Original Article

Glycaemic Adverse Drug Reactions from Anti-Neoplastics Used in Treating Pancreatic Cancer

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Abstract

Purpose: Pancreatic carcinoma is the most lethal cancer, with a 5-year survival rate of <5%. Hyperglycemia is one of the severe adverse drug reactions (ADRs) in cancer treatment. The aim was to analyze the blood glucose-related ADR of antineoplastics in treating pancreatic cancer. **Materials and Methods:** Antineoplastic drugs were selected from Martindale-The Complete Drug Reference (36th edition). ADR data were extracted from VigiBase, the WHO Uppsala Monitoring Centre, and the WHO's specialist center for drug safety. **Results:** Nineteen antineoplastic drugs were selected; VigiBase provided their ADR records including total 235,625 records and 27 heading ADR items, 1348 records of glucose metabolism disorders (GMDs), and 807 records of hyperglycemia. Based on the emphasized nine antineoplastic drugs with high hyperglycemic ADR incidence, we found: fluorouracil, sorafenib and pemetrexed with high ADR record of metabolism and nutrition disorders; fludarabine and flutamide with high ADR of GMD ratio. All the hyperglycemia ratios of the 9 antineoplastics were more than 50.0%, except pemetrexed and sorafenib. Thoroughly, doxorubicin carried high absolute records and ratios in hyperglycemic conditions. **Conclusions:** Pancreatic carcinoma is an aggressive malignancy typically associated with severe hyperglycemia. Furthermore, hyperglycemia is one of the severe ADRs from antineoplastics, which must be paid special attention to when treating in pancreatic carcinoma, especially doxorubicin, fluorouracil, and gemcitabine. Such real-time monitoring or pretreatment gene test can be suggested.

Keywords: *Adverse drug reaction, antineoplastic, hyperglycemia, pancreatic cancer, VigiBase*

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Introduction

Pancreatic carcinoma is the most lethal cancer, with a 5-year survival rate of <5%.[1] The incidence and mortality rates of pancreatic cancer are increasing; it is the fourth leading cause of cancer deaths in the US in 2015.[2] Its estimated new cancer cases and deaths (thousands) are 48.96 (new cases) and 40.56 (deaths) in the US, as well as 90.1 (incidence) and 79.4 (mortality) in China, both in 2015, respectively.[2,3] Pancreatic carcinoma is associated with a very poor prognosis, with a 6%–10% 5-year survival rate and 60%–75% of patients dying within the 1st year of diagnosis. Overall, only 12%–15% of patients with pancreatic carcinoma are candidates for surgical resection.[4]

About 85% of pancreatic carcinoma is already unresectable at diagnosis, prevention through modification of its risk factors is chiefly important.[8] With high mortality and low cure rate, the process of pancreatic carcinoma treatment should be paid excessive attention, especially on the relevant blood glucose. Diabetes mellitus (DM) or hyperglycemia is common in pancreatic cancer patients[6] because insulin secretion is greatly affected by the pancreas; further understanding

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of the antineoplastic drugs on the role of blood glucose may provide opportunities for early checking/treating pancreatic carcinoma process. Effective blood glucose control will be useful to improve pancreatic carcinoma prognosis.

Hyperglycemia is associated with high mortality rates and occurs in patients with or without a previous history of diabetes.[7] Patients with a solid tumor cancer are at risk for hyperglycemia, and some chemotherapeutic regimen will inevitably cause hyperglycemia.[5] Hyperglycemia might increase the risk of pancreatic cancer by providing more glucose to fuel tumor growth. Hyperglycemia can also enhance proliferation and invasion ability of pancreatic cancer cells. Fasting hyperglycemia is a dose-dependent risk factor for pancreatic cancer, and prediabetes is also a risk factor for pancreatic cancer.[8]

Hyperglycemia can enhance proliferation and invasion ability of pancreatic cancer cells.[9-11] Hyperinsulinemia and hyperglycemia, however, are already present at the stage of prediabetes (blood glucose between normal and diabetes), which precedes type 2 diabetes.[12] Taken together, these observations suggest that prediabetes could also increase the risk of pancreatic cancer.[5] On the contrary, one animal experiment showed that sports-induced blood sugar decline may prevent development of pancreatic ductal adenocarcinoma.[13]

Till now, reports on pancreatic carcinoma and hyperglycemia are very limited, and researches on adverse drug reactions (ADRs) from the pancreatic carcinoma treating antineoplastics on blood glucose have not been investigated. Interestingly, on the one hand, pancreatic carcinoma needs chemotherapy; on the other hand, chemotherapy will cause the severe ADR of hyperglycemia. The purpose of this study was to analyze the ADR records in an attempt to determine the prevalence of the influences from these antineoplastics.

Materials and Methods

Drug selection

Antineoplastic drugs were selected from Martindale-The Complete Drug Reference (36th edition). Inclusion criteria were as follow: antineoplastics used or administrated in pancreatic cancer, pancreatic endocrine tumors, or pancreatic adenocarcinoma. Exclusion criteria were as follow: drugs with adverse effects and precautions of pancreatitis, or subclinical damage to the pancreas.

Data source

ADR data were extracted from VigiBase ®, the WHO Uppsala Monitoring Centre (UMC), and the World Health Organization's specialist center for drug safety. As UMC's main database, VigiBase gathers more than 12 million adverse reaction reports from over 100 countries as the world's largest collection of drug safety information, becoming the first-choice source of medicinal product information for both user groups – a global hub of products, services, and scientific research focused on clinical data and patient Safety. Public access to overview statistics from VigiBase can be gained through the VigiAccess website.[14]

In this study, the included antineoplastic drug data were extracted from summary statistics from VigiBase on December 12, 2016, and ADR war classified following original presentation from VigiBase.

Statistical analysis

Descriptive analysis and figures were performed using IBM SPSS Statistics (Version 19) (IBM, Armonk, NY, USA).

Results

Overall, a total number for 19 antineoplastics (doxorubicin, fluorouracil, gemcitabine, erlotinib, sorafenib, trastuzumab, pemetrexed, fludarabine, axitinib, flutamide, mitomycin, tegafur, porfimer, cilengitide, nimotuzumab, rubitecan, imexon, edrecolomab, and streptozotocin in incidence sequence) retrieved 235,625 records and 27 heading ADR items, in which 19,180 records on metabolism and nutrition disorders (MNDs), 1348 records on glucose metabolism disorders (including DM) (GMD), and 807 records on hyperglycemia. Of the 19 antineoplastics, ADR records weight most on Asia and America geographically [Figure 1] and 45–74 years old on age group distribution,

We counted the incidence of hyperglycemia and analyzed these antineoplastics in more than 20 records on hyperglycemia. Although pancreatitis has been reproted with sorafenib,[17] with its specific hypoglycaemic effect, we also discussed sorafenib in the context. In Figure 2, we compared the records of MND with total retrieved records. From doxorubicin to flutamide, the total records decrease while the MND ratio of fluorouracil, sorafenib, and pemetrexed was highest (around 10.0%) and that of fludarabine and flutamide were lowest (4.7% and 5.0%, respectively).

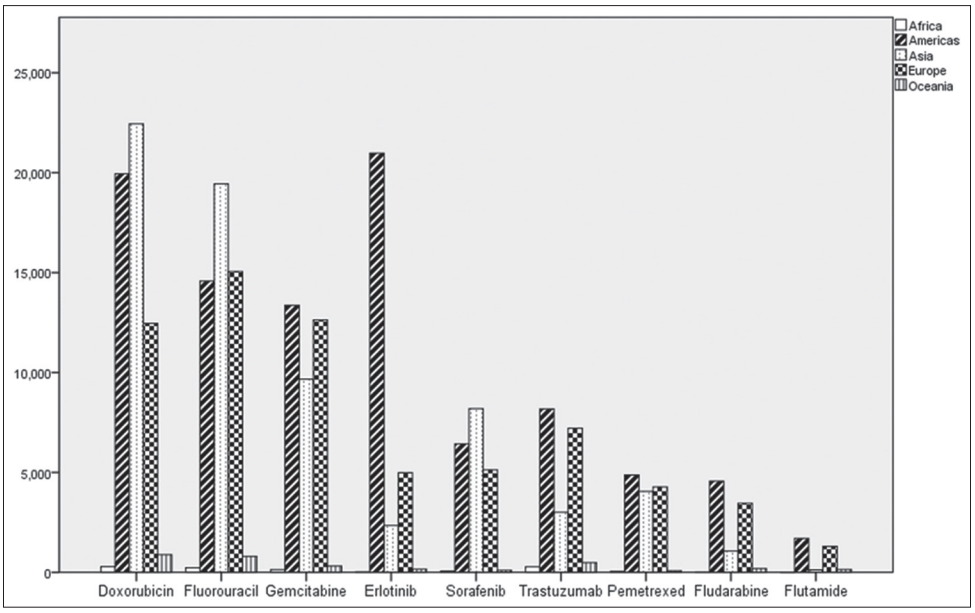

Figure 1: Geographical distribution of selected antineoplastic

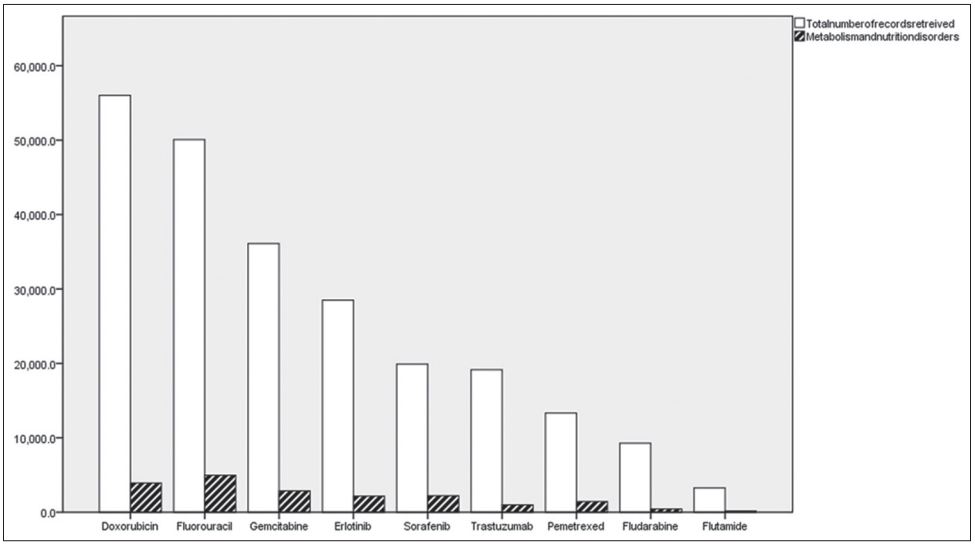

Figure 2: Record numbers on general adverse drug reactions (metabolism and nutrition disorder ratio = metabolism and nutrition disorder/total number of records retrieved)

The sequence in Figure 3 is completely different to that in Figure 2. Fluorouracil, doxorubicin, and gemcitabine were in series on the top three in absolute MND record. Due to high incidence of MND, the GMD ratio of fluorouracil (4.9%) was at lowest level, near that of pemetrexed (4.2%). Due to low records of MND, fludarabine and flutamide were with high GMD ratio (11.0% and 26.8% respectively). However, GMD ratio of doxorubicin (Adriamycin) was 10.4% with both high records of MND and GMD so that doxorubicin should be paid special attention to.

Figure 4 is the detailed records of GMD, in which hyperglycemia was the vast majority in hyperglycemic conditions. Doxorubicin, fluorouracil, and gemcitabine were in series on the top three in absolute hyperglycemic record. Hyperglycemia ratio of the nine antineoplastics was more than 50.0%, except pemetrexed. Sorafenib was an opposite exception whose hypoglycemic condition ratio was excessively high. As for doxorubicin, its hyperglycemic ratio was highest. According to doxorubicin's total record, MND, and GMD, the high glycemic ADR should be excessively paid attention to.

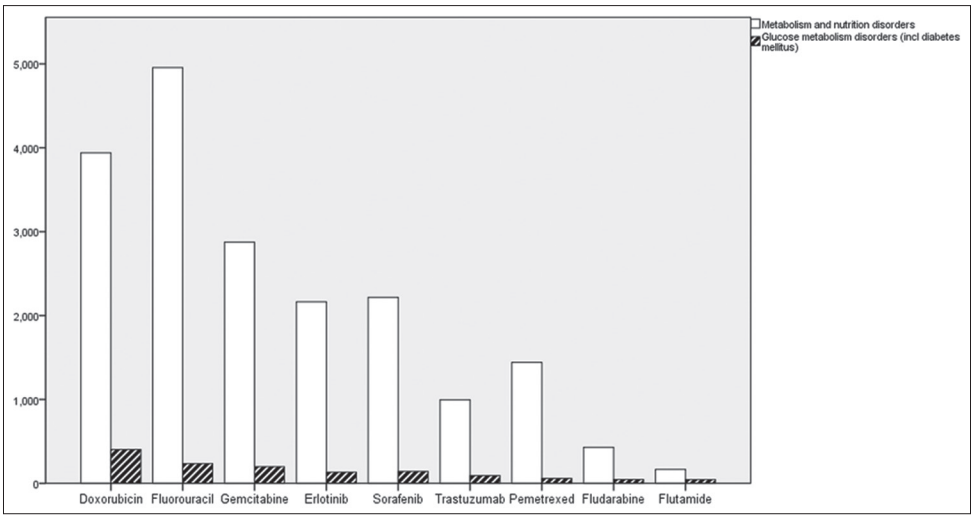

Figure 3: Record numbers on metabolism disorders (glucose metabolism disorder ratio = glucose metabolism disorder/metabolism and nutrition disorder)

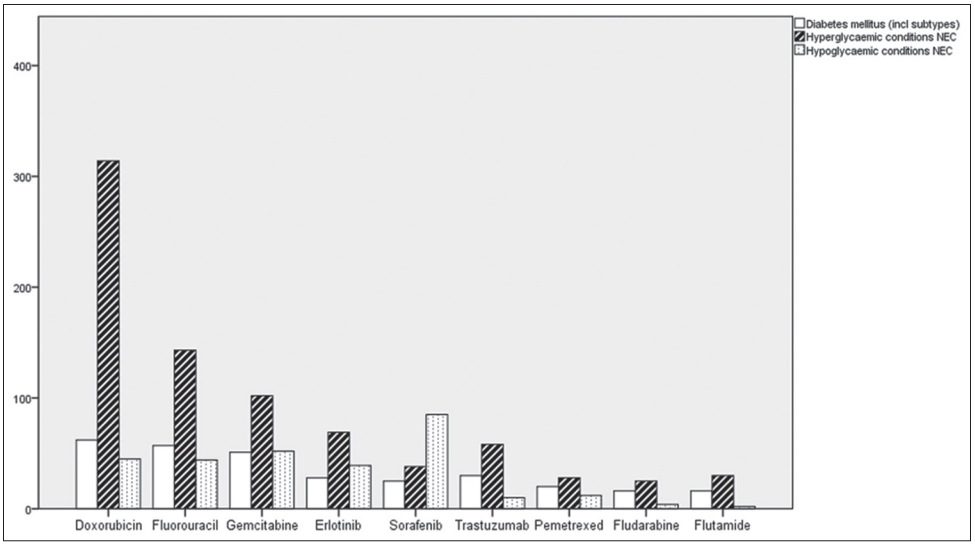

Figure 4: Record numbers on glucose metabolism disorders (hyperglycemia ratio = hyperglycemic condition/glucose metabolism disorder)

Discussion

Hyperglycemia is a severe adverse effect in pancreatic carcinoma treatment

Pancreatic adenocarcinoma has a very poor prognosis and lack of effective therapies.[15] Surgical resection is primary therapy for solitary pancreatic endocrine tumors.[16] DM is a manifestation of the disease, but there is also some evidence that it may be a predisposing factor.[17]

DM has long been purported as a potential risk factor for pancreatic cancer but is an ineffective screening prompt because its prevalence is so high, whereas that of pancreatic cancer is so low.[18] Poorly controlled DM is a well-known risk factor associated with decreased OS for many if not most benign and malignant conditions.[4]

Fasting hyperglycemia is a dose-dependent risk factor for pancreatic cancer. One dose-response meta-analysis shows that every 0.56 mmol/L increase in fasting blood glucose is associated with a 14% increase in the rate of pancreatic cancer. Prediabetes is also a risk factor for pancreatic cancer and provides an opportunity for prevention of pancreatic carcinoma.[8]

Patients with early postoperative hyperglycemia had increased rates of surgical and nonsurgical complications, infectious complications, and relaparotomy. Poor perioperative glycemic control may be an independent risk factor for worse outcomes. Perioperative hyperglycemia is generally associated with poor prognostic outcomes in a variety of benign and malignant conditions.[4]

Possible mechanisms of pancreatic carcinoma and hyperglycemia

Several theories have been put forth to provide the possible mechanisms, which may explain the association between hyperglycemia and pancreatic carcinoma.

Wang *et al*.[19] reported that insulin resistance may lead to upregulation of insulin-like growth factor-1 receptors, leading to islet cell hyperplasia and resultant hyperinsulinemia in asymptomatic patients with pancreatic carcinoma. This theory relies on the supposition that a tumor-secreted diabetogenic agent may block insulin receptors leading to peripheral insulin resistance and glucose intolerance.[20] Pannala *et al*. have demonstrated that removal of such a diabetogenic factor may explain the resolution of new-onset DM in nearly 60% of patients with pancreatic carcinoma after tumor resection.[21]

In patients with new-onset pancreatic carcinoma-associated DM undergoing neoadjuvant chemoradiation therapy with surgical intent, fasting glucose response may mirror the extent of tumor destruction. This finding lends further support to the hypothesis that, in many patients, pancreatic ductal adenocarcinoma produces a diabetogenic substance, which triggers reversible pancreatic β-cell destruction.[22] If the tumor infiltration of the islet-rich body and tail were the cause of pancreatic carcinoma-associated DM, insulin, and C-peptide levels should be low as a result of β-cell destruction.[4]

The hypothesis that pancreatic tumors secrete a diabetogenic factor create a diabetogenic state or induce peripheral insulin resistance, and thereby, glycemic control improves after resection may explain our observation that nearly 34% of patients experience improved or complete resolution of their diabetes after surgery.[18]

Possible causes from antineoplastic drugs

The acute effects of antineoplastic drugs often include nausea and vomiting, sometimes extremely severe.[17] This study includes five mechanical kinds of antineoplastics: antitumor antibiotics, antimetabolites, epidermal growth factor receptor (EGFR) inhibitors, monoclonal antibodies, and antitumor hormones. Herein, doxorubicin's ADR records are the most so is its influence on blood glucose. Mechanisms of doxorubicin can be divided into four aspects: combination with DNA, free radical production, combination with metal ions, and combination with cytomembrane. Based on the published papers, doxorubicin's influence on hyperglycemia probably relates to free radical production. The second rank of hyperglycemic incidence drugs is flutamide and trastuzumab. Records of GMD on fluorouracil are abundant as well as high ratio of hyperglycemic ADR in the kind of antimetabolites. In the kind of EGFR inhibitors, though its high records of GMD, the hyperglycemic incidence is relatively low (sorafenib is the lowest in the included drugs).

Recommended prevention methods

Alterations in blood glucose levels after surgical resection for pancreatic carcinoma may, therefore, depend on a number of factors including the type of pancreatic resection performed, duration of hospital stay, postoperative complications, and perhaps most importantly, whether DM is of new-onset or long-standing type.[4] Hence, blood glucose control should base on the patient situations. As far as the hot gene test nowadays, glucose metabolism is also control by some genes individually. A real-time glucose monitoring or to test the pancreatic carcinoma patients genetically are a good advice for blood glucose control.

During neoadjuvant therapy, it is reasonable to consider following fast blood glucose (FBG) levels as an adjunctive measurement of treatment response. Although normalization of FBG does not guarantee a Grade IV response, the data indicate that a Grade IV response is unlikely if FBG normalization does not occur. In addition, this response seems to be an "all or nothing response," that is, the FBG measurement should be used as a categorical, and not a continuous, measurement variable.[22]

Limitation

This study is extracted from spontaneously reported database as with any retrospective analysis. Underreporting and missing data in spontaneous reports are well-known problems in this type of studies. Reasons for missing data are unavailable information, or the reporter did not consider certain facts as relevant.[23] The consequence could not represent the precise results of the ADR analysis. Furthermore, the statistical data results were not detailed enough as other reports from VigiBase; more information was needed such as distribution from gender, age, and districts. As for a certain drug utilities, it is also needed the information on usage and dosage, as well as stage of illness. Of course, it will be the next target of our research.

Conclusions

In summary, pancreatic carcinoma is an aggressive malignancy typically associated with hyperglycemia as incidental symptom. Blood glucose level has become one of the indicators for pancreatic carcinoma prognosis. Hyperglycemia is also one of the severe ADRs from antineoplastics, especially in pancreatic carcinoma-treating drugs. The present research based on metabolic ADRs of pancreatic carcinoma-treating antineoplastics, it being statistical analysis on blood glucose conditions at the first time. Herein, doxorubicin was at the first stage both in absolute ADR record and

relative ratio of hyperglycemic conditions. On the next step, future studies are needed to analyze its utilities including usage, dosage, and stages of illness deeply, handle full information on the influence of blood glucose in pancreatic carcinoma patients, so as to make correct control solution for clinical workers.

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Conflicts of interest

There are no conflicts of interest.

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