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Research Article

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PEG-rhG-CSF Use Reduces Glucose Level Significantly in Cancer Patients Receiving Chemotherapy

Short title: Hypoglycemia secondary to PEG-rhG-CSF use

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[Abstract] ***Background:*** In patients receiving anti-cancer chemotherapy, polyethylene glycolated recombinant human granulocyte-colony stimulating factor (PEG-rhG-CSF) was used for prophylaxis of chemotherapy-induced neutropenia. However, the side effect of PEG-rhG-CSF use on fasting blood glucose (FBG) level remains unclear. ***Materials and Methods:*** Cancer patients receiving chemotherapy and PEG-rhG-CSF were enrolled in our study. Baseline glucose (Glucose 1) was measured before PEG-rhG-CSF use, a second FBG test (Glucose 2) was performed after PEG-rhG-CSF use. Mean glucose levels were compared using t test. ***Results:*** The time interval between PEG-rhG-CSF use and the second glucose test was 2.4±1.5 days. The mean Glucose 1 was 5.18±0.53 mmol/L, and Glucose 2 was 3.80±1.13 mmol/L. Statistical analysis showed a significant difference between Glucose 1 and 2 existed (P<0.001). ***Conclusion:*** Our study identifies a hypoglycemic side effect of PEG-rhG-CSF occurs in cancer patients undergoing anti-cancer chemotherapy. Our results highlight the caution required when using PEG-rhG-CSF for prophylaxis of chemotherapy-induced neutropenia.

Keywords: Hypoglycemia; PEG-rhG-CSF; Complication; Chemotherapy; Cancer

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1 Introduction

Chemotherapy is still a main therapeutic strategy of cancer treatment. The toxicity of chemotherapy is mainly haematological, resulting in a severe neutropenia. Thus, neutropenia is frequent during chemotherapy. Neutropenia is a major risk factor for potentially life-threatening infections and febrile neutropenia, which requires a dosage reduction or discontinuation of chemotherapy. However, if we can reduce the incidence of febrile neutropenia (FN), the safety of chemotherapy will be improved significantly.

Granulocyte-colony stimulating factor (G-CSF) can be produced by many types of cell, such as T cells, macrophages, endothelial cells and fibroblasts, upon receipt of the necessary stimulus [1]. It then acts as a pro-inflammatory agent that recruits neutrophils, monocytes and lymphocytes to sites where they are needed. G-CSF is useful to prevent neutropenia caused by cytotoxic chemotherapy [2]. Currently, the recombinant human G-CSF (rhG-CSF) has been approved for clinical practice and proved the role of increasing white blood cell counts and reducing the duration of neutropenia, hospitalization, and the occurrence of opportunistic infections [3].

PEG-rhG-CSF is a long-acting form of rhG-CSF. When combined with polyethylene glycol (PEG), rhG-CSF stability becomes more ensured and is not easy to be degraded. Therefore, serum concentration of rhG-CSF becomes more stable, and the elimination half-life gets prolonged [4]. Previous clinical studies

showed that PEG-rhG-CSF had good efficacy and safety, and exhibited a more convenient treatment regimen than rhG-CSF [5-7]. In recent studies, further comparison was performed and showed that PEG-rhG-CSF is as effective and safe as rhG-CSF for prophylaxis of chemotherapy-induced neutropenia [8, 9].

The complications of PEG-rhG-CSF, including bone pain, headache, myalgias, fatigue, nausea, insomnia, and redness at the injection site, are similar to those of rhG-CSF[10]. GM-CSF could increase glucose utilization significantly[11, 12]. PEG-rhG-CSF use may have the capability to influence serum level of glucose. Therefore, a retrospective study was performed to explore the role of PEG-rhG-CSF use on serum glucose in cancer patients receiving chemotherapy.

2 Patients and methods

This study was approved by the Ethics Committee of Binzhou People's Hospital. Written informed consent was waived because of the retrospective design of the study and anonymous nature of the data collection.

Between April and July 2019, consecutive cancer patients receiving chemotherapy and PEG-rhG-CSF (Xinruibai; Qilu Pharmaceutical, Shandong, China) were enrolled in our study. At first, patients was given chemotherapy. After chemotheray, on the second or third day, baseline glucose (Glucose 1) was measured before PEG-rhG-CSF use. Then, in the next few days, a second fasting blood glucose (FBG) test (Glucose 2) was performed. Diabetes mellitus (DM) patients and patients who had FBG level ≥ 7 mmol/L and HbA1c level ≥ 7.0% were excluded. Demographic data and the period between PEG-rhG-CSF use and glucose 2 were collected. Serum glucose was measured on a chemistry auto-analyzer (Advia 2400; Siemens Healthcare Diagnostics, Tokyo, Japan) using a Siemens kit.

Patient characteristics were summarized using means and standard deviations for continuous variables and counts/percentages for categorical variables. Mean glucose levels were compared using t test. A two-sided P value < 0.05 was considered significant for all analyses. Data analysis was carried out using SPSS 16.0 (IBM Corp., Armonk, United States).

3 Results

A total of 69 eligible patients were retrieved, and 7 patients were excluded for DM (3 patients) and FBG level ≥ 7 mmol/L (4 patients). Finally, 62 patients were enrolled for further analysis. The average age of the patients was 58.4±11.5 years (range, 38 to 86 years). Male comprised of 53.2% (33/62) of the participants. The five most frequent cancer types were lung (*n*=17), gastric(*n*=17), colorectal (*n*=9), breast (*n*=7) and ovarian cancer (*n*=4). Before chemotherapy, 16 patients have received surgical treatment.

The time interval between PEG-rhG-CSF use and the second glucose test was 2.4±1.5 days (range, 1-6 days). As shown in Table 1, the mean Glucose 1 was 5.18±0.53 mmol/L (range, 3.80-6.48 mmol/L), and Glucose 2 was 3.80±1.13 mmol/L (range, 0.91-5.70 mmol/L). The difference between Glucose 1 and corresponding Glucose 2 was 1.41±0.99 (range, -0.75-3.63 mmol/L), and only four patients had an increasing in FBG levels. It is noteworthy that 8 patients had a FBG glucose < 2.5mmol/L after PEG-rhG-CSF use.

A comparison between Glucose 1 and 2 was performed. Statistical analysis showed a significant difference between them existed (*P*<0.001).

Table 1. Fasting blood glucose levels before and after PEG-rhG-CSF use in cancer patients receiving chemotherapy

Period* (days)	Cases (*n*)	Glucose 1† (mmol/L)	Glucose 2‡ (mmol/L)	Glucose level		*P*
				Increasing (*n*)	Decreasing (*n*)	
1	12	5.15±0.36	4.04±1.16	11	1	
2	8	5.39±0.52	3.79±1.02	8		
3	23	5.08±0.47	3.36±1.18	23		
4	14	5.25±0.70	4.16±1.15	12	2	
5	3	5.67±0.51	4.21±0.20	3		
6	2	4.54±0.35	4.37±0.04	1	1	
Total	62	5.18±0.53	3.80±1.13	58	4	<0.001

*Period represents the time interval between PEG-rhG-CSF use and the second glucose test. † Glucose 1 represents baseline glucose which was measured before PEG-rhG-CSF use. ‡ Glucose 2 represents the second fasting blood glucose was tested after PEG-rhG-CSF use.

4 Discussion

PEG-rhG-CSF has been widely used in prophylaxis of neutropenia caused by chemotherapy in cancer patients, and many complications has been reported. However, its effect on FBG levels has not been determined. Therefore, in the study, we evaluated the effect of PEG-rhG-CSF influencing FBG levels in the special subjects. Our results found that a hypoglycemic complication occurs secondary to PEG-rhG-CSF use.

Although PEG-rhG-CSF reduces the incidence of FN significantly, but its use must be balanced against rare but severe adverse effects and the cost. Bone pain is the most commonly reported adverse event with PEG-rhG-CSF. In a series of clinical trials, its incidence ranged from 25% to 38% in patients receiving pegfilgrastim, when using pegfilgrastim as primary prophylaxis of FN in patients undergoing chemotherapy [13]. Moreover, others include leukocytosis, back pain, anemia and secondary malignancies risk, but no fatal complication was noted [14-16]. In fact, all of these adverse events appear to be related, and the toxicities are associated with PEG-rhG-CSF efficacy and with an increased neutrophil count [17]. In the study, we found a common hypoglycemic complication secondary to PEG-rhG-CSF use. Sienkiewicz D et al. reported that G-CSF treatment can decrease the glucose level in patients with Duchenne muscular dystrophy [18]. On the basis of our review of the literature, this was the first report of PEG-rhG-CSF induced hypoglycemia in cancer patients undergoing chemotherapy.

According to previous studies, there are three potential mechanisms behind the hypoglycemic complication. First, G-CSF could increase macrophage glycolytic capacity by up-regulating c-myc and glucose transporter expressions, and increase the extent of glycolysis in macrophages [19]. Second, a positive correlation between G-CSF and insulin sensitivity was observed [20, 21]. Third, leptin controls glucose metabolism regardless of the impact on energy balance [22]. Thus, the decreased glucose level in the patients may be explained by the leptin-like effect of G-CSF treatment.

Although some valuable findings were obtained, a number of limitations should be mentioned. First, this study has a retrospective design with a single-center data, the result might not generalize in a useful way. Second, although we adopted self-control design, the results need to be confirmed by a larger study. Third, a major limitation is that the sample size was insufficient for evaluation of risk factors associated with hypoglycemia in cancer patients receiving PEG-rhG-CSF. However, further analysis will be done to focus this issue.

In summary, this study identifies a hypoglycemic side effect of PEG-rhG-CSF occurs in cancer patients undergoing anti-cancer chemotherapy. Our results highlight the caution required when using PEG-rhG-CSF for prophylaxis of chemotherapy-induced neutropenia.

Author contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Xin-Qiang Liu. The first draft of the manuscript was written by Sha-sha Cui and Ying Wang. All authors read and approved the final manuscript.

Disclosure Statement

The authors have no conflicts of interest to declare.

References

[1] Bru A, Bosch R, Cespedes MV, Carmona-Guedes S, Pascual E, Bru I, et al: Antitumoral effect of maintained neutrophilia induced by rhG-CSF in a murine model of pancreatic cancer. Sci Rep 2019;9:2879.

[2] Welte K, Gabrilove J, Bronchud MH, Platzer E, Morstyn G: Filgrastim (r-metHuG-CSF): the first 10 years. Blood 1996;88:1907-1929.

[3] Lydaki E, Bolonaki E, Stiakaki E, Dimitriou H, Kalmantis T, Kalmanti M: Efficacy of recombinant human granulocyte colony-stimulating factor and recombinant human granulocyte-macrophage colony-stimulating factor in neutropenic children with malignancies. Pediatr Hematol Oncol 1995;12:551-558.

[4] Tanaka H, Satake-Ishikawa R, Ishikawa M, Matsuki S, Asano K: Pharmacokinetics of recombinant human granulocyte colony-stimulating factor conjugated to polyethylene glycol in rats. Cancer Res 1991;51:3710-3714.

[5] Yang BB, Savin MA, Green M: Prevention of chemotherapy-induced neutropenia with pegfilgrastim: pharmacokinetics and patient outcomes. Chemotherapy 2012;58:387-398.

[6] Li L, Ma S, Wu M, Tan X, Zhong S, Lang J: The prophylactic effects of long-acting granulocyte colony-stimulating factor for febrile neutropenia in newly diagnosed patients with epithelial ovarian cancer: a randomised controlled study. BMJ Support Palliat Care 2019

[7] Green MD, Koelbl H, Baselga J, Galid A, Guillem V, Gascon

P, et al: A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. Ann Oncol 2003;14:29-35.

[8] Zhou C, Huang Y, Wang D, An C, Zhou F, Li Y, et al: A Randomized Multicenter Phase III Study of Single Administration of Mecapegfilgrastim (HHPG-19K), a Pegfilgrastim Biosimilar, for Prophylaxis of Chemotherapy-Induced Neutropenia in Patients With Advanced Non-Small-Cell Lung Cancer (NSCLC). Clin Lung Cancer 2016;17:119-127.

[9] Kuan JW, Su AT, Leong CF: Pegylated granulocyte-colony stimulating factor versus non-pegylated granulocyte-colony stimulating factor for peripheral blood stem cell mobilization: A systematic review and meta-analysis. J Clin Apher 2017;32:517-542.

[10] Anderlini P: Effects and safety of granulocyte colony-stimulating factor in healthy volunteers. Curr Opin Hematol 2009;16:35-40.

[11] Schuler A, Spolarics Z, Lang CH, Bagby GJ, Nelson S, Spitzer JJ: Upregulation of glucose metabolism by granulocyte-monocyte colony-stimulating factor. Life Sci 1991;49:899-906.

[12] Spielholz C, Heaney ML, Morrison ME, Houghton AN, Vera JC, Golde DW: Granulocyte-macrophage colony-stimulating factor signals for increased glucose uptake in human melanoma cells. Blood 1995;85:973-980.

[13] Lambertini M, Del Mastro L, Bellodi A, Pronzato P: The five "Ws" for bone pain due to the administration of granulocyte-colony stimulating factors (G-CSFs). Crit Rev Oncol Hematol 2014;89:112-128.

[14] Lyman GH, Yau L, Nakov R, Krendyukov A: Overall survival and risk of second malignancies with cancer chemotherapy and G-CSF support. Ann Oncol 2018;29:1903-1910.

[15] Fietz T, Luck A, Schulz H, Harde J, Losem C, Grebhardt S, et al: Prophylaxis of chemotherapy-induced neutropenia and febrile neutropenia with lipegfilgrastim in 2489 cancer patients: final results from the non-interventional study NADIR. Curr Med Res Opin 2019;35:1127-1138.

[16] Wolff T, Schulz H, Losem C, Reichert D, Hurtz HJ, Sandner R, et al: Prophylaxis of chemotherapy-induced neutropenia and febrile neutropenia with lipegfilgrastim in patients with non-Hodgkin lymphoma (NADIR study). Eur J Haematol 2019;102:174-181.

[17] Bongiovanni A, Recine F, Fausti V, Rossi B, Mercatali L, Liverani C, et al: Clinical role of filgrastim in the management of patients at risk of prolonged severe neutropenia: An evidence-based review. Int J Clin Pract 2019:e13404.

[18] Sienkiewicz D, Kulak W, Paszko-Patej G, Okurowska-Zawada B, Sienkiewicz J, Kulak P: Biochemical Changes in Blood of Patients with Duchenne Muscular Dystrophy Treated with Granulocyte-Colony Stimulating Factor. Biomed Res Int 2019;2019:4789101.

[19] Na YR, Gu GJ, Jung D, Kim YW, Na J, Woo JS, et al: GM-CSF Induces Inflammatory Macrophages by Regulating Glycolysis and Lipid Metabolism. J Immunol 2016;197:4101-4109.

[20] Plubell DL, Fenton AM, Wilmarth PA, Bergstrom P, Zhao Y, Minnier J, et al: GM-CSF driven myeloid cells in adipose tissue link weight gain and insulin resistance via formation of 2-aminoadipate. Sci Rep 2018;8:11485.

[21] Kim DH, Sandoval D, Reed JA, Matter EK, Tolod EG, Woods SC, et al: The role of GM-CSF in adipose tissue inflammation. Am J Physiol Endocrinol Metab 2008;295:E1038-1046.

[22] Fernandez-Formoso G, Perez-Sieira S, Gonzalez-Touceda D, Dieguez C, Tovar S: Leptin, 20 years of searching for glucose homeostasis. Life Sci 2015;140:4-9.