Article published online: 2024-09-16

THIEME OPEN ACCESS

Practice Patterns and Incidence of Febrile Neutropenia in Patients Receiving Triplet Drug Chemotherapeutic Regimens in GUT Cancers: Do We Need to Add WBC Growth Factors? (ForGeT GCSF Study)

Kapu Venkatesh[1] Anant Ramaswamy[1] Noorzia Sultana[1] Prabhat Bhargava[1] Sujay Srinivas[1] Mannavi Suman[1] Mehak Trikha[1] Vikas Ostwal[1]

[1] Dept. of Medical Oncology, Tata Memorial Hospital, Homi Bhabha National Institute (HBNI), Dr. E Borges Road, Parel, Mumbai, India

South Asian J Cancer

Address for correspondence Vikas Ostwal, MD, DM, Professor, Dept. of Medical Oncology, Tata Memorial Hospital, Homi Bhabha National Institute (HBNI), Dr. E Borges Road, Parel, Mumbai – 400 012, India (e-mail: dr.vikas.ostwal@gmail.com).

Abstract

Vikas Ostwal

Background and Objectives: There are limited data on the requirement and duration of white blood cell (WBC) growth factor (GF) administration in patients receiving biweekly docetaxel, oxaliplatin, leucovorin, 5 Fluorouracil (mFLOT) or modified FOLFIRINOX (oxaliplatin, irinotecan, leucovorin, 5 Fluorouracil (mFOLFIRINOX) regimens.

Methods: The data of 749 patients with pancreatic, gastric, and colorectal adenocarcinomas treated with mFOLFIRINOX or mFLOT for at least three cycles between January 2018 and December 2022 were retrieved.

Results: Of the 749 patients, 387 (52%) received mFLOT, while 362 (48%) received mFOLFIRINOX. Increased use of GF was seen in patients with diabetes mellitus (70 vs. 53%; $p < 0.001$), prior chemotherapy (82 vs. 49%; $p < 0.001$), prior pelvic radiotherapy (89 vs. 54%; $p < 0.001$), prior surgery (70 vs. 49%; $p < 0.001$), and stage I to III cancers as opposed to stage IV cancers (61 vs. 48%; $p = 0.006$). The use of GF resulted in a statistically lesser incidence of all-grades neutropenia (2.6 vs. 18.4%; $p < 0.001$), grade 3/4 neutropenia (1.2 vs. 12.5%; $p < 0.001$), and the primary endpoint of febrile neutropenia (FN; 1.2 vs. 6.1%; $p = 0.001$). There were no differences in the incidence of all grades of neutropenia (3.7 vs. 1.9%; $p = 0.527$), grade 3/4 neutropenia, and the primary endpoint of FN (1.2 vs. 1.1%; $p = 0.079$) in patients receiving single-day versus multiday GF, respectively.

Interpretation and Conclusion: The use of GF reduces the rates of FN by approximately 80% in patients receiving mFLOT and mFOLFIRINOX, although incidences of FN are low with these regimens. The incidence of febrile neutropenia was similar with single-dose versus multiday GF in efficacy when administered with mFLOT and mFOLFIRINOX chemotherapy.

Keywords

- WBC growth factor
- G-CSF
- GM-CSF
- mFLOT
- mFOLFIRINOX
- febrile neutropenia

DOI https://doi.org/10.1055/s-0044-1789590 ISSN 2278-330X

How to cite this article: Venkatesh K, Ramaswamy A, Sultana N, et al. Practice Patterns and Incidence of Febrile Neutropenia in Patients Receiving Triplet Drug Chemotherapeutic Regimens in GUT Cancers: Do We Need to Add WBC Growth Factors? (ForGeT GCSF Study). South Asian J Cancer 2024;00(00):00–00.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

White blood cell (WBC) growth factors like granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and Peg filgrastim (peg-GCSF) have been used as primary and secondary prophylaxis in patients being treated with myelosuppressive chemotherapy.[1] Recommendations for primary prophylaxis (G-CSF to be considered in dose-dense regimens as well as in those regimens where expected febrile neutropenia [FN] rates are ≥20%) and secondary prophylaxis (G-CSF recommended for patients with solid tumors who experienced a neutropenic complication from a prior cycle of chemotherapy without the use of G-CSF) are reasonably established, with enough leeway given for patients with special situations (e.g., age ≥65 years, multiple comorbidities, expected prolonged neutropenia, etc.).[2,3]

While the initial recommendations for the use of WBC growth factors as primary prophylaxis came from two trials evaluating docetaxel in metastatic breast cancer and the cyclophosphamide-doxorubicin-etoposide regimen in non-small-cell lung cancer, a number of chemotherapeutic regimens do not have firm recommendations to support or avoid the use of growth factors.[4,5] Two such commonly used multidrug regimens are the FLOT and FOLFIRINOX regimens, which are used in gastric cancers, and pancreatic and colorectal cancers. The rates of grade 3/4 neutropenia and febrile neutropenia with FOLFIRINOX were 45.4 and 5.4%, respectively, in phase 3 UNICANCER – PRODIGE (Unicancer Gastrointestinal Group and Partenariat de Recherche en Oncologie Digestive) trial and 51 and 2%, respectively, with the FLOT regimen in phase III FLOT4 – Arbeitsgemeinschaft Internistische Onkologie (AIO) trial.[6,7] Both regimens are considered relatively myelosuppressive and toxic, although the seminal trials did not mandate the use of growth factors in the study. Additionally, whether single-day or multiday use of WBC growth factors is required is also unclear. Considering their common usage, it is instructive to evaluate the use of WBC growth factors in patients receiving these regimens as well as evaluate the incidence of neutropenia and resulting febrile neutropenia, with or without the use of growth factors in a large cohort.

Materials and Methods

Patient Selection

The current study is conducted after the institutional review board (IRB) approval (Institutional Ethics Committee, Tata Memorial Centre, Mumbai) of three projects evaluating outcomes of patients with colorectal cancer, gastric adenocarcinomas, and pancreatic adenocarcinomas (IEC/900711 and IEC/900655). The study was conducted according to the ethical standards laid down by the 1964 declaration of Helsinki. Since the study was a retrospective study, the ethics committee granted consent waiver. The data of consecutive patients receiving either mFLOT or mFOLFIRINOX regimen were retrieved from a prospectively maintained GI Medical Oncology database and electronic medical records. Patients treated between January 1, 2019 and December 31, 2022 were considered for the study. Patients selected for entry into the study satisfied the criteria of having histologically proven colorectal, pancreatic, or gastric adenocarcinoma; received either mFLOT (docetaxel [50 mg/m^2 D1], oxaliplatin [85 mg/m^2 D1], leucovorin [200 mg/m^2 D1], and 5-fluorouracil [2,400 mg/m^2 D1 and D2 continuous intravenous infusion over 46 hours every 2 weeks) or mFOLFIRINOX (oxaliplatin 65 mg/m^2 intravenous [IV] over 2 hours, irinotecan 135 mg/m^2 IV over 90 minutes, leucovorin 300 mg/m^2 IV over 2 hours, and 5-FU 1,800 mg/m^2 IV over 46 hours of continuous infusion every 2 weeks); received at least the first three cycles of chemotherapy at Tata Memorial Hospital; documented receipt of growth factors including duration (single day or multiple days) and type of growth factors (G-CSF or peg-GCSF) or not; and data for the presence or absence of grade 3/4 neutropenia and febrile neutropenia. The outcomes and toxicity patterns with the mFLOT and mFOLFIRINOX regimens used in the study have been previously published and are considered standard of care in our institution.[8,9] While the initial dose of mFOLFIRINOX was used as mentioned above in all patients, initial dose reductions at baseline were allowed for mFLOT based on treating physician assessment and were carried out during the course of chemotherapy based on British Columbia Cancer chemotherapy guidelines modifications.

Data Collection and Statistical Analysis

Baseline demographic and clinical variables, including incidence and grade of neutropenia, febrile neutropenia, and other toxicities during chemotherapy, were collected retrospectively from the database and entered in SPSS software version 25. Descriptive statistics were used to compute these variables. The primary endpoints of the study were twofold: comparison of the febrile neutropenia post first cycle of chemotherapy in patients receiving WBC growth factors and no growth factors, and comparison of febrile neutropenia rates post first cycle of chemotherapy in patients receiving single-day or multiday WBC growth factors (peg-GCSF was considered as multiday growth factor for the purpose of analysis). Secondary endpoints included a comparison of neutropenia rates, non-neutropenic fever rates, and admission rates during the first cycle of chemotherapy; and incidence of neutropenia, febrile neutropenia, non-neutropenic fever rates, and admission rates during further chemotherapy. The primary analysis was on an intent-to-treat basis and the incidence of febrile neutropenia was compared using the log-rank test. A stratified Cox proportional hazards regression model was used to evaluate the association of pretreatment clinical variables with endpoints. Statistical analyses were performed using SPSS 21.0 software for Windows (SPSS Inc., Chicago, IL, United States).

Results

Baseline Characteristics and Incidences of Neutropenia and Related Complications

A total of 749 patients were available for analysis, with 388 patients (52%) receiving mFLOT and 361 patients (48%) receiving mFOLFIRINOX regimens. A detailed description is provided in ►Table 1.

Table 1 Baseline characteristics

Variable	Number (%)
Median age, y (range) • Age ≥60	53 (17–81) 235 (31)
Male gender	477 (64)
Comorbidities	
• Hypertension • Diabetes mellitus • Cardiac dysfunction	141 (19) 171 (23) 21 (3)
Prior cancer directed therapy	
• Chemotherapy • Curative intent resection • Radiotherapy	173 (23) 252 (34) 84 (11)
Disease stage	
• 1–3 • 4	480 (64) 269 (36)
Primary site of tumor	
• Stomach • Pancreas • Colorectal	387 (52) 244 (33) 118 (16)
Drug regimen	
• Modified FOLFIRINOX • Modified FLOT	362 (48) 387 (52)
Drug dosing	
• Full dose • Reduced dose	635 (85) 114 (15)
Receipt of growth factors	
• None • Single-day G-CSF • Multiday G-CSF • Peg-GCSF	326 (44) 162 (22) 164 (22) 97 (13)

Abbreviations: G-CSF, granulocyte colony-stimulating factor; Peg-GCSF, Peg filgrastim granulocyte colony-stimulating factor|

Of the 749 patients receiving chemotherapy, 71 patients (9%) had all grades of neutropenia, while 46 of those patients (6%) had grade 3 or 4 neutropenia. Twenty-five patients (3%) had febrile neutropenia, 90 patients (12%) had non-neutropenic fever, and there was 1 death (<1%) due to neutropenic complications. Seventeen patients (2%) required a delay in starting the next cycle of chemotherapy due to complications in the first cycle of chemotherapy. A further 72 patients (10%) were administered growth factors in later cycles due to complications in cycle 1 of chemotherapy. A detailed description is given in ►Table 2.

Factors Associated with Growth Factor Use

The presence of diabetes mellitus (70 vs. 53%; $p < 0.001$), receipt of prior chemotherapy (82 vs. 49%; $p < 0.001$), prior surgery (70 vs. 49%; $p < 0.001$), prior pelvic radiotherapy (89 vs. 52%; $p < 0.001$), and stage I to III versus stage IV disease (61 vs. 48%; $p = 0.006$) were associated with increased growth factor use. Increased age, gender, presence of hypertension, and dose reductions at baseline were not associated with increased growth factor use (table 3).

Table 2 Neutropenic complication rates and effects on further chemotherapy

Variable	Number (%)
Neutropenic complication rates during the first cycle of chemotherapy	
Neutropenia	
• Nil • Grades 1 and 2 • Grade 3 • Grade 4	678 (91) 25 (3) 35 (5) 11 (2)
Febrile neutropenia	
• Nil • Grade 3 • Grade 4	724 (97) 17 (3) 8 (1)
Non-neutropenic fever	90 (12)
Blood culture positivity	2 (0.3)
Admissions for febrile neutropenia	13 (2)
Death due to neutropenia related complications	1 (<1)
Thrombocytopenia	
• Nil • Grades 1 and 2 • Grades 3 and 4	680 (91) 61 (8) 8 (1)
Neutropenic complication rates during further chemotherapy	
Delay in initiation of next cycle of chemotherapy	
• Nil • ≤1 wk • >1 wk	732 (98) 10 (1) 7 (1)
Dose modifications in further chemotherapy	10 (1)
Increased use of G-CSF in further chemotherapy	72 (10)
Neutropenia	
• Nil • Grades 1 and 2 • Grade 3 • Grade 4	743 (99) 4 (1) 1 (<1) 1 (<1)
Febrile neutropenia	
• Nil • Grade 3 • Grade 4	746 (100) 1 (<1) 1 (<1)
Non-neutropenic fever	136 (18)
Admissions for febrile neutropenia	1 (<1)

Correlation Between Growth Factor Use and Neutropenia and Neutropenia-Related Complications

The use of growth factors resulted in a decreased incidence of all grades of neutropenia (2.6 vs. 18.4%; $p < 0.001$), grade 3 and 4 neutropenia (1.2 vs. 12.5%; $p < 0.001$), febrile neutropenia (1.2% vs. 6.1%; $p = 0.001$), and non-neutropenic fever (8.7 vs. 16.2%; $p = 0.002$), but there was no difference in

Table 3 Univariate and multivariate Cox proportional hazards regression analysis of baseline variables and growth factor use

Variable	Use of growth factors (%)	*p*-value
Age (y)		
• ≥60 • <60	132/235 (56) 291/514 (57)	0.909
Sex		
• Female • Male	142/272 (52) 281/477 (59)	0.075
Diabetes mellitus		
• Yes • No	119/171(70) 304/578 (53)	<0.001
Hypertension		
• Yes • No	89/141 (63) 334/608 (55)	0.077
Prior chemotherapy		
• Yes • No	141/173 (82) 282/576 (49)	<0.001
Prior surgery		
• Yes • No	177/252 (70) 245/496 (49)	<0.001
Prior pelvic RT		
• Yes • No	75/84 (89) 348/665 (52)	<0.001
Stage		
• I–III • IV	293/480 (61) 130/269 (48)	0.006
Baseline dose		
• Reduced dose • Full dose	68/115 (59) 355/634 (56)	0.532

admission rates for neutropenic complications (1.2 vs. 2.7%; $p = 0.156$). With regard to further chemotherapy, the incidence of dose modifications in further cycles of chemotherapy (1.4 vs. 1.2%; $p = 0.821$) and delays in initiation of chemotherapy (1.7 vs 3.1%; $p = 0.198$) were not statistically different in patients receiving growth factors or not receiving the same. There were no statistical differences in the incidence of all-grades thrombocytopenia (9.8 vs. 8.7%; $p = 0.38$) as well as grade 3/4 thrombocytopenia (1.4% vs. 0.6%; $p = 0.27$) in patients receiving growth factors or not.

On comparing patients who received single-day ($n = 162$) versus multiday growth factor ($n = 261$), there were no differences in all grades of neutropenia (3.7 vs. 1.9%; $p = 0.527$), febrile neutropenia (1.2 vs. 1.1%; $p = 0.079$), non-neutropenic fever (9.2 vs. 8.4%; $p = 0.769$), and admissions due to neutropenic complications (1.9 vs. 0.7%; $p = 0.307$). There were no differences in the duration of delay for further chemotherapy (1.2 vs. 1.9%; $p = 0.593$), the requirement of dose modifications during the next cycles of chemotherapy (1.2 vs. 1.5%; $p = 0.801$), or increased use of growth factors during the next cycle of chemotherapy (3 vs. 5%; $p = 0.348$). Additionally, during further chemotherapy, there were no statistical differences in the incidence of all-grades neutropenia (<1 vs. 0%; $p = 0.204$), febrile neutropenia (<1 vs. 0%; $p = 0.204$), and non-neutropenic fever (17.9 vs. 20.3%; $p = 0.796$) between patients who received single-day or multiday WBC growth factor during the first cycle of chemotherapy.

Discussion

The current study examines the use of growth factors in patients receiving mFOLFIRINOX and mFLOT in various gastrointestinal cancers and suggests that the use of growth factors reduces the incidences of neutropenia and neutropenia-related complication rates in the first cycle of chemotherapy, but had limited effects on neutropenia-related parameters during further doses of chemotherapy. It also suggests that there were no statistical differences in neutropenia and neutropenia-related complications between patients receiving single-day growth factors and those receiving multi-day growth factors for these regimens.

The American Society of Clinical Oncology (ASCO) clinical oncology practice guideline update in 2015 with regard to the use of WBC growth factors is based primarily on studies conducted primarily in hematological malignancies and breast cancer patients, with some evidence from lung cancers as well. The multidrug regimens evaluated in this study, mFOLFIRINOX and mFLOT, were uncommonly used at the time of the initial 2006 ASCO update with increasing use only from 2011 onward. Additionally, pancreatic cancers and gastric cancers, which comprise the majority of patients using these regimens, commonly present in the seventh decade. Finally, while the regimens may not be technically considered dose dense (as they do not have well-established 3-weekly dosing counterparts for comparison) in terms of duration, both regimens are biweekly and use multiple myelosuppressive drugs with the potential for significant neutropenia and related complications. It is likely in view of the above-mentioned ambiguity with respect to these regimens and the factor of advanced age that the trials evaluating FOLFIRINOX in advanced pancreatic cancers and FLOT in resectable gastric cancers allowed the primary use of WBC growth factors without making it necessary.[6,7]

The increased use of WBC growth factors in diabetic patients, patients with prior history of surgery and pelvic radiotherapy, and patients with prior chemotherapy is keeping in consonance with the use of these factors as per published data and guidelines.[10,11] Interestingly, there was increased use of growth factors in patients with stage I to III as opposed to stage IV cancer. This is likely a reflection of attempting to reduce delays in curative intent chemotherapy as opposed to reduced use in patients being treated with palliative intent therapy.

The incidence of neutropenia in the current study was markedly lower than that seen in the seminal studies, and this is likely due to a number of reasons—modified (reduced) doses of both regimens used, a significant proportion of patients receiving prophylactic WBC growth factors, and a lesser frequency of blood panel monitoring in clinical

practice as opposed to that in clinical trials. Within the confines of these differences, we can still draw certain conclusions from this study. Primarily, as expected, incidences of all-grades neutropenia, febrile neutropenia, and non-neutropenic fever were decreased with the use of WBC growth factors, and this was statistically significant. While the incidences of FN without WBC growth factors do not reach the 20% cutoff as per the ASCO guidelines, the greater than 80% reduction (from 6.1 to 1.2%) is a clinically relevant endpoint that is worth considering for clinical practice. In high-risk patients (such as those with prior diabetes mellitus, pelvic radiotherapy, surgery, etc.), the incidence of FN will likely be higher without WBC growth factors and such patients should be considered for WBC growth factors when mFOLFIRINOX or mFLOT is used. The current study cannot identify these factors as high risk for FN as a large proportion of patients with such pretreatment variables already received WBC growth factors. A number of outcomes with relation to further chemotherapy (dose modifications, delays in chemotherapy, etc.) were not influenced by the use of primary prophylaxis with WBC growth factors possibly due to the small number of events in the study as well as the known equipoise with regard to the effect of WBC growth factors on further chemotherapy.

While the duration of WBC growth factors to be administered for primary prophylaxis is based on the recovery of neutrophil counts through the nadir period in clinical trials, daily visits and repeated blood work for the same in clinical practice may not be feasible in high-volume busy cancer centers. From a logistic point of view, identifying whether single-day or multiday WBC growth factors are appropriate is important. It is also important to note that peg-GCSF is a more expensive option, although it is given for a single day. Within the confines of the retrospective nature of this analysis, there were no statistical differences in a majority of neutropenia and neutropenia-related complications like FN between patients receiving single-day or multiday WBC growth factors. The takeaway from this finding is that in patients receiving regimens like mFOLFIRINOX and mFLOT where guidelines on the use of GCSF are unclear due to lesser than 20% rates of expected FN, a single dose of WBC growth factor might be adequate as opposed to multiple doses of WBC growth factors. This also applies, therefore, to the lack of requirement of the longer-acting peg-GCSF with such regimens.[12]

While the study attempts to evaluate a niche area with respect to the use of WBC growth factors, multiple caveats must be recognized. We have combined the data for mFLOT and mFOLFIRINOX regimens due to the similar rates of neutropenia as per published literature, although both regimens differ in their composition and efficacy, as well as primarily being used in the treatment of different cancers. The doses of mFOLFIRINOX and mFLOT used in the current study are based on institutional practice and do not correspond exactly with that used in the seminal trials. Markedly lower rates of neutropenia were seen in the current study compared to trial data, although we have previously explained some of the reasons for the same. The use of WBC growth factors and their duration was based on individual physician choice as opposed to institutional guidelines and hence there is variance with regard to their use. The low rates of admission due to neutropenia-related complications are lower than the FN rates because of logistic issues in terms of being able to admit patients for these complications.

Conclusion

In conclusion, the use of WBC growth factors reduces the rates of febrile neutropenia by approximately 80% in patients receiving mFLOT and mFOLFIRINOX, although incidences of FN are low with these regimens. In patients receiving mFLOT or mFOLFIRINOX being considered for WBC growth factors, a single dose of WBC growth factor appears to be similar in efficacy to multiday WBC growth factors with regard to the incidence of febrile neutropenia.

Authors' Contribution

All the authors contributed equally in data collection, data analysis, and approval of the final manuscript.

Conflict of Interest

None declared.

References

1 Link H. Current state and future opportunities in granulocyte colony-stimulating factor (G-CSF). Support Care Cancer 2022;30 (09):7067–7077
2 Smith TJ, Bohlke K, Lyman GH, et al; American Society of Clinical Oncology. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2015;33(28):3199–3212
3 Crawford J, Caserta C, Roila FESMO Guidelines Working Group. Hematopoietic growth factors: ESMO Clinical Practice Guidelines for the applications. Ann Oncol 2010;21(Suppl 5):v248–v251
4 Vogel CL, Wojtukiewicz MZ, Carroll RR, et al. First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study. J Clin Oncol 2005;23(06):1178–1184
5 Crawford J, Ozer H, Stoller R, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. N Engl J Med 1991;325(03):164–170
6 Conroy T, Desseigne F, Ychou M, et al; Groupe Tumeurs Digestives of Unicancer PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364(19): 1817–1825
7 Al-Batran SE, Homann N, Pauligk C, et al; FLOT4-AIO Investigators. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet 2019;393 (10184):1948–1957
8 Ramaswamy A, Shah D, Bhargava P, et al. Modified FOLFIRINOX compared to Gemcitabine & nab-Paclitaxel in advanced pancreatic ductal adenocarcinoma: results of a match-pair analysis. Indian J Med Res 2023;157(01):57–65

9 Ramaswamy A, Bhargava P, Srinivas S, et al. Perioperative modified FLOT versus EOX in locally advanced resectable gastric and gastro-oesophageal junction adenocarcinoma: results of a matched-pair analysis. J Gastrointest Cancer 2023;54(03):820–828
10 Culakova E, Thota R, Poniewierski MS, et al. Patterns of chemotherapy-associated toxicity and supportive care in US oncology practice: a nationwide prospective cohort study. Cancer Med 2014;3(02):434–444
11 Weycker D, Li X, Edelsberg J, et al. Risk and consequences of chemotherapy-induced febrile neutropenia in patients with metastatic solid tumors. J Oncol Pract 2015;11(01):47–54
12 Crawford J, Moore DC, Morrison VA, Dale D. Use of prophylactic pegfilgrastim for chemotherapy-induced neutropenia in the US: a review of adherence to present guidelines for usage. Cancer Treat Res Commun 2021;29:100466

