# Descriptive Analysis of Filgrastim use in four adult University Teaching Hospitals in Quebec, Canada

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Programme de GESTION THÉRAPEUTIQUE des médicaments

## Introduction

Neutropenia and febrile neutropenia (FN) are among the most important toxicities associated with myelosuppressive chemotherapy.

Clinical implications : decreased total chemotherapy dose, delayed chemotherapy treatment schedule, hospitalization, broad-spectrum antimicrobial exposure, treatment failure.

Hematopoietic granulocytes colony-stimulating factors (G-CSF) have been shown to:
1- Reduce the duration and severity of neutropenia and the risk of FN;
2- Enable delivery of more intensive or dose-dense chemotherapy when indicated.

Remaining concerns with respect to adverse events and costs have led the American Society of Clinical Oncology (ASCO) to develop clinical practice guidelines for the use of G-CSF.
The latest update was published in 2015.

According to ASCO: use of G-CSF in the prevention of FN in patients presenting < 20% risk should be questioned by physicians and patients (complete list of recommendations at: http://www.choosingwisely.org/societies/american-society-of-clinical-oncology/ )

We conducted a descriptive analysis on the use of G-CSF in four Quebec university teaching hospitals (UTH).

## Methods

### Objectives

- Determine real life use of filgrastim in hospitalized patients (indication, dose, number of dose received, absolute neutrophil counts (ANC) at the start and end of treatment when appropriate (ex: treatment of FN);
- Identify additional FN risk factors presented by patients receiving filgrastim in primary or secondary prophylaxis;
- Identify additional risk factors associated with a poor clinical outcome in patients treated for FN who received filgrastim.

### Participants

- With the support of participating hospital-based pharmacy computer systems, patients receiving filgrastim during their hospital stay between August 1st 2014 and July 31st 2015 were identified;
- Through the medical records of participating centers, patients diagnosed with FN during the same timeframe were identified. FN patients were cross-matched with those receiving G-CSF (filgrastim , peg-filgrastim*);
- Based on these criteria: analyses included 100 randomly selected FN patients receiving filgrastim and 100 patients receiving filgrastim for other indications.

*Since peg-filgrastim is not on hospital formularies, all patients received filgrastim.

### Methods

- Study design: retrospective descriptive analysis;
- Clinical data information sources: medical files (paper or electronic), pharmacy and oncology nursing notes, laboratory results and any other useful documentation;
- Data management: Information was collected on a standardized data collection sheet and entered into an ACCESS database;
- Statistical analyses: Descriptive data are presented as mean ± SD, median (range) or %.

The complete protocol is available at: http://www.pgtm.qc.ca

## Results

A total of 1863 episodes of care (EC) in 1213 patients were identified where patients received filgrastim during the study period. Of those EC, 808 (approximately 43% of the total) were randomly selected and further studied in 739 patients.

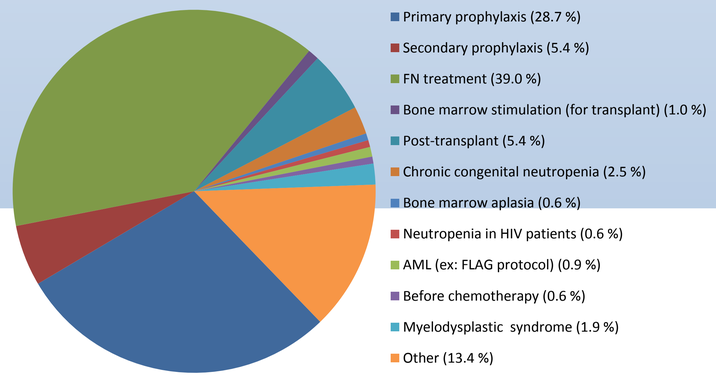
### General population

Table 1. Patient characteristics

| | NUMBER OF PATIENTS (N = 739) |
|---|---|
| Episodes of care (EC)* | 808* |
| Male (%) / Female (%) | 373 (50.5 %) / 366 (49.5 %) |
| Age (mean) | 60.2 years (Range : 18 to 93) |
| Age 65 or more | 323 (43.7 %) |
| Weight (mean) | 72.5 kg |
| Mean length of stay per EC (median length) | 15.4 days (9 days) |

*50 patients had 2 EC, 8 patients had 3 EC and 1 patient had 4 EC

Figure 1. Filgrastim indication during the study period (N = 808)




## Results (continued)

Table 2. Mean number of filgrastim doses received according to treatment indication

| Indication (N = 808) | Mean number of doses received (hospital) | Mean number of doses received (outpatient) | Mean number of doses received (total) |
|---|---|---|---|
| Primary prophylaxis (n = 232) | 4.03 (median = 3) | 3.11 (median = 2) | 7.14 (median = 7) |
| Secondary prophylaxis (n = 44) | 5.27 (median = 3) | 3.05 (median = 1.5) | 8.32 (median = 7) |
| FN treatment (n = 315) | 4.13 (median = 3) | 0.62 (median = 0) | 4.75 (median = 4) |
| Stem cell stimulation (n = 8) | 3.75 (median = 3) | 5.13 (median = 6.5) | 8.88 (median = 9.5) |
| Post-transplant (n = 44) | 5.91 (median = 6) | 0.05 (median = 0) | 5.95 (median = 6) |
| Other* (n = 165) | 3.93 (median = 2) | 0.56 (median = 0) | 4.49 (median = 3) |

*Other: chronic congenital neutropenia, bone marrow aplasia, neutropenia in HIV patients, AML patients, before chemotherapy, myelodysplastic syndrome and other unapproved indications

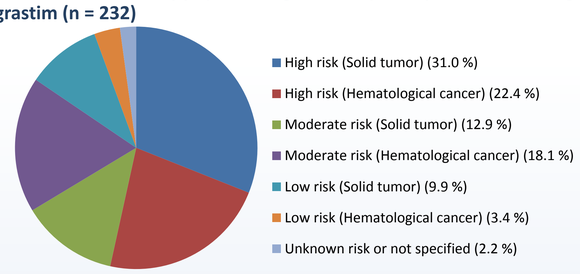
### Primary prophylaxis

There was a total of 232 EC where patients received filgrastim for primary prophylaxis.

FN risk was stratified according to high (≥ 20 %), moderate (10 to 20 %) or low (< 20 %) risk through consideration of patient-, disease- and treatment-related characteristics to determine each patients' overall risk.

Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is indicated to prevent neutropenia and FN in high FN risk (≥ 20 %) patients.

Figure 2. FN risk of chemotherapy (according to CCO) for patient receiving primary prophylactic filgrastim (n = 232)




78.4% of adequate primary prophylaxis (in high FN risk patients):
- 124 EC where patients had received high risk chemotherapy
- 58 EC where patients had received moderate risk chemotherapy with other risk factor*

21.6% of potentially inadequate primary prophylaxis (in low or unknown FN risk patients):
- 14 EC where patients had received moderate risk chemotherapy with no other risk factor
- 31 EC where patients had received low risk chemotherapy
- 5 EC where patients had received chemotherapy with unknown or unspecified risk

*Most frequently reported: Age > 65 (50 %), poor ECOG (22.2%), previous chemotherapy (19.4%)

### Febrile neutropenia treatment

During the study, there were a total of 1123 EC of FN in our UTH.

In 591 (52.6%) of 1123 EC, patients received filgrastim during their hospital stay, either as a continuation of their prophylaxis or prescribed as an adjunct treatment for FN.

Per-protocol, 379 (64 %) of these 591 EC were randomly selected :
- 64 EC were in continuation of prophylaxis
- 315 EC were for FN treatment

Table 3. Number of ASCO associated poor clinical outcome risk factor in patients with FN treated with filgrastim (n = 315)

| | |
|---|---|
| EC where patients presented at least 1 risk factor* | 260 (82.5 %) |
| EC where patients presented 1 risk factor | 31 (9.8 %) |
| EC where patients presented 2 risk factors | 63 (20.0 %) |
| EC where patients presented 3 risk factors | 76 (24.1 %) |
| EC where patients presented 4 risk factors | 90 (28.6 %) |

*Most frequently reported: Severe bacterial or viral infection (59.3%), age > 65 (36.9 %), profound neutropenia (< 0.1 X $10^9$/L) (17.9 %), hospitalized at time of fever (17.0 %)

Table 4. Efficacy of filgrastim in patients treated for FN (n = 315)

| Absolute neutrophil count (ANC) | Percentage of episodes of care | | |
|---|---|---|---|
| | At start of filgrastim* | At end of filgrastim* | At hospital discharge |
| Less than 0.5 x $10^9$/L | 215 (68.9 %) | 34 (10.9 %) | 15 (4.8 %) |
| Between 0.5 and 0.9 x $10^9$/L | 47 (15.1 %) | 31 (9.9 %) | 15 (4.8 %) |
| Between 1.0 and 1.4 x $10^9$/L | 11 (3.5 %) | 29 (9.3 %) | 15 (4.8 %) |
| Between 1.5 and 1.9 x $10^9$/L | 4 (1.3 %) | 27 (8.7 %) | 28 (8.9%) |
| 2.0 x $10^9$/L or higher | 4 (1.3 %) | 153 (49.0 %) | 163 (51.7 %) |
| Duration of filgrastim treatment | Mean: 4.75 days (median = 4) | | |

*Information concerning ANC was missing in 30 EC at start and 38 at end of filgrastim

## Results (continued)

Table 5. EC where potentially unnecessary doses of filgrastim were administered according to ANC in patients treated for FN (n=315)

| ANC (x $10^9$/L) | Greater than or equal to 2 | Greater than or equal to 3 | Greater than or equal to 5 | Greater than or equal to 10 |
|---|---|---|---|---|
| Number of EC (% of total EC) | 91 (28.9 %) | 66 (21.0 %) | 42 (13.3 %) | 17 (5.4 %) |
| Filgrastim doses | 127 | 89 | 56 | 24 |

## Discussion

According to the 2015 "Recommendations for the Use of WBC Growth Factors: ASCO Practice Clinical Guideline Update":
- primary prophylaxis is recommended and should be given to patients who have an approximately 20 % or higher risk for FN based on patient-, disease- and treatment-related factors, i.e. patients receiving high FN risk chemotherapy protocols, but also in patients receiving moderate FN risk protocols if they also presented a patient- or disease-related risk factor.

In more than 20 % of the EC for the primary prophylaxis population (6.2% of global population), filgrastim was used in patients at low global risk (< 20 %) of FN

- G-CSF should not be used routinely as adjunctive treatment with antibiotics for patients with fever and neutropenia. It should, however, be considered in patients with FN who are at high risk for complications or have prognostic factors predictive of poor clinical outcome.

For close to 20% of the EC for FN treatment (6.8% of global population), no poor clinical outcome risk factors where identified in patients receiving filgrastim as an adjunctive treatment

- filgrastim should be continued until reaching ANC ≥ 2 - 3 X $10^9$/L

In 21 to 29% of the EC in FN treatment (66 to 91 EC out of 315; or 8.2 to 11.2% of global population), potentially unnecessary doses of filgrastim were administered to patient as an adjunctive treatment to antibiotics in FN

Treatment indications should also be reviewed with treating physicians, especially for the ones that are not currently in the Canadian monograph (ex: to raise the ANC before chemotherapy or surgery in patient with low ANC and other indications [approximately 16% of global population])

Due to the low number of patients that received filgrastim for secondary prophylaxis, bone marrow stimulation and in the post-graft setting, no conclusion can be made in these particular populations.

Table 6. Potential savings resulting from optimal use of filgrastim (mean of 4 doses per EC)

| | Neupogen® ($ 175.19 per 300 mcg) | Grastofil® ($ 146.31 per 300 mcg) |
|---|---|---|
| Potential savings (no filgrastim misuse) in 808 EC (Studied population) | $ 150 138 to $ 172 387 | $ 125 388 to $ 143 969 |
| Potential savings (no filgrastim misuse) in 1863 EC (Global population) | $ 345 317 à $ 396 490 | $ 288 392 to $ 331 129 |

## Conclusion

In approximately one third of the EC where filgrastim was prescribed there was a potential for misuse (it either was not indicated [approximately 25%] or patients received to many doses [approximately 8 to 11 %]).

Based on published clinical practice guidelines, criteria should be developed and ANC follow-up strengthened to optimize filgrastim use in our UTH.

### Limitations

- Retrospective study (Main limitation)
- Identification of patients prior to release of ASCO and CCO guidelines for G-CSF use
- Completeness of notes in patient files may vary between clinicians
- Limited number of patients selected

### Acknowledgements

We would like to thank all pharmacy students who help collect patient information.

### References

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