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Review Article

Acute pancreatitis-induced by platinum compounds in patients with cancer: a review of the literature

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ABSTRACT

The purpose of this review of the literature was to describe the relationship between use of platinum-based antineoplastics and development of acute pancreatitis in patients with cancer. A literature search was conducted using PubMed, Science Direct and Google scholar databases for articles published from 1985 to 2014. The headings and/or text words (platinum compounds), (acute pancreatitis-induced by platinum compounds), and (cisplatin, carboplatin, and oxaliplatin) were entered, and the search was limited to articles describing case reports in adults with cancer. A total of 12 cases were reported between 1985 and 2012; including three platinum compounds; cisplatin, carboplatin, and oxaliplatin. In conclusion, it is highly recommended to include baseline assessment for acute pancreatitis risk factors and to consider acute pancreatitis in the differential diagnosis of abdominal pain in patients who have received platinum-based chemotherapy.

Keywords: Acute pancreatitis, Platinum compounds, Cisplatin, Carboplatin, Oxaliplatin

INTRODUCTION

Platinum compounds are immensely used in patients with cancer as one of the most effective antineoplastics agents. Although, all platinum compounds share a similar chemical structure, but their toxicities are different in certain levels. Drug-induced pancreatitis is usually a diagnosis of exclusion. Drug-induced pancreatitis is not very common and the overall incidence ranges from 0.1% to 2% of pancreatitis cases.[1,2] Acute pancreatitis is a surgical emergency characterized by upper abdominal pain, nausea, and vomiting, with elevated serum amylase and/or lipase.[3] The pathogenesis is suspected to involve enzymatic autodigestion of the pancreas; gallstones and alcohol account for over 80% of cases; hypertriglyceridemia, hypercalcemia, drugs, and infection are rarer causes; drugs are implicated in only up to 2% of cases.[1,3] Although the frequency of drug-induced acute pancreatitis is generally low, the disease is associated with substantial morbidity and mortality, which makes timely identification of the offending agent important. Mechanisms suggested for drug-induced pancreatitis include pancreatic duct constriction; immunosuppression; cytotoxic, osmotic, pressure, or metabolic effects; arteriolar thrombosis; direct cellular toxicity; and hepatic involvement.[4]

A comprehensive literature search was performed to collect all available data on drug-induced pancreatitis. Strong evidence for an association with acute pancreatitis has been described

for anticholinesterases, calcium 2',3'-dideoxyinosine, estrogen, L-asparaginase, salicylates, thiazide-diuretics, valproic acid, and vinca alkaloids. Weak evidence has been found for antituberculous agents, azathioprine, biguanides, cisplatinum, cyclosporine A, H2-blocking agents, loop diuretics, 6-mercaptopurine, metronidazole, pentamidine, steroids, sulfonamides, sulindac, and tetracycline.[5]

STUDY OBJECTIVE AND SIGNIFICANCE

There have been a huge amount of research studies focusing on the ototoxicity, gastrointestinal (nausea, vomiting and mucositis), renal, bone marrow, neurological toxicities of platinum-based antineoplastics; including mainly, cisplatin, carboplatin and oxaliplatin with relatively lower risk due to marked differences in their therapeutic use, pharmacokinetics and adverse effects. Acute pancreatitis caused by platinum-based antineoplastics has been poorly discussed by the literature in compared with other toxicities. Furthermore, knowledge regarding acute pancreatitis-induced by platinum compounds is crucial to early diagnosis of cases and institute effective treatment in patients who are undergoing chemotherapy. The purpose of this review of the literature is to describe the relationship between use of platinum-based antineoplastics and development of acute pancreatitis in patients with cancer.

METHODS

Search strategy and eligibility criteria

A literature search was conducted using PubMed, Science Direct and Google scholar databases for articles published from 1985 to 2014. The headings and/or text words (platinum compounds), (acute pancreatitis-induced by platinum compounds), and (cisplatin, carboplatin, and oxaliplatin) were entered, and the search was limited to articles describing case reports in adults with cancer. The resulting abstracts were screened, and published in English journals describing the association between platinum compounds and acute pancreatitis was retrieved for review. Meeting abstracts, letters, comments, animal or *in-vitro* studies, pharmacokinetic, pharmacodynamic studies, and meta-analysis were excluded. Reference lists of the articles reviewed were also searched to locate additional eligible references. Care was taken to ensure that each independent study was represented only once.

ACUTE PANCREATITIS-INDUCED BY PLATINUM COMPOUNDS

Cisplatin

Cisplatin is one of the most widely used anticancer chemical drugs. It has been used to treat a range of tumors including head and neck, lung, breast, ovarian and cervical cancers.[6] As an anticancer agent, cisplatin exerts its cytotoxic role in tumor cells by damaging DNA through the formation of covalent bonds with purine bases.[7] Cisplatin is classified as Class II drugs associated with pancreatitis (>10 but <20 reported cases of acute pancreatitis with or without positive rechallenge).[8] In another review, cisplatin was classified as Class IV (many single case reports exist in the literatures that describe the association of various medications with the development of acute pancreatitis. These drugs have the weakest association to pancreatitis. Some of the cases are not clearly written, do not describe rechallenges, and the cases do not have a pattern of latency).[9] Total of five cases were reported.[10-13]

Oxaliplatin

Oxaliplatin is a third-generation platinum-based alkylating agent. The chemical structure of oxaliplatin consists of a square planar platinum center. In comparison to cisplatin and carboplatin, it contains a bidentate ligand 1, 2 diaminocyclohexane in place of the two monodentate ammine ligands. It also has a bidentate oxalate group. The cytotoxicity of oxaliplatin is thought to result from the formation of DNA adducts and inhibition of DNA synthesis in cancer cells.[14]

A series of six cases of acute pancreatitis has been reported presumably related to exposure to oxaliplatin which had different gastrointestinal malignancies and were being treated with oxaliplatin in combination with other chemotherapeutic drugs. All other related causes of acute pancreatitis were excluded before implicating oxaliplatin as a possible cause. In all cases, oxaliplatin was stopped and patients had resolution of their signs and symptoms, along with a decrease in serum amylase and lipase levels.[14]

Carboplatin

Carboplatin is a chemotherapy drug used against some forms of cancer (mainly ovarian carcinoma, lung, head, and neck cancers as well as endometrial, esophageal, bladder, breast and cervical; central nervous system or germ cell tumors; osteogenic sarcoma, and as preparation for a stem cell or bone marrow transplant). It was introduced in the late 1980s and has since gained popularity in clinical treatment due to its vastly reduced side-effects compared to its parent compound cisplatin.[15] Carboplatin is a cisplatin analog without significant clinical nephrotoxicity.[16]

One case has been reported for a 60 years old Caucasian female presented with Stage IIA (T2N0M0) estrogen- and progesterone-negative and HER2-positive breast cancer. She was started on an adjuvant chemotherapy regimen of docetaxel, carboplatin, and trastuzumab (TCH). She tolerated the first two cycles of the TCH regimen well. However, 3-4 days after the third and fourth cycles, she developed acute pancreatitis. Elevated pancreatic enzymes and abdominal computed tomography imaging findings

Table 1: Summary of the platinum compounds might induce acute pancreatitis.

Author	Number of cases	Platinum agent	Other agents	Dose	Development of symptoms	Diagnosis criteria	Exclusion of other causes
Singh *et al.*, 2010[17]	1	Carboplatin	*TCH	N/A	3-4 days after the third and fourth cycles	Having any two of the following three features: (i) Abdominal pain characteristic of acute pancreatitis, (ii) serum amylase and/or lipase ≥3 times the upper limit of normal and (iii) CT scan of the abdomen	All other causes of acute pancreatitis, including alcohol, gallstones and other drugs were excluded
Butt *et al.*, 2010[14]	6	Oxaliplatin	FOLFOX and bevacizumab (2), GEMOX (4)	N/A	N/A		
Bunin *et al.*, 1985[10]	1	Cisplatin	-	N/A	N/A		
Tarin *et al.*, 1994[11]	1	Cisplatin	Vindesine	N/A	N/A		
Bilir *et al.*, 2012[12]	1	Cisplatin	Gemcitabine	Cisplatin 100 mg/m^2 IV day I. Gemcitabine 1000 mg/m^2 IV days 1, 8, 15 every 28 days	2nd day of the first dose		
Socinski and Garnick, 1988[13]	2	Cisplatin	Bleomycin, and vinblastine	N/A	7th day of the first cycle		

*Previously reported paclitaxel associated acute pancreatitis. Kumar DM, Sundar S, Vasanthan S. A case of paclitaxel induced pancreatitis. Clin Oncol (R Coll Radiol) 2003;15 (1):35. TCH: Docetaxel, carboplatin, and trastuzumab, CT: Computerized tomography, IV: Intravenously

confirmed the diagnosis of acute pancreatitis. Common causes of pancreatitis were ruled out. Given the time course it was assumed that the chemotherapy was the cause of pancreatitis in our patient. The patient did not receive any further docetaxel and carboplatin chemotherapy but continued on adjuvant trastuzumab alone for a planned duration of 1-year without any recurrence of acute pancreatitis.[17]

SUMMARY OF RESULTS (TABLE 1)

A total of 12 case reports have been published for the last 30 years highlighting the relationship between platinum compound and development of acute pancreatitis in patients with cancer. Six series of acute pancreatitis cases were reported in link with Oxaliplatin; five cases with Cisplatin and only one case with Carboplatin. There was a limited information about the given dose and duration of treatment which might be linked with the development of signs and symptoms of acute pancreatitis. Further clinical and translational studies are needed to confirm this relationship and the synergism with other Antineoplastic agents.

CONCLUSION

Acute pancreatitis induced by platinum compounds is uncommon, but it might have a devastating complications and an additional burden for patients with cancer. The purpose of this review of the literature was to describe the relationship between use of platinum-based antineoplastics and development of acute pancreatitis in patients with cancer. A total of 12 cases were reported between 1985 and 2012; including three platinum compounds; cisplatin, carboplatin, and oxaliplatin. Based on the current literature, it is highly recommended to include baseline risk assessment for acute pancreatitis factors and to consider acute pancreatitis in the differential diagnosis of abdominal pain in patients who have received platinum-based chemotherapy.

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