Journal of Pharmacovigilance
ISSN: 2329-6887

Alshehri et al., J Pharmacovigil 2017, 5:6
DOI: 10.4172/2329-6887.1000248

Research Article Open Access

Evaluation of the Use of Granulocyte Colony-Stimulating Factors (G-CSFs) for Neutropenia Primary Prophylaxis in Solid Tumors at a Tertiary Care Hospital, Retrospective Study

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Abstract

Objective: First, to determine the appropriate prescribing of granulocyte colony-stimulating factors (G-CSFs) for febrile neutropenia (FN) as primary prophylaxis during the first cycle of chemotherapy in breast, lung, gastric, esophageal, nasopharyngeal or colorectal cancer patients. Second, to compare the incidence of FN between patients who received G-CSF appropriately and inappropriately.

Methods: This was a retrospective cohort study conducted at the Princess Norah bint Abdulrahman Al Faisal Oncology Center. We used cancer registry report which included adult patients with newly diagnosed solid tumors, such as breast, lung, gastric, esophageal, nasopharyngeal and colorectal cancer between January 2013 and December 2013. Patients were excluded if they did not receive chemotherapy after diagnosis and had renal or liver impairment. The appropriate indication of G-CSFs for FN primary prophylaxis was evaluated based on the National Comprehensive Cancer Network (NCCN) guidelines and published data.

Results: G-CSFs were appropriately prescribed as primary prophylaxis in 85% of patients. The incidence of FN between the appropriate and inappropriate groups were not statistically significant (p=0.315). However, G-CSF use was inappropriate in 28 of the 29 patients who received chemotherapy regimens with high risk of developing FN; among these patients only three patients developed FN.

Conclusion: The prescribing of G-CSFs for FN primary prophylaxis at our institution was found to be inappropriate on some occasions; mostly when G-CSFs were not prescribed with regimens associated with high risk of FN.

Keywords: GCSF, Primary prophylaxis, Solid tumors, Febrile neutropenia, Chemotherapy

Introduction

Febrile neutropenia (FN) is a serious and life-threatening condition that may increase hospitalization due to fever and potentially fatal infections after chemotherapy [1,2]. The National Comprehensive Cancer Network (NCCN) defines FN as a single oral temperature of ≥ 38.3°C (≥ 100.9°F) or sustained 38.0°C (≥ 100.4°F) for 1 hour and an absolute neutrophil count of<500 neutrophils/mm³ or <1000 neutrophils/mm³ with a predicted decline to <500 neutrophils/mm³ over the following 48 h [3]. Medications such as granulocyte colony-stimulating factors (G-CSFs) are used for primary prophylaxis to reduce the incidence of FN in cancer patients during chemotherapy. G-CSFs increase production and activation of neutrophils and then promote their migration [4,5]. Patients with solid cancers, who do not receive prophylactic G-CSFs, exhibit a higher incidence of FN in comparison to patients who receive G-CSFs as part of the chemotherapy regimen [6-9]. NCCN guidelines recommend using primary prophylaxis with G-CSFs in patients undergoing chemotherapy regimen with ≥ 20% risk of developing FN.3 For chemotherapy regimens associated with intermediate-risk of FN (10-20%), NCCN guidelines recommend not to use G-CSFs unless patients display poor renal function, liver dysfunction, advanced age (>65 years), previous chemotherapy with neutropenia, previous radiation therapy with neutropenia, preexisting neutropenia or bone marrow involvement with tumor, previous infection or open wounds, recent surgery, poor performance status or HIV-infection.3 For low-risk FN chemotherapy regimens (<10%), NCCN guidelines recommend not to use G-CSFs [3]. G-CSFs use associated with serious adverse effect like thrombocytopenia and splenic rupture that increase with appropriate use [10,11]. However, previous studies showed an improvement in quality of life and a negligible difference in cost when using or not G-CSFs for primary prophylaxis [12-14]. Moreover, The Federal Drug Administration (FDA) restricted the use of G-CSFs (Eg: Filgrastim) for: no myeloid malignancies, acute myeloid leukemia following induction or consolidation chemotherapy, bone marrow transplantation, hematopoietic radiation injury syndrome, peripheral blood progenitor cell mobilization for collection and therapy for severe chronic neutropenia. For the previous reasons, we evaluated the prescribing pattern of G-CSFs for FN primary prophylaxis during the first cycle of chemotherapy in solid tumors since there is no previous evaluation of G-CSFs utilization in our institution.

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Received: November 01, 2017; **Accepted** November 29, 2017; **Published** December 06, 2017

Citation: Alshehri AF, Alnatsheh A, Aseeri M, Al Fayea T (2017) Evaluation of the Use of Granulocyte Colony-Stimulating Factors (G-CSFs) for Neutropenia Primary Prophylaxis in Solid Tumors at a Tertiary Care Hospital, Retrospective Study. J Pharmacovigil 5: 248. doi:10.4172/2329-6887.1000248

Methods

This is a retrospective cohort study conducted at the Princess Norah bint Abdulrahman Al Faisal Oncology Center at the King Abdul-Aziz Medical City, Western Region. The study was approved by the King Abdullah International Medical Research Center on September 1, 2015. Between January 2013 and December 2013 entries in the cancer registry included adult patients with newly diagnosed breast, lung and gastric, esophageal, nasopharyngeal and colorectal cancers. Patients were excluded if they did not receive chemotherapy after diagnosis, had renal impairment or liver impairment. The appropriate use of G-CSFs for FN primary prophylaxis was evaluated based on NCCN guidelines and published data.

G-CSFs prescribing were considered appropriate in patients who received chemotherapy regimens associated with high-risk of developing of FN or intermediate risk of FN with comorbidities. FN risks associated with specific chemotherapy regimens were derived from NCCN guidelines and previous studies (Appendix Table 1). Descriptive statistics and Chi-square test were used when summarizing the results for primary and secondary outcomes.

Results

A total of 274 patients met the inclusion criteria. They consisted mainly of breast and colorectal cancer patients which represents 49% and 29% in respective (Figure 1). Most of the patients were female (66%) and the median age was 52 yrs. Percent of patients received chemotherapy induce high, intermediate or low risk of FN was 10.5%, 22.5%, 67% respectively (Table 1). While, the prescribing of G-CSFs in patients who received chemotherapy inducing intermediate-risk FN without comorbidity and low-risk FN was considered inappropriate (Table 2). Overall, G-CSFs were prescribed appropriately for FN primary prophylaxis in 232 patients and inappropriately in 42 patients which represents 85% and 15%

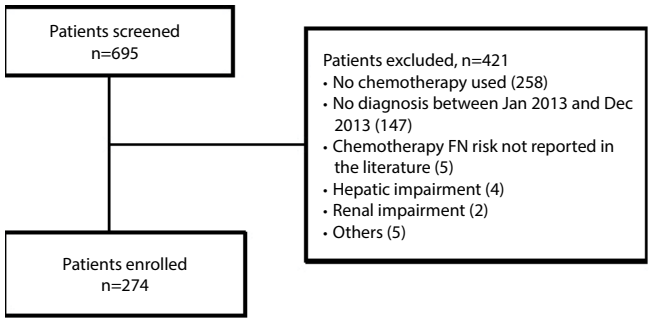

Figure 1: Patient enrollment flow chart.

Chemotherapy regimen	FN risk	Study
Doxorubicin+Cyclophosphamide	<10	Nabholtz [19] Chan [20]
Docetaxel+Cyclophosphamide	>20	Kosaka [22]
5-fluorouracil+Epirubicin+Cyclophosphamide	>20	Jenkins [22]
Paclitaxel+Carboplatin+Trastuzumab weekly	<10	Perez [23]
Paclitaxel+Carboplatin+Trastuzumab q3w	10-20	Perez [23]
Docetaxel+Carboplatin+Trastuzumab	10-20	Gilbar [24] Valero [25]
Trastuzumab+Docetaxel	10-20	Valero [25]
Bevacizumab + Capecitabine	<10	Gligorov [26]
Oxaliplatin+Capecitabine	<10	Diaz-Rubio [27]
Oxaliplatin+Leucovorin+Fluorouracil	<10	Hacibekiroglu [28] Andre [29]
Irinotecan +Leucovorin+Fluorouracil+Bevacizumab	<10	Comella [30]
Leucovorin+Fluorouracil	<10	Boku [31]
Oxaliplatin+Bevacizumab+Capecitabine	<10	Schmiegel [32]
Irinotecan+Bevacizumab+Capecitabine	<10	Schmiegel [32]
Irinotecan+Capecitabine	<10	Li W [33]
Irinotecan Fluorouracil/Leucovorin	<10	Douillard [34]
Pemetrexed+Cisplatin	<10	Scagliotti [35]
Vinorelbine+Carboplatin	>20	Agelaki [36] LeCaer [37]
Cisplatin+Etoposide	<10	Hanna [38]
Rituximab+Doxorubicin+Vincristine+Cyclophosphamide+Prednisolone every 21 days	10-20	Cunningham [39]
Rituximab+Doxorubicin+Vincristine+Cyclophosphamide+Prednisolone every 14 days	<10	Cunningham [39]
Pemetrexed	<10	Hanna N [40]
Pemetrexed+Carboplatin	<10	Pereira [41]
Etoposide+Carboplatin	<10	Hanna [38]
Carboplatin+Gemcitabine	10-20	Nasr [42]
Epirubicin+Cisplatin+Capecitabine	<10	Cho [43]
Epirubicin+Oxaliplatin+Capecitabine	<10	Cunningham [44]Sumpter [45]
Docetaxel+Carboplatin+Fluorouracil	10-20	Lin [46]
Epirubicin+Oxaliplatin+Fluorouracil	<10	Zhao [47]
Cisplatin+Epirubicin+Fluorouracil	<10	Ozkan [48]
Docetaxel+Cisplatin+Fluorouracil	10-20	Maruyama [49] Sendur MA [50] Hacibekiroglu [28]

Appendix Table 1: FN risks associated with chemotherapy regimens compiled from previous studies.

	Overall	Appropriate use	Inappropriate use
	N=274	N=232	N=42
Age (years), median (IQR)	52 (44-60)	52 (43-59)	56 (49-66)
Sex			
F, N (%)	181(66)	148 (82)	33 (18)
M, N (%)	93 (34)	84 (90)	9 (10)
Weight (kg), median (IQR)	71 (59-82)	70 (58-82)	77 (66-85)
Height (cm), median (IQR)	158 (153-165)	159 (154-166)	157 (153-163)
Breast Cancer, N (%)	135 (49)	106 (79)	29 (21)
Colorectal Cancer, N (%)	78 (29)	76 (97)	2 (3)
Lung Cancer, N (%)	20 (7)	17 (85)	3 (15)
Gastric Cancer, N (%)	14 (5)	12 (86)	2 (14)
Oesophageal Cancer, N (%)	4 (2)	4 (100)	0 (0)
Nasopharyngeal Cancer, N (%)	23 (8)	17 (74)	6 (26)
Prophylaxis G-CSFs used, N (%)	6 (2)	1 (17)	5 (83)
Total bilirubin ≤ 60 mmol/L, N (%)	274 (100)	232 (85)	42 (15)
AST level ≤ 140 U/L, N (%)	274 (100)	232 (85)	42 (15)
ALT level ≤ 200 U/L, N (%)	274 (100)	232 (85)	42 (15)
CrCl>30 mL/min, N (%)	274 (100)	232 (85)	42 (15)
Chemotherapy regimen risk for FN			
≥ 20%, N (%)	29 (10.5)	1 (3)	28 (97)
10-20%, N (%)	62 (22.5)	50 (81)	12 (19)
<10%, N (%)	183 (67)	181 (99)	2 (1)

M: Male; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; CrCl: Creatinine Clearance; F: Female; FN: Febrile Neutropenia; G-CSFs: Granulocyte-Colony Stimulating Factors; IQR: Interquartile Range

Table 1: Summary of baseline demographics and patient characteristics.

Appropriate prescribing	1) Chemotherapy associated with high-risk FN. 2) Chemotherapy associated with intermediate-risk FN with the following criteria (poor renal function, liver dysfunction, advanced age (>65 years), previous chemotherapy with neutropenia, previous radiation therapy with neutropenia, preexisting neutropenia or bone marrow involvement with tumor, previous infection or open wounds, recent surgery, poor performance status, or HIV-infection).
Inappropriate prescribing	1) Chemotherapy associated with intermediate-risk FN (without the previous criteria). 2) Chemotherapy associated with low-risk FN.

Table 2: Appropriate and inappropriate criteria to evaluate the prescribing pattern of G-CSFs for neutropenia primary prophylaxis.

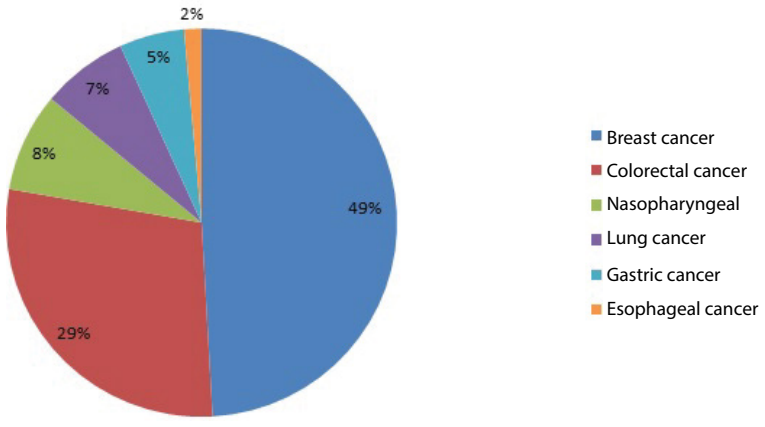

Figure 2: Patient distribution based on cancer type.

respectively (Figures 2-4). G-CSFs were not prescribed in (97%) 28 out of 29 patients in high risk FN, which considered inappropriate. Additionally, G-CSFs were prescribing appropriately in (81%) 50 out of 62 patients in intermediate-risk. Moreover, G-CSFs were not prescribed in (99%) 181 out of 183 patients in low-risk, which considered appropriate. Twenty-two patients (8%) developed FN among those 17 patients used G-CSF appropriately and for 5 patients G-CSFs was used inappropriately. Only 3 patients who did not receive G-CSFs with chemotherapy induce high-risk developed FN. But interestingly, FN was devolved in 16 out of 22 patients with low-risk chemotherapy and did not receive G-CSFs. The incidence of FN between the appropriate and inappropriate groups did not differ significantly (p=0.315).

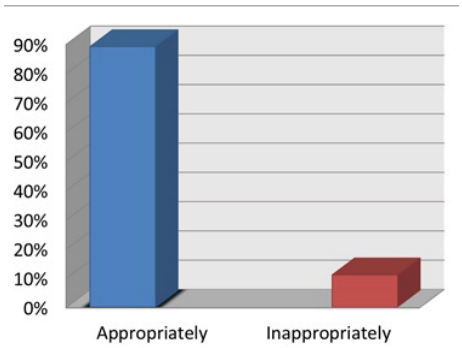

Figure 3: Appropriate vs. inappropriate use of G-CSFs for FN primary prophylaxis.

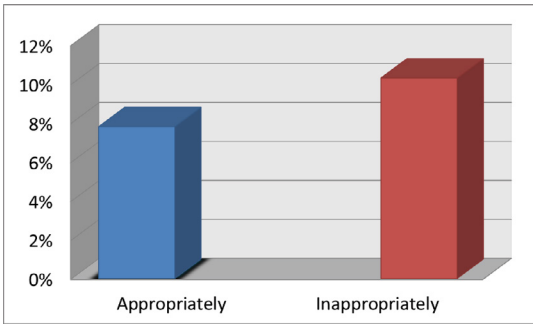

Figure 4: FN incidence in relation to appropriate vs. inappropriate use of G-CSFs for FN primary prophylaxis.

Discussion

Previous studies showed that approximately 63%-69% of patients complied with G-CSFs prescribing guidelines for primary prophylaxis [15,16]. At 85%, compliance with the prescribing of G-CSFs for primary prophylaxis is higher at our than at other institutions. Another study found that G-CSFs was being over utilized in patients undergoing chemotherapy associated with low risk of FN and underutilized in patients with high risk of FN. This finding is similar to ours, whereby G-CSFs were underutilized in patients with high risk of FN[17-25]. However, G-CSFs were prescribed appropriately in intermediate-and low-risk patients at our institution. In previous study inappropriate prescribing of G-CSFs increase FN episodes with lung and colorectal cancer on chemotherapy regimens receiving G-CSFs, the probability of high, intermediate and low risk FN was 17%, 18% and 10%, respectively; and 96% of G-CSFs use were not based on guidelines [25-36]. In our study, the appropriateness of G-CSFs use was not associated with FN incidence in patients received chemotherapy regimens with high risk of FN potential.

Although, the appropriate prescribing is 85% in our institution, developing of hospital guidelines should establish to reduce the impact of inappropriate G-CSFs use. The guidelines should include the risk of FN of each chemotherapy regimen used and whether to prescribe G-CSFs or not. Adding the G-CSFs to the chemotherapy protocol will dramatically decrease inappropriate prescribing [37-45]. This study is limited by the fact that it was a retrospective study, carried out at a single institution and over a single year. Additionally, some of the chemotherapy FN risks were not reported in the guidelines or in the literature, resulting in the exclusion of five patients. Furthermore, poor documentation made it difficult to determine the inappropriate use of G-CSFs in intermediate-risk cases [45-50]. Nevertheless, to the best of our knowledge, this is the first report evaluating the use of G-CSFs in Saudi Arabia in general.

Conclusion

At our institution, the prescribing of G-CSFs for FN primary prophylaxis was inappropriate on some occasions. We noticed that the main cause for inappropriate prescribing was lack of G-CSFs prescription with regimens associated with recognized high risk of FN. Pharmacists and clinical pharmacists play major role beside oncology physicians in improving inappropriate prescribing of G-CSFs. Therefore, the development of comprehensive hospital guidelines may reduce the impact of an inappropriate prescribing of G-CSFs. As well as, future studies needed to highlight the FN risk associated with chemotherapy regimens used in practice.

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