Risk of Chemotherapy-Induced Febrile Neutropenia (FN) with Early Discontinuation of Pegfilgrastim Prophylaxis (PP) in US Clinical Practice from 2010-2015

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BACKGROUND

- Neutropenia is a common side effect of myelosuppressive chemotherapy that, when severe or combined with fever (ie, febrile neutropenia [FN]), can lead to chemotherapy dose-delays, dose-reductions, and discontinuation as well as hospitalization[1,2]
- Colony-stimulating factors (CSF) are effective in reducing FN risk, and the most commonly used prophylactic CSF agent in US clinical practice is pegfilgrastim[3-5]:
  - Pegfilgrastim requires only a single dose per chemotherapy cycle, while other CSF agents require daily dosing
- Pegfilgrastim prophylaxis (PP) is recommended for administration in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy associated with a clinically significant incidence of FN
- Accumulating evidence suggests that some patients do not receive prophylaxis after the first cycle of chemotherapy, and that such patients may be at elevated risk of FN[6-7]

STUDY OBJECTIVE

- To estimate the cycle-specific incidence proportion for FN—beginning with the second cycle and ending with the last cycle—among patients who received PP in that cycle and all previous cycles versus those who received PP in all previous cycles only

STUDY METHODS

Study Design and Data Sources

- Retrospective matched-cohort design
- Two integrated healthcare claims repositories comprising medical and outpatient pharmacy data from private US health plans (2010–2015)[8]

Source Population

- Patients aged ≥18 years who received ≥1 course of myelosuppressive chemotherapy for a single primary solid tumor or non-Hodgkin's lymphoma (NHL)
- For each patient in the source population, the first qualifying course of chemotherapy was identified, as was each cycle within the course and the chemotherapy regimen
- Patients who received a regimen classified as intermediate/high-risk for FN were retained

Study Population

- Beginning with the second cycle:
  - All patients in the source population whose course spanned ≥2 cycles and who received PP in all previous cycles (ie, the first cycle) were identified
  - From this subset, all patients who did not receive PP in the second cycle ("comparison patients") were matched to those who received it ("PP patients") in that cycle
  - Once matched, both patients were included in the study population and removed from the source population
  - Same process was repeated for each subsequent cycle—using patients remaining in source population after matching in prior cycles—ending with 8th cycle of chemotherapy

Matching

- Matching was implemented for each patient who did not receive second-cycle PP by first identifying all "candidate" patients who received second-cycle PP and had the same cancer type and chemotherapy regimen
- From all such candidates for each patient, the candidate with the closest propensity score was selected as the matched patient using a fixed 1:1 ratio (without replacement) and nearest neighbor approach:
  - Propensity scores were estimated via logistic regression with second-cycle PP as the dependent variable and baseline characteristics as independent variables
- The same approach was employed to match patients in subsequent cycles

Pegfilgrastim Prophylaxis

- PP was defined as receipt 1-3 days following completion of myelosuppressive chemotherapy in a given cycle, and was identified based on HCPCS Level II codes

FN Episodes

- A specific diagnostic code for FN does not exist, and thus a mapped algorithm was employed to identify episodes (broad definition)[4,7]:
  - FN requiring inpatient care ("Inpatient FN"): hospital admission with a diagnosis—principal or secondary—of neutropenia, or fever, or infection
  - FN requiring outpatient care only ("Outpatient FN"): an encounter in the ambulatory setting with a diagnosis of neutropenia, or fever, or infection and—on the same date—a HCPCS Level II code for IV administration of antimicrobial therapy
  - A narrow definition that considers only the diagnosis code for neutropenia was employed in sensitivity analyses
- FN episodes were identified beginning 4 days following chemotherapy completion (ie, after the period for identifying prophylaxis) and ending on the last day of that cycle

Statistical Analyses

- Adequacy of matching in terms of patients' baseline characteristics was evaluated using standardized differences; a value <0.1 was assumed to indicate a negligible difference
- Comparisons of cycle-specific FN odds between comparison patients and PP patients was evaluated using GEE regression models; a binomial distribution and logistic link function were specified, and models were fit using an exchangeable correlation structure

Study Schematic

- Schema is an exemplar of the characterization of chemotherapy courses/cycles/regimens, use of supportive care, and occurrence of FN (Figure 1)
- In this example, patients (ie, those who received PP in cycle 1) were stratified based on receipt of PP in cycle 2, and FN episodes were identified from 4 days after completion of myelosuppressive chemotherapy (ie, cycle day 5) in cycle 2 to the end of cycle 2

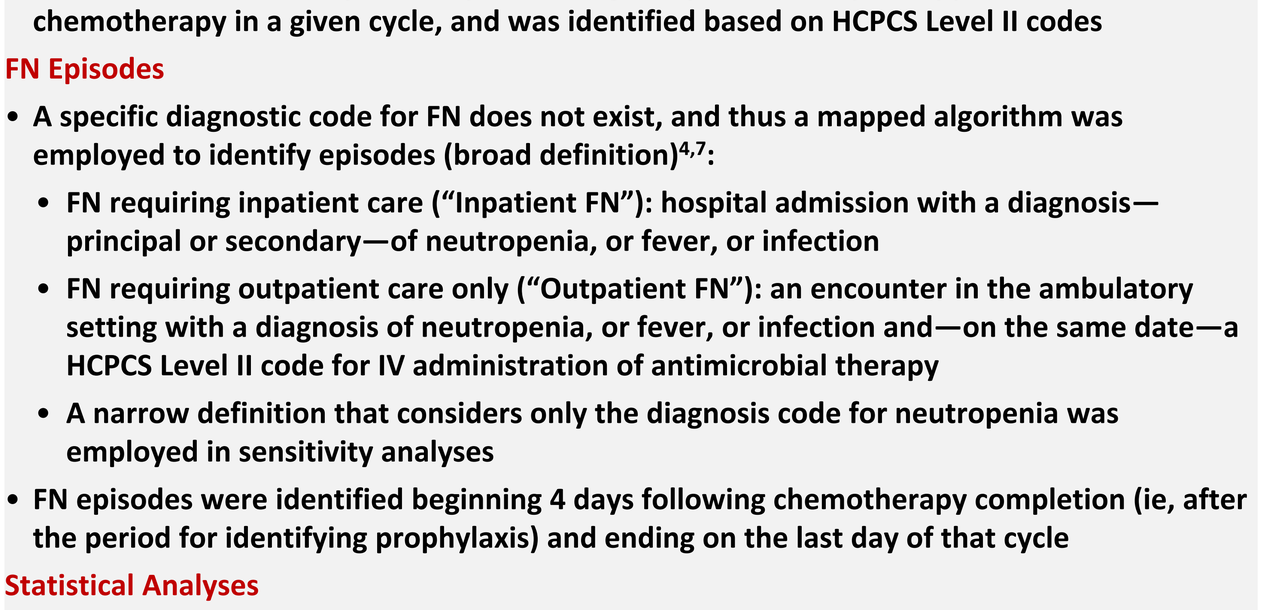


Figure 1. Schematic of chemotherapy course (in this example, patient received only two cycles, all chemotherapy was administered on cycle day 1, and cycle periodicity = Q3W)

RESULTS

Patient Characteristics

- Among the source population including 38,250 patients, 8,450 pairs of PP patients and comparison patients were matched by cancer, regimen, and propensity score in cycle 2 and subsequent cycles (ie, cycle 3 – cycle 8); cohorts were well balanced on their baseline characteristics (Table)

Table. Baseline characteristics of pegfilgrastim patients and matched comparison patients

	All Cancers/Regimens, All Cycles		
	Pegfilgrastim Patients (n=8,450)	Comparison Patients (n=8,450)	Standard Difference
Baseline Characteristics (partial list)			
Age (years), mean (SD)	53.6 (10.3)	53.9 (10.4)	0.03
Male, %	4.8	5.1	0.02
Chronic Comorbidities, %			
Cardiovascular Disease	5.5	5.1	0.02
Diabetes	9.0	8.6	0.02
Liver Disease	2.2	2.3	0.01
Lung Disease	2.7	2.4	0.02
Renal Disease	1.4	1.2	0.02
Osteoarthritis	6.7	6.2	0.02
Rheumatoid Disease	0.9	0.8	0.01
Thyroid Disorder	11.8	11.3	0.02
History of Other Conditions/Events, %			<0.001
Anemia	11.8	10.9	0.03
Hospitalization for Any Reason	27.2	26.0	0.03
Infection	30.9	30.4	0.01
Neutropenia	4.2	3.9	0.01
Other Blood Disorders	5.1	4.8	0.01
Radiation Therapy	3.3	3.2	<0.001
Surgery (within prior 90 days)	62.5	62.1	0.01
Pre-Chemotherapy Expenditures ($), mean±SD	34,770 (26,020)	34,320 (28,040)	0.02
Cancer Type and Chemotherapy Regimen, %			
Breast Cancer	89.1	89.1	—
AC and AC-T (Dose Dense)	*52.0*	*52.0*	—
TAC	*4.8*	*4.8*	—
TC	*30.7*	*30.7*	—
TCH	*12.5*	*12.5*	—
Colorectal Cancer — FOLFOX	0.6	0.6	—
Lung Cancer — CAR +PAC	1.6	1.6	—
Non-Hodgkin's Lymphoma	6.5	6.5	—
CHOP	10.5	10.5	—
CHOP-R	89.5	89.5	—
Ovarian Cancer — CAR + PAC	2.2	2.2	—

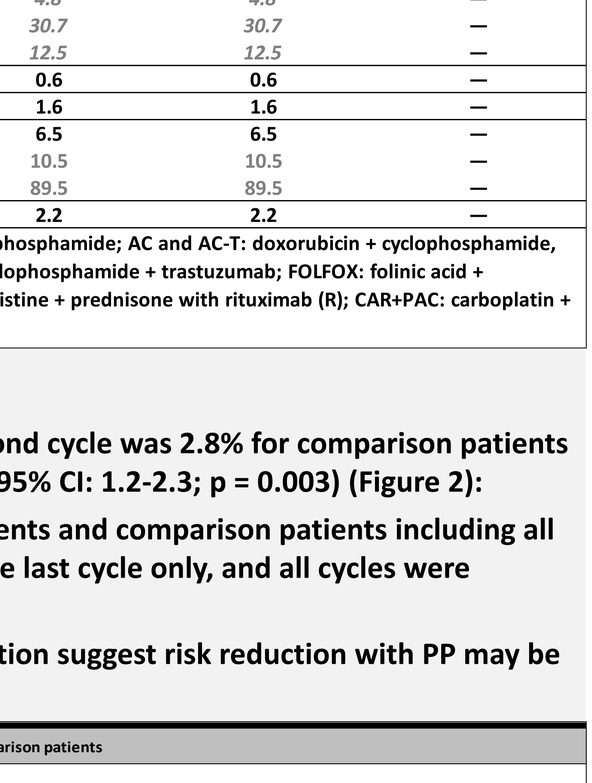
TC: docetaxel + cyclophosphamide; TAC: docetaxel + doxorubicin + cyclophosphamide; AC and AC-T: doxorubicin + cyclophosphamide, with or without subsequent docetaxel or paclitaxel; TCH: docetaxel + cyclophosphamide + trastuzumab; FOLFOX: folinic acid + fluorouracil + oxaliplatin; CHOP: cyclophosphamide + doxorubicin + vincristine + prednisone with rituximab (R); CAR+PAC: carboplatin + paclitaxel

Incidence Proportions for FN

- FN incidence proportion (broad def.) during second cycle was 2.8% for comparison patients versus 1.7% for PP patients; odds ratio was 1.7 (95% CI: 1.2-2.3; p = 0.003) (Figure 2):
  - Results from evaluations of FN among PP patients and comparison patients including all cycles from the third through the last cycle, the last cycle only, and all cycles were comparable to those observed for cycle 2
  - Odds ratios for FN based on the narrow definition suggest risk reduction with PP may be even greater

Figure 2. Odds ratios for febrile neutropenia for pegfilgrastim patients (PP) vs. matched comparison patients

	All Cancers, All Regimens					
				95% CI		
Cycle of Observation	n	% with Episode	Odds Ratio	Lower Limit	Upper Limit	p-value
Cycle 2						
Broad Definition						
Comparison Patients (N=3,366)	95	2.8	1.7	1.2	2.3	0.0003
PP Patients (N=3,366)	58	1.7	—	—	—	—
Narrow Definition						
Comparison Patients (N=3,366)	64	1.9	4.3	2.5	7.6	<0.001
PP Patients (N=3,366)	15	0.4	—	—	—	—
Cycle 3 - Last Cycle*						
Broad Definition						
Comparison Patients (N=5,084)	117	2.3	1.6	1.2	2.1	0.0003
PP Patients (N=5,084)	76	1.5	—	—	—	—
Narrow Definition						
Comparison Patients (N=5,084)	58	1.1	2.7	1.6	4.4	<0.001
PP Patients (N=5,084)	22	0.4	—	—	—	—
Last Cycle**						
Broad Definition						
Comparison Patients (N=923)	36	3.9	3.1	1.6	5.9	<0.001
PP Patients (N=923)	12	1.3	—	—	—	—
Narrow Definition						
Comparison Patients (N=923)	23	2.5	11.8	2.8	50.2	<0.001
PP Patients (N=923)	2	0.2	—	—	—	—
All Cycles***						
Broad Definition						
Comparison Patients (N=8,450)	212	2.5	1.6	1.3	2.0	<0.001
PP Patients (N=8,450)	134	1.6	—	—	—	—
Narrow Definition						
Comparison Patients (N=8,450)	122	1.4	3.3	2.3	4.8	<0.001
PP Patients (N=8,450)	37	0.4	—	—	—	—



*Analysis included all qualifying chemotherapy cycles from third through last; **Analysis included last chemotherapy cycle only (if qualifying, and irrespective of cycle number); ***Analysis included all qualifying chemotherapy cycles from second through last

LIMITATIONS

- PP patients and comparison patients may be systematically different, and to the extent such differences are unobserved, study results may be biased
- ICD-9-CM diagnosis code for FN is not available, and thus an operational algorithm employing codes for neutropenia, fever, and infection was used as proxy
- Accuracy of algorithms/variables capturing acute and chronic conditions is less than perfect, and because histories are not fully observable, some patients may be misclassified in terms of their comorbidity profile and/or pre-chemotherapy healthcare experience
- Study population is comprised (principally) of patients aged <65 years with coverage from private US health plans; study results may not reflect US patients treated in clinical practice across US

CONCLUSIONS

- In this retrospective evaluation of cancer patients who received intermediate/high-risk chemotherapy and first-cycle PP in US clinical practice, a clinically relevant minority did not continue to receive PP through the end of their chemotherapy course
- FN odds among these patients were substantially higher in the cycle of PP discontinuation versus those who continued prophylaxis
- Accordingly, the clinical decision to discontinue PP during the chemotherapy course should be carefully considered against the associated increased risks of FN

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