Descriptive Analysis of Filgrastim Use in Children in Four University Teaching Hospitals in Québec, Canada

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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:

- **Reduce the duration and severity of neutropenia and the risk of FN**
- **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 (complete list of recommendations at: http://www.choosingwisely.org/societies/american-society-of-clinical-oncology/)

Filgrastim use in primary prophylaxis (PP) of FN in children is generally guided by specific research protocols. Its use in FN treatment for this population is also common. As part of a descriptive analysis of filgrastim conducted by the PGTM in 2016, an assessment of its use was performed in the pediatric population in four university teaching hospitals (UTH) in Québec.

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

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 PP 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, pediatric 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 a maximum of 50 randomly selected FN patients receiving filgrastim and 50 patients receiving filgrastim for other indications per UTH.**

***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 %.**

Results

A total of 175 episodes of care (EC) in 148 patients were identified where patients received filgrastim during the study period.

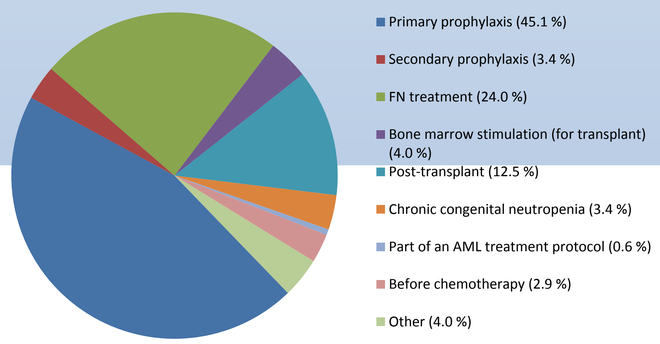
General population

Table 1. Patient characteristics

	NUMBER OF PATIENTS (N = 148)
Episodes of care (EC)*	175*
Male (%) / Female (%)	90 (60.8 %) / 58 (39.2 %)
Age (mean)	7.95 years (Range : Newborn to 17.6)
Weight (mean)	31.3 kg
Mean length of stay per EC (median length)	21.6 days (8 days)

*23 patients had 2 EC and 2 patients had 3 EC

Figure 1. Filgrastim indications during the study period (N = 175)



Results (continued)

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

Indication (N = 175)	Mean number of doses received (hospital)	Mean number of doses received (outpatient)	Mean number of doses received (total)
Primary prophylaxis (n = 79)	4.5 (median = 1)	5.7 (median = 6)	10.2 (median = 9)
Secondary prophylaxis (n = 6)	8.0 (median = 5.5)	3.3 (median = 2.5)	11.3 (median = 9)
FN treatment (n = 42)	4.5 (median = 4)	1.2 (median = 0)	5.7 (median = 4.5)
Stem cell stimulation (n = 7)	3.3 (median = 3)	0.7 (median = 0)	4.0 (median = 3)
Post-transplant (n = 22)	13.6 (median = 11.5)	0.6 (median = 0)	14.2 (median = 12)
Other* (n = 19)	2.6 (median = 2)	1.1 (median = 0)	3.7 (median = 3)

***Other: chronic congenital neutropenia, bone marrow aplasia, as part of an AML treatment protocol, before chemotherapy and other unapproved indications**

Primary prophylaxis (PP)

There was a total of 79 EC where patients received filgrastim for PP.

In all but 4 EC, filgrastim was given as part of a clinical study or a protocol identical to a closed study.

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. It was estimated independently by two oncology pediatric pharmacists based on the drugs who are part of each individual protocol and known risk of similar protocols in adults (as per CCO GCSF Recommendations 2016).

In our study, 64.5 % of patients on PP received a high risk chemotherapy, while 35.4 % received a moderate risk chemotherapy.

Table 3. FN risk of chemotherapy for patient receiving PP filgrastim (n = 79)

Indication	Patients (n)	Estimated FN risk factor
Solid tumor		
Neuroblastoma	15	High
Medulloblastoma	14	High
Ewing's sarcoma	11	High
Rhabdomyosarcoma	5	High
Hepatoblastoma	3	Moderate
Osteosarcoma	2	Moderate
Wilms tumor	2	High
Retinoblastoma	1	High
Carcinoma	1	Moderate
Hematological cancer		
Hodgkins lymphoma	13	Moderate
Non-Hodgkin's lymphoma	9	Moderate
Leukemia	3	High

In 57 EC (72.2 %) filgrastim was continued after hospital discharge.

During or following the 79 EC where filgrastim was administered as PP, an infection has developed or hospitalization for FN was required in 17 episodes (21.5 %).

Febrile neutropenia (FN) treatment

During the study, there were a total of 42 EC of FN in our UTH:

- **In 21 EC, patients were receiving or had received filgrastim prophylaxis**
- **In 12 EC, patients were on active filgrastim treatment at admission**
- **In 30 EC, filgrastim was prescribed upon admission**

Table 4. Number of poor clinical outcome risk factors in patients with FN treated with filgrastim (n = 42)

EC where patients presented at least 1 risk factor*	30 (71.4 %)
EC where patients presented 1 risk factor	10 (23.8 %)
EC where patients presented 2 risk factors	8 (19.0 %)
EC where patients presented 3 risk factors	6 (14.3 %)
EC where patients presented 4 risk factors	6 (14.3 %)

***Most frequently reported: Severe bacterial or viral infection, alteration of "barriers" by irradiation, presence of catheter or mucositis, prior episode of FN**

Table 5. Efficacy of filgrastim in patients treated for FN (n = 42)

Absolute neutrophil count (ANC)	Percentage of episodes of care (EC)		
	At start of filgrastim*	At the end of filgrastim*	At hospital discharge*
Less than 0.5 x 10^9/L	33 (78.6 %)	6 (14.3 %)	7 (16.7 %)
Between 0.5 and 0.9 x 10^9/L	4 (9.5 %)	9 (21.4 %)	10 (23.8 %)
Between 1.0 and 1.4 x 10^9/L	1 (2.4 %)	3 (7.1 %)	3 (7.1 %)
Between 1.5 and 1.9 x 10^9/L	-	3 (7.1 %)	3 (7.1 %)
2.0 x 10^9/L or higher	-	14 (33.3 %)	15 (35.7 %)
Duration of filgrastim treatment	Mean: 5.7 days (median = 4.5)		

***Information concerning ANC was missing in 4 EC at start, 7 at the end of filgrastim and 4 at discharge**

Results (continued)

Table 6. EC where potentially unnecessary doses of filgrastim were administered according to ANC in patients treated for FN (n = 42)

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)	6 (14.3 %)	4 (9.5 %)	1 (2.4 %)	0
Number of filgrastim doses	6	4	1	0

Discussion

Most of the time, the use of filgrastim for PP in pediatrics will be guided by research protocols. As with adults, the use of filgrastim is reasonable in PP for pediatric patients with a high probability of FN. PP in patients at moderate risk of FN should also be considered if patients present at least one other FN risk factor.

Compared with the adult population, there is no officially published pediatric FN management guide available to clinicians. The decision to use filgrastim in FN is usually determined within each treatment protocol or the protocol leaves the decision-making to the clinician, based on a case-by-case clinical evaluation.

In adults, ASCO, NCCN, and IDSA suggest that hematopoietic colony-stimulating factors may be considered for the treatment of patients at risk for significant complications related to infections or with poor prognostic factors such as when patients are at risk for severe neutropenia (neutrophils less than 0.1 x 10^9/L) and prolonged (more than 10 days), have uncontrolled primary disease, pneumonia, hypotension, failure of multiple organs (septic syndrome), an invasive fungal infection, or if they were hospitalized at the time the fever developed.

In the pediatric setting, neither the Children Oncology Group (COG) nor the SickKids in Ontario mention the use of filgrastim in its recommendations for the management of FN. In contrast, the clinician may initiate treatment with filgrastim, based on his or her clinical judgment, if the patient's condition is rapidly deteriorating.

If one of the objectives of using filgrastim is to shorten the duration of FN, it is important to monitor the ANC results closely. In the adult population, ASCO recommends continuing filgrastim administration until ANC is at least 2 to 3 x 10^9/L, whereas the product monograph advises stopping the treatment if the ANC exceeds 10 x 10^9/L after the nadir. The latter also specifies that the daily administration should be spread out over a maximum of two weeks after the anticipated nadir of the chemotherapy regimen but the duration of the treatment necessary for the attenuation of neutropenia may depend on the myelosuppressive potential of the selected chemotherapeutic regimen. In some pediatric protocols, the COG recommends stopping the use of filgrastim after having an ANC greater than 0.5 or 1.5 x 10^9/L for 2 days, while in other protocols, no value is specified.

Conclusion

Tools to help clinicians with filgrastim prescription outside of clinical research protocols (pre-printed orders, FN guidelines, standardised ANC for filgrastim discontinuation) should be developed and shared to optimize its use.

Limitations

- Retrospective study
- 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

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