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The current G-CSF use in cancer patients with chemotherapy

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Abstract ***Objective:*** The purpose of the study was to survey current G-CSF use in cancer patients, investigate whether the use of granulocyte colony-stimulating factor (G-CSF) is standardized. ***Methods:*** From July 2012 to October 2012, patients in a third-grade class-A hospital were investigated by self-designed questionnaires, according to ASCO's recommendations for white blood cell growth factors in 2006 and NCCN myeloid growth factors guideline in 2012. ***Results:*** Two hundred and twenty-two patients treated with 724 courses of chemotherapy were included. In prophylactic use, 259 (35.8%) cases used G-CSF that the guideline doesn't recommend, which belonged to excessive use, the dose were 274 700 μg, accounting for 59.7% of the totle prophylactic use; 105 (14.5%) didn't use while the guideline recommend, belonging to lack of use. 89.0% of the prophylactic use were 24–72 h after chemotherapy, only a few (5.4%) on the day of chemotherapy. In therapeutic use, only 3.1% were standardized, with the dose of 23 000 μg, accounting for 7.4% of the total. So 92.6% were excessive. 14.2% of the therapeutic use were 24–72 h after chemotherapy, 21.2% on the day of chemotherapy. ***Conclusion:*** More than 50% use of G-CSF weren't standardized, especially the excessive use.

Key words granulocyte colony-stimulating factor (G-CSF); ASCO white blood cell growth factors guideline; NCCN myeloid growth factors guideline; febrile neutropenia; standardized use

Neutropenia is the most common adverse reaction and primary dose-limiting toxicity of chemotherapy. Subsequent febrile neutropenia (FN) can lead to life-threatening infections, which would result about 7%–11% mortality rate [1–3]. Granulocyte colony-stimulating factors (G-CSFs) may reduce the incidence of neutropenia, FN and infection, the risk of infection-related deaths and a variety of early death risk, and also the incidence of chemotherapy reductions and delays [4–8]. While G-CSF has been widely used to reduce chemotherapy-induced neutropenia, there wasn't enough attention of standardized use. Baker J *et al* [9] investigated G-CSFs' use of a third-grade class-A hospital according to ASCO guidelines published in 1994, pointing out that 12% of G-CSF use is not standardized. Tuffaha HW *et al* [10] conducted a survey on the outpatient of King Hussein Cancer Center, and found that during 99 chemotherapy, 46 (47%) were outside guideline recommendations. Potosky AL *et al* [11] found that 96% of G-CSF use wasn't in accordance with the guidelines in United States. Taking into account the limitations of medical cost, some patients didn't use G-CSF or for shorter duration [12–13], which resulted underutilization. A survey compared use of pegfilgrastim in the outpatient clinics of Virginia Common-wealth University Health System according to ASCO guidelines published in 2006 found that 46% use could be avoided, saving about $ 712,264. Hence, understanding the status of the clinical use of G-CSF is significative for standardized use and raising cost-effect. The author investigated G-CSF use during chemotherapy in a tertiary hospital patients.

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Materials and methods

Patients survey

From July 2012 to October 2012, all patients age ≥ 18 years old underwent chemotherapy during a third-grade class-A hospital in Wuhan were included. The patient's basic information, diagnosis and treatment were all recorded.

Evaluation criteria

According to ASCO's recommendations for white blood cell growth factors in 2006 [14] (Table 1) and NCCN myeloid growth factors guideline in 2012, G-CSF's primary prophylactic, secondary prophylactic and therapeutic use were stated as follows. Primary prophylaxis

Table 1 Incidence of FN associated with selected chemotherapy regimens (ASCO, 2006)

Cancer type and regimens	FN (%)
Bladder cancer	
MVAC	14
Breast cancer	
AC→T	3
TAC	> 20
Docetaxel	5.7 (1st line), 21 (2nd line)
Doxorubicin	12.3 (1st line)
AC	10 (1st line)
Docetaxel + capecitabine	16
Non-small-cell lung cancer	
Paclitaxel+ cisplatin	16
Docetaxel + cisplatin	11
Paclitaxel + carboplatin	4
Docetaxel + carboplatin	3.7
Docetaxel	12.7 (2nd line)
Gemcitabine + cisplatin	4
Small cell lung cancer	
Etoposide	28 (recurrent)
Colorectal cancer	
FOLFOX4	6 (advanced)
FOLFIRI	9.3 (advanced)
Head/neck cancer	
Docetaxel + cisplatin	6
Docetaxel + cisplatin + 5-Fu	19
Non-Hodgkin's lymphomas	
CHOP-21+ rituximab	18
Ovary cancer	
Topotecan	18
Germ cell tumor	
VeIP	71 (recurrent)

MVAC: methotrexate, vinblastine, doxorubicin, cisplatin; AC→T: doxorubicin, cyclophosphamide→paclitaxel; TAC: docetaxel, doxorubicin, cyclophosphamide

was recommended when the regimens' risk of FN was approximately 20% or higher. The following cases could also be considered of primary prophylaxis, even if the regimens' risk of FN < 20%: patient age ≥ 65 years; poor performance status; previous episodes of FN; extensive prior treatment including large radiation ports; administration of combined chemoradiotherapy; cytopenias due to bone marrow involvement by tumor; poor nutritional status; the presence of open wounds or active infections; more advanced cancer; preexisting neutropenia, as well as other serious comorbidities. Secondary prophylaxis with G-CSFs was recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome. Therapeutic use should be considered in patients with fever and neutropenia who were at high-risk for infection-associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features include expected prolonged (10 days) and profound (0.1×10^9/L) neutropenia, age greater than 65 years, uncontrolled primary disease, pneumonia, hypotension and multi-organ dysfunction (sepsis syndrome), invasive fungal infection, or being hospitalized at the time of the development of fever.

G-CSF should be given 24 to 72 h after the administration of myelotoxic chemotherapy. In adults, the recommended G-CSF doses were 5 μg/kg/d.

According to the guidelines recommend, "standardized use" were defined as the use of G-CSF in line with the guidelines; "excessive use" were defined as G-CSF used but the guidelines didn't recommend or for higher doses; " lack of use" were defined as G-CSF unused but guidelines recommend or for lower doses.

Statistical analysis

Quantitative data were described by frequencies and percentages, and qualitative data were expressed as $\chi \pm s$. Chi-square test (α= 0.01) and analysis of variance (α = 0.05) were calculated by SPSS 20.0.

Results

Patients information

Two hundred and twenty-two patients were included during the study period, with a total of 724 courses of chemotherapy. Among them, 5 courses happened in Gastrointestinal Surgery Department, 1 in Breast Surgical Department, 13 in Gynecology Department, and the other 697 in Oncology Department.

Prophylactic use

Five hundred and twenty-six (73%) courses received low FN-risk (< 10%) chemotherapy, the most commonly encountered were gemcitabine-cisplatin (n = 78, 10.8%), cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP, n = 49, 6.8%), irinotecan-leucovorin-5-fluorouracil (FOLFIRI, n = 49, 6.8%). 133 courses (18%) received intermediate FN–risk (10%–20%) chemotherapy, frequently encountered regimens included rituximab + cyclophosphamide-doxorubicin-vincristine-prednisone (R-CHOP, n = 17, 2.3%), lung cancer patients with paclitaxel-cisplatin (TP, n = 16, 2.2%). 65 (9%) received high FN-risk (> 20%) chemotherapy, the most commonly encountered chemotherapy regimens were doxorubicin-ifosfamide (n = 16, 2.2%), and doxorubicin-cisplatin (n = 9, 1.2 %), bleomycin-etoposide-cisplatin (n = 9, 1.2%).

One hundred and sixty-six courses existed patient-specific risk factors. Extensive prior treatment (n = 98, 13.5%), preexisting neutropenia (n = 44, 6.0%), patient age ≥ 65 years (n = 34, 4.7%) were the most commonly

identified risk factors.

Three hundred and sixty (49.7%) times G-CSF use were in line with the guidelines. 259 (35.8%) times used but the guidelines didn't recommend, which belonged to "excessive use". 105 (14.5%) didn't use G-CSF when guidelines recommend, belonged to "lack of use".

Three hundred and ninety-two (54.1%) courses have prophylactic use of G-CSF, with a total doses of 459, 750 μg. 274,700 μg (59.7%) were used when the guidelines didn't recommend. A few cases changed types or doses of G-CSF, so the total number of G-CSF use was 402. According to the guidelines recommended dose of 5 μg/kg/d, 198 (49.3%) courses' actual doses higher than standard doses, 30 (7.5%) courses in consistent with the standard doses, while 174 (43.2%) less than the standard doses.

G-CSF should be given 24–72 h after the administration of myelotoxic chemotherapy. 89% use of G-CSF were in accordance with the guidelines. However, 5.4% used G-CSFs on the same day with chemotherapy, which was not allowed by the guidelines.

Therapeutic use

Three hundred and fifty-eight courses experienced neutropenia. 303 courses used G-CSF with a total dose of 312,600 μg. Only 11 courses (11/358, 3.1%) used in case of FN and high risk factors for infection, with a dose of 23,000 μg, which was 7.4% of the total doses. That is, 92.6% of the therapeutic use was overused.

According to the guidelines recommended dose of 5 μg/kg/d, 179 (56.6%) courses' actual doses higher than standard doses, 21 (6.6%) courses in consistent with the standard doses, while 116 (36.7%) less than the standard doses.

The therapeutic use (14.2%) were given 24–72 h after chemotherapy. 48.7% used 24–72 h before chemotherapy. 67 (21.2%) used G-CSFs on the same day with chemotherapy; among these, five courses were intravenous chemotherapy, 62 were oral chemotherapy.

Discussion

This study was a retrospective investigation, so there existed some limitations. The data acquired by existing medical records which may be potentially inaccurate and incomplete. Relying on these records to determine patient risk factors may underestimate the risk of FN. In addition, patients outside the hospital may use G-CSF but not be recorded, which would influence the evaluation of the relationship between G-CSF use and FN.

Our study found that the proportion of non-standardized use of G-CSF was high. Hence, there is a big difference between clinical practice and guidelines. Excessive use and lack of use both existed, especially excessive use. This was highly related with clinician's awareness and attitudes to the guidelines. Meanwhile, our study based on the foreign recommendations which may be not entirely suitable for Chinese. Therefore, strengthening the clinicians' knowledge about G-CSF use, and looking forward to establishing our own guidelines as soon as possible, will better regulate the use of G-CSF.

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