ORIGINAL ARTICLE

# Variations of blood glucose in cancer patients during chemotherapy

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## Abstract

**Purpose:** The aim of this study was to analyze the blood glucose (BG) variations in cancer patients during chemotherapy according to tumor types and chemotherapeutic regimens.

**Materials and Methods:** Patients were examined from the Department of Medical Oncology of Cancer Hospital and Institute, Chinese Academy Medical Sciences from January 2012 to December 2014. The patients' ages, genders, body mass index, associated disease history, and corresponding BG values were recorded.

**Results:** Among these 2029 patients, 331 (16.3%) patients encountered high BG during chemotherapy except diabetic patients. Of these patients, 208 (62.8%) were males, and 123 (37.2%) were females, with age ranged from 17 to 84 years. The 331 cases included 23 tumor types and 77 regimens. Totally, BG values increased up to 7.4 ± 1.3 mmol/L during chemotherapy.

**Conclusions:** No previous studies in the literature have examined systematically so numerous cases of hyperglycemia during chemotherapy. This study has pointed out possible high-risk chemotherapeutic regimens and tumor types, which should be paid attention to prevent the occurrence of hyperglycemia.

**Key words:** Blood glucose, cancer patients, chemotherapy, hyperglycemia

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## Introduction

Hyperglycemia is a common side effect among in-patients, especially cancer patients during chemotherapy. Common Terminology Criteria for Adverse Events in US National Cancer Institute had put chemotherapeutic impacts on blood glucose (BG) in cancer patients into chemotherapeutic toxicity and side effect assessment system.

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Patients with a solid tumor cancer are at risk for hyperglycemia. Hyperglycemia may decrease the response to chemotherapeutic agents, directly affect the cell growth and induce the drug resistance of tumor cells. The occurrence of hyperglycemia during the period of inductive remission chemotherapy is an independent risk factor toward the early recurrence and high mortality.[1-3] Hyperglycemia contributes to the risk for adverse outcomes such as infections and nonmalignancy-related mortality. The association between hyperglycemia and infections during induction chemotherapy has been reported in a number of hematologic disorders.[4,5]



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In addition to the effects of hyperglycemia on the biological behavior of tumor cells, the prevalence of transient hyperglycemia during induction chemotherapy has been observed, and existing evidence revealed another role of hyperglycemia in tumor treatment. Hyperglycemia during chemotherapy for hematologic and solid tumors is correlated with increased toxicity.[6] Considering associations between hyperglycemia and malignancies, the effect of hyperglycemia on cancer progression in cancer patients with abnormal BG should not be neglected.

BG level of cancer patients is greatly impacted by regimens, and our previous study found that cancer patients' BG varied differently during total parenteral nutrition treatment according to tumor types.[7] Although, there are many reports on hyperglycemia from chemotherapeutic agents such as methotrexate, cyclophosphamide, paclitaxel (PTX), which could cause diabetes, no detailed analysis of the chemotherapeutic agents and hyperglycemia are reported. To best of our knowledge, this study is the first retrospective analysis of the largest number of cancer cases in the literature. The aim of this study was to analyze the clinical features of BG in chemotherapeutic agents and regimens and discuss possible mechanism and recommend solutions in cancer patients.

## Materials and Methods

The data for this study were obtained by reviewing patient electric medical records of all cancer patients within chemotherapy from the Department of Medical Oncology of Cancer Hospital and Institute, Chinese Academy Medical Sciences, from January 2012 to December 2014 to evaluate the BG level during chemotherapeutic period. The BG values are fasting plasma glucose from the record. If the patient was treated with several chemotherapy regimens, BG values were recorded separately in each regimen. Before chemotherapy, all the values of BG, blood routine test, blood biochemical test, HBA1c of the patients are normal. The patients with diabetes mellitus or treated with glucocorticoid (cortisone, metacortandracin, etc.) and leukocyte-increasing drugs (recombinant human granulocyte colony-stimulating factor, recombinant human thrombopoietin, etc.) during chemotherapy are excluded from the study.

The collected data were compiled, tabulated, and analyzed with SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). Pictures were drawn with Microsoft Excel Professional 2013. Test for association was done using Chi-square. The value of $P < 0.05$ was considered to be statistically significant.

The study was approved by the Ethics Committee of Cancer Hospital and Institute, Chinese Academy of Medical Sciences.

## Results

### Overall condition

Among these 2029 patients, there were 331 (16.3%) patients with high BG during chemotherapy except diabetic patients. Of these patients, 208 (62.8%) were males, and 123 (37.2%) were females. The age of the patients ranged from 17 to 84 years (mean age: 56.9). A detailed distribution of the samples according to the demographic characteristics was listed in Table 1.

The 331 patients included 23 types of tumor/cancer: Lung cancer 68 (LC, 20.5%), colon cancer 63 (CC, 19.0%), rectal cancer 54 (RC, 16.3%), gastric cancer 54 (GC, 16.3%), breast cancer 30 (BC, 9.1%), lymphoma 19 (5.7%) as well as 77 types of regimens in which oxaliplatin+capecitabine, oxaliplatin+tegafur, irinotecan+capecitabine, oxaliplatin+5-fluorouracil (5-FU), and gemcitabine+cisplatin were the top 5 high-frequent used regimens. The BG levels of these patients were located in the normal range (3.89～6.1 mmol/L) before chemotherapy and rose up onto varying degrees (7.4 ± 1.3 mmol/L).

### Blood glucose varieties

#### *Blood glucose values variation in different tumor types*

The patients were ranked according to tumor types, and each tumor type was divided into two subgroups according to genders. BG increment in different tumor types during chemotherapy was CC>BC>GC>LC>RC in sequence [Figure 1].

The five tumor types in the high morbidity were also on the top list of effecting BG in Figure 1. The BG values were higher in female than male in RC, BC, GC, LC, and Mes, where RC differentiated the gender factor mostly. In Figure 1, BG values in male were higher than that in female in other tumor types, where more distinctions existed in PC, BN, and CN.

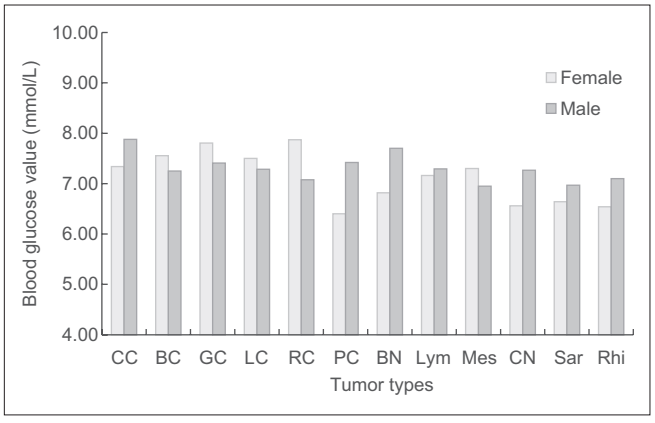


**Figure 1:** Blood glucose values in various tumor types. CC=Colon cancer, BC=Breast cancer, GC=Gastric cancer, LC=Lung cancer, RC=Rectal cancer, PC=Pancreatic cancer, BN=Bladder neoplasm, Lym=Lymphoma, Mes=Mesothelioma, CN=Cardiac neoplasm, Sar=Sarcoma, Rhi=Rhinocarcinoma

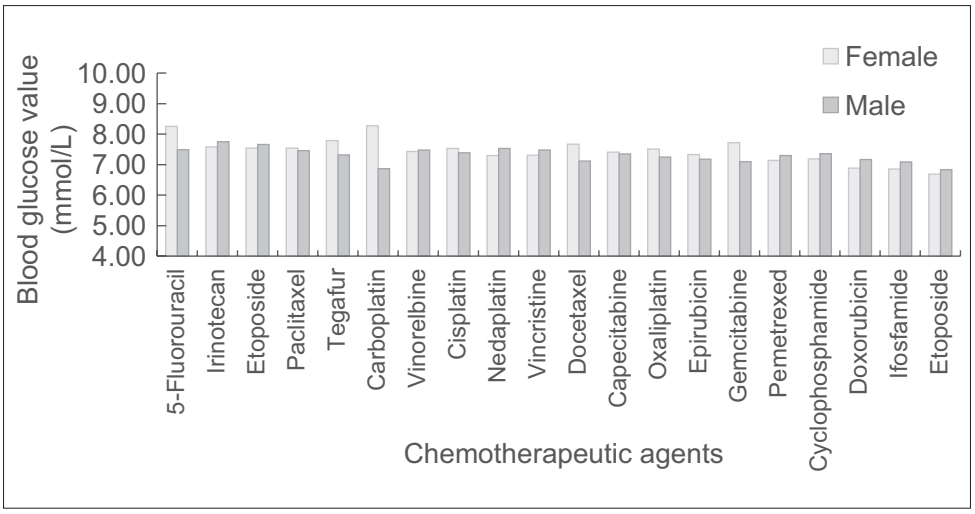


**Figure 2:** Blood glucose values in various chemotherapeutic agents

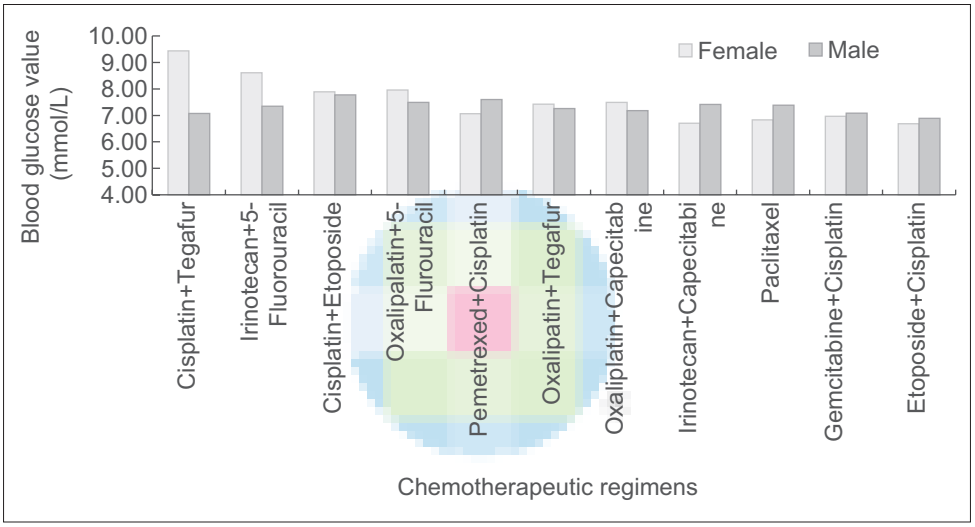


**Figure 3:** Blood glucose values in various chemotherapeutic regimens

**Table 1: General demographic characteristics of subjects**

| Items | Female | Male | Total | *P** |
|---|---|---|---|---|
| *n* (%) | 123 (37.2) | 208 (62.8) | 331 | - |
| Age, years | 55.1±9.7 | 58.0±10.9 | 56.9±10.6 | 0.014 |
| BMI, kg/m$^2$ | 23.9±3.9 | 24.2±3.3 | 24.1±3.6 | 0.380 |
| Family cancer history, *n* (%) | 21 (17.1) | 40 (19.2) | 61 (18.4) | 0.625 |
| Hypertension, *n* (%) | 33 (26.8) | 45 (21.6) | 78 (23.6) | 0.282 |
| Drug allergy, *n* (%) | 12 (9.8) | 16 (7.7) | 28 (8.5) | 0.514 |
| Tobacco and alcohol addiction, *n* (%) | 7 (5.7) | 119 (57.2) | 126 (38.1) | 0.000 |

*Age and BMI *P* values were tested with *t*-test, double tails. Other *P* values were tested with Chi-square. BMI=Body mass index

### *Blood glucose values variation in different chemotherapeutic regimens*

As there were so many chemotherapeutic regimens of the patients that there existed only one recorded case in some regimens; therefore, these kinds of cases were excluded in the following comparisons. Figures 2 and 3 listed out the common chemotherapeutic agents/regimens results, excluding one-case conditions.

The chemotherapeutic regimens were classified and aggregated according to chemotherapeutic agents and ranked according to BG values. The BG values increased much within 5-FU, irinotecan, etoposide, PTX, and tegafur. Gender factor differentiated much within 5-FU, carboplatin, docetaxel, gemcitabine [Figure 2].

Since 5-FU, irinotecan, and oxaliplatin are currently used as "three carriages" in chemotherapy. Our study displayed that all the BG values increased highly after chemotherapy in cancer patients, especially within 5-FU, irinotecan.

Most patients are treated with regimens instead of single chemotherapeutic agent; here, BG values were highest within cisplatin+tegafur and lowest within

etoposide+cisplatin in sequence in Figure 3 and gender factor differentiated much in two regimens of cisplatin+tegafur and irinotecan+5-FU.

## Discussion

Cancers of lung, female breast, stomach, liver, colon and rectum, esophageal, cervix, uterus, prostate, and ovary were the most common cancers; LC, liver cancer, stomach cancer, esophageal cancer, colorectal cancer, female BC, pancreatic cancer, brain tumor, cervical cancer, and leukemia were the leading causes of cancer death.[8]

### Mechanism of chemotherapy-induced hyperglycemia

Recently, cancer doctors increasingly concerned chemotherapy-induced hyperglycemia or secondary diabetes mellitus. Glycometabolism disorders emerged after chemotherapy, which caused BG values significantly high or even diabetes mellitus. It would pause chemotherapy and impact patient life quality. Hyperglycemia, the most important features of diabetes, may be responsible for the excess glucose supply for these glucose-hungry cells and it contributes to apoptosis resistance, oncogenesis, and tumor cell resistance to chemotherapy.[3] Cancer and T2M follow similar pathogenesis with immune disorders, nuclear factor kappa-light-chain-enhancer of activated B cells, etc., When cancer and diabetes mellitus coexist, the mutual effects deteriorate patients' condition.[9,10]

Hyperglycemia favors proliferation of MCF-7 cells and increases expression of cell cycle regulatory proteins cyclin E and cyclin-dependent kinases-2. Hyperglycemia enhances the cytotoxicity of carboplatin and 5-FU in MCF-7 cells. Hyperglycemia reduces the expression of P-glycoprotein and promotes cell killing by increasing drug accumulation.[11]

Some chemotherapeutic agents damage insulin β cell, impact insulin synthesis and secretion, block BG control, and induce diabetes. In addition, the agents damage hepatic or renal function to influence glycometabolism. Renal dysfunction reduces the insulin inactivation in kidney and insensitivity of insulin receptor so as to influence glycometabolism.

The target of PTX is microtubule and microfilament system. PTX inhibits insulin secretion and releases to increase BG. The mechanism of capecitabine-induced hypertriglyceridemia may be due to the decreased the activities of lipoprotein lipase and hepatic triglyceride lipase.[12] 5-FU-induced hyperglycemia appears to be mediated in part by a relatively deficient insulin secretion to glucose stimulation. A relative deficiency in insulin secretion following 5-FU treatment appears to be related to β cells function impairs with islet cell ultrastructural changes induced by 5-FU.[13] HG attenuates growth inhibition of 5-FU and decreased cell death and increased DNA replication may account for the attenuating effect of a high-glucose environment on 5-FU-induced tumor growth inhibition.[14]

### Influence from tumor types

Cancer itself could also cause glycometabolism disorder. A significantly higher incidence of impaired glucose metabolism (IGM) appears to occur in colorectal cancer patients than in the healthy population. There was a significantly higher incidence of (IGM-diabetes mellitus or IGT) in colorectal cancer subjects.[15]

Serum glucose and insulin levels were higher in the patients with colorectal cancer than in healthy controls. Hyperinsulinemia is occasionally seen in patients with colorectal cancer. Hyperinsulinemia may be one of the causes of colorectal cancer, and we have to control hyperinsulinemia to prevent recurrence of colorectal cancer even after curative resection.[16]

### Recommended solutions

Controlling hyperglycemia may have important therapeutic implications in cancer patients. Strict BG control with intensive insulin therapy also has been shown to reduce morbidity and mortality among critically ill patients in a surgical intensive care unit.[17] Basically, the inductive chemotherapy-induced hyperglycemia is still using the insulin to control the BG clinically.[5]

Therefore, in the clinical works, the monitoring toward the BG level should be paid attention to during the inductive chemotherapy, especially toward the population with high-risk of hyperglycemia, it should be active to prevent the occurrence of hyperglycemia.[5] First, patients must be completely evaluated before treatment, and set up intact BG record and related drug usage record, especially HbA1 monitoring before and during chemotherapy to prevent T2M. Second, except preventing cardiac, renal, or hepatic toxic drugs, patients should be supplied blood volume, corrected water and electrolyte disorders, adjusted insulin dosage and controlled blood pressure, reduced blood viscosity so as to prevent side effects, such as chemotherapy-induced nausea and vomiting, severe dehydration, hyperglycemia, diabetic ketoacidosis, and hyperosmolar nonketotic coma etc.

The hyperglycemic incidence (16.3%) in this paper was close to the literature (19.9%, 14%).[1,18] The limits of this study lied in the use of a retrospective analysis. Thus, the impacts of insulin therapy intensity toward the prognosis of hyperglycemic cancer patients could not be assessed. Therefore, the number of patients with overt hyperglycemia may be underestimated. As for the direct comparison during chemotherapy in this paper, there were

also some neglected aspects, such as therapeutic outcomes, prognosis, and follow-up visits. Glucose levels were not checked in a standardized fashion, and there was no standard for glucose control because of the retrospective nature of this study.

## Conclusions

Therefore, in the clinical works, the monitoring toward the BG level should be paid attention to during the inductive chemotherapy, especially toward the population with high-risk of hyperglycemia, it should be active to prevent the occurrence of hyperglycemia.

Future research is needed that focuses on the association between glycemic control and adverse outcomes in patients with a solid tumor cancer who are at risk for treatment-induced hyperglycemia.

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### Conflicts of interest

There are no conflicts of interest.

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