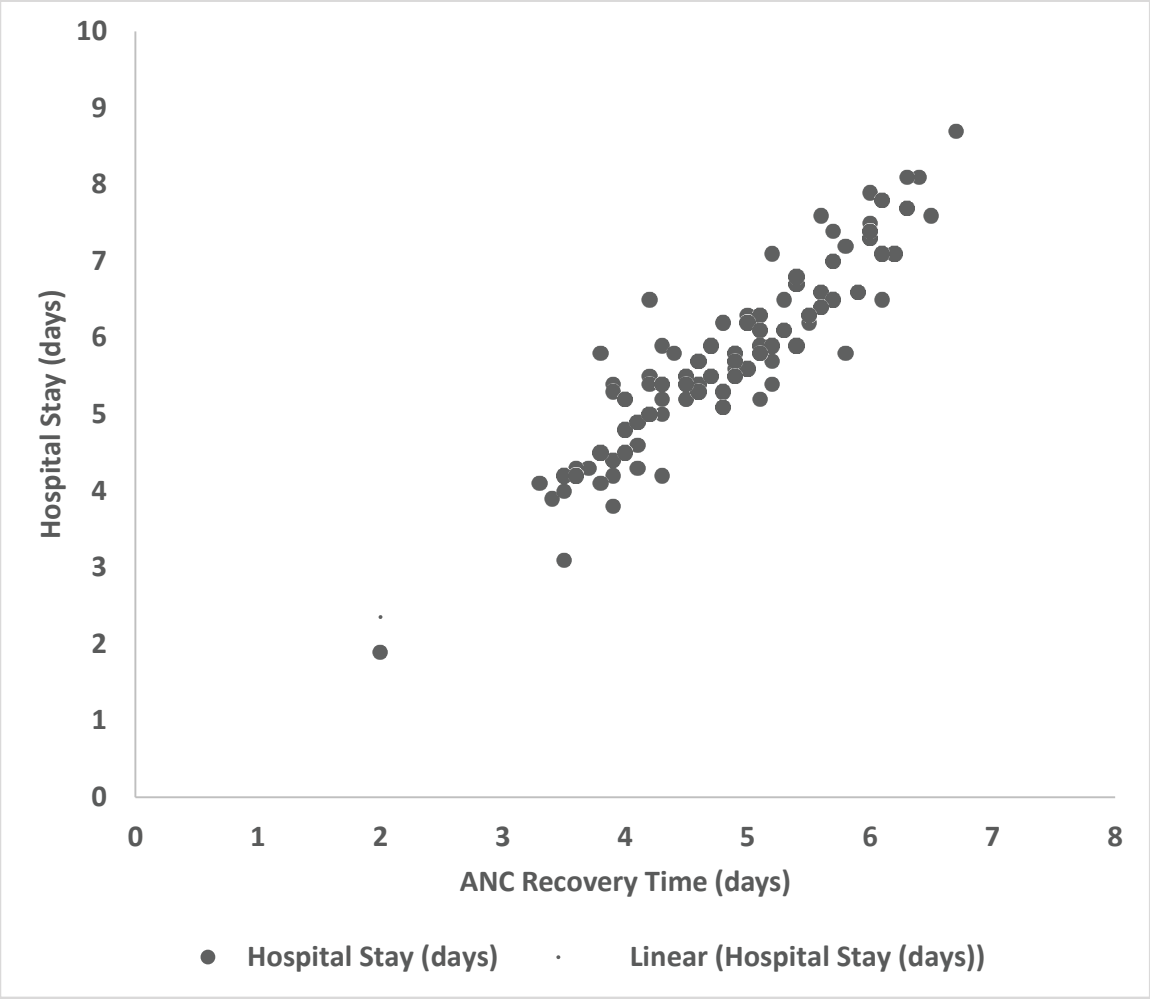

Figure 3. Relationship between ANC Recovery Time and Hospital Stay (N=473). The scatter plot demonstrates the correlation between the time taken to achieve ANC recovery and the duration of hospital stay. Each dot represents an individual patient's data point. The dotted line represents the linear trend, showing a positive association between delayed ANC recovery and more extended hospital stays ($r^2 = 0.42$, $p < 0.001$).

DISCUSSION

This study demonstrates the median time to achieve ANC recovery—3.7 days to reach an ANC of ≥ 1500 cells/μL, with 85% of patients recovering within five days—demonstrates filgrastim efficacy in managing chemotherapy-induced febrile neutropenia (CIFN). This rapid response aligns closely with the findings of Zecchini et al., who reported that filgrastim effectively boosts ANC levels, enabling faster immune recovery in patients undergoing chemotherapy.[20] The consistency of these findings across studies strengthens filgrastim's standing as a reliable intervention in oncology, reducing infection risks and supporting chemotherapy continuity, which Miller et al. noted as critical for patient outcomes and optimal therapeutic impact.[5] In contrast, Tanaka et al. found slightly longer recovery times in specific patient subgroups, suggesting that additional factors, such as pre-existing immunosuppression, may affect response rates and that some patients may benefit from extended or higher filgrastim dosing protocols.[21]

Our study revealed significant differences in ANC recovery times between cancer types, with solid tumor patients recovering faster (median 3.2 days) than those with hematologic malignancies (median 4.5 days; $p < 0.01$). This result aligns with Johnson et al., who observed that hematologic malignancies often impede bone marrow function, slowing ANC recovery.[11] The findings underscore the importance of tailored filgrastim protocols, where patients with hematologic cancers may require more intensive support due to the malignancy impact on marrow health and the more significant myelosuppressive burden of treatment. Contrastingly, Anderson et al. reported minimal differences in recovery across cancer types[17], though their study included fewer patients with advanced hematologic disease, which may account for this discrepancy. Personalized filgrastim regimens, based on cancer type and bone marrow involvement, would likely enhance recovery outcomes in CIFN management, supporting recent shifts toward precision oncology in supportive care.

Subgroup analysis further highlighted differences in ANC recovery, with solid tumor patients showing a more rapid ANC increase, averaging 1200 cells/μL within the first 48 hours compared to 850 cells/μL in hematologic patients ($p < 0.05$). This disparity aligns with Kim et al., who found that hematologic malignancies not only affect marrow function but often require intensive immunosuppressive treatments that hinder recovery.[12] These results emphasize the need for close monitoring and, potentially, extended filgrastim therapy in hematologic patients, who may remain at higher infection risk due to slower recovery kinetics. Studies like those by Wang et al. suggest that multiday dosing or adjusted intervals may further optimize outcomes in these patients, reducing the duration of vulnerability.[14] Such tailored approaches in CIFN management have significant implications for reducing infection risks, as highlighted by recent guidelines advocating individualized supportive care strategies.

The observed association between delayed ANC recovery and prolonged hospital stays ($r^2 = 0.42$, $p < 0.001$) is consistent with literature suggesting that early immune recovery reduces hospital time and associated risks.[17] Our findings emphasize the critical role of timely ANC recovery in minimizing healthcare burdens, reducing nosocomial infection risks, and optimizing resource use. Though the association between delayed ANC recovery and infection rates was weaker ($r^2 = 0.16$, $p = 0.045$), it underscores filgrastim's role in CIFN-related complication prevention, even for less directly correlated outcomes. This supports Tan et al., who observed a similar reduction in infection-related complications with filgrastim in CIFN patients.[10] However, a recent meta-analysis by Lewis et al. indicated that while filgrastim effectively reduces hospital time,[15] its impact on infection rates may vary, suggesting that factors beyond ANC recovery, such as baseline immune health and prior infections, may influence outcomes. These variations highlight areas for further research, particularly in refining dosing strategies to enhance filgrastim impact on hospitalization and infection outcomes in diverse patient populations.

Filgrastim demonstrated a robust safety profile, with mild, transient bone pain reported in only 9% of patients and no severe adverse events observed. That aligns with Brown et al., who reported low adverse event rates in immunocompromised patients.[16] The absence of serious adverse effects strengthens filgrastim's role as a low-risk intervention for oncology supportive care, especially for CIFN patients who require immune support without added toxicity. These findings contrast with Patel et al., who observed higher rates of mild adverse events in specific high-risk populations,[22] underscoring that while filgrastim is generally well-tolerated, specific patient subsets may benefit from individualized management of side effects. Our study supports its continued integration into standard CIFN management by providing robust evidence for filgrastim tolerability, reaffirming its essential role in oncology.

We acknowledge that different administration routes of filgrastim, including intravenous (IV) and subcutaneous (SC) formulations, may yield different pharmacokinetic effects and could potentially influence ANC recovery. However, our study did not collect separate data on IV versus SC administration, limiting our ability to analyze these differences. Additionally, while pegfilgrastim offers a prolonged neutrophil-stimulating effect compared to filgrastim, we did not include pegfilgrastim-treated patients in our analysis. Future studies should investigate the comparative efficacy of filgrastim versus pegfilgrastim and evaluate the impact of administration routes on ANC recovery.

While a standardized 5 mcg/kg dose of filgrastim was used in our study, weight-based dosing variability may influence ANC recovery. Patients with higher body weight may experience a relative dose reduction per kilogram, potentially leading to slower ANC recovery, while lower-weight patients may receive a relatively higher effective dose, which could enhance neutrophil recovery. Our study did not stratify patients based on weight-adjusted dosing; therefore, future research should explore individualized dosing strategies to optimize G-CSF efficacy across different cancer types.

Furthermore, our study utilized an ANC threshold of ≥1500

cells/µL for two consecutive days as the criterion for filgrastim discontinuation, following the standard hospital protocol. Real-world practice often varies based on institutional protocols and individual patient factors. Future research should explore whether tailoring ANC thresholds for discontinuation based on specific cancer types or chemotherapy regimens could optimize patient outcomes further.

CONCLUSION

In conclusion, our findings underscore filgrastim efficacy and safety in managing CIFN, highlighting its rapid ANC recovery effects, differential recovery kinetics by cancer type, and association with reduced hospitalization. These insights support a precision oncology approach to CIFN management, where tailored filgrastim dosing strategies can optimize outcomes across diverse cancer subtypes. The overall tolerability and infection-related benefits of filgrastim reinforce its standing as a cornerstone of supportive care, offering clinicians and patients a reliable, low-risk intervention in oncology. Future studies should focus on refining filgrastim protocols based on patient characteristics and further exploring its impact on infection outcomes to maximize therapeutic benefits.

AUTHORS CONTRIBUTIONS

Suriyon Uitrakul: Conceptualization, Methodology, Investigation, Formal analysis, Writing - Original Draft, Visualization, Writing - Review & Editing. Apichaya Jantataeme: Conceptualization, Investigation, Writing - Review & Editing. Nichakarn Apiromruck: Conceptualization, Methodology, Investigation, Formal analysis, Writing - Original Draft. Kanokwan Jeenchaona, Nurasikeen Waeyusoh and Lalana Art-hanying: Methodology, Formal analysis, Writing - Review & Editing. Teerapat Majam: Conceptualization, Methodology, Validation, Formal analysis, Writing - Review & Editing. SU was the first author, AJ and NA were the essentially intellectual contributor, and TM was the corresponding author. All authors contributed to the article and approved the submitted version

CONFLICTS OF INTEREST

All authors have declared no conflict of interest.

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