

Pancreatitis associated with newer classes of antineoplastic therapies

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Newer anticancer therapies including tyrosine kinase inhibitors, immune modulators, immunotherapies, and chemotherapies have been reported to cause acute pancreatitis. This review gathers data from multiple case reports and small case series that associate these agents with pancreatitis. The mechanism of the pancreatitis may be direct toxicity, elevated triglycerides, immune mediated, or injury with direct injection into the liver, pancreas, or its blood supply. As abdominal pain, nausea, vomiting are associated with cancer chemotherapy itself, the diagnosis of acute pancreatitis might be missed.

Patients with advanced malignancies may develop pancreatitis during therapy for their cancer. Acute pancreatitis is inflammation of the pancreas. Common symptoms include abdominal pain, nausea, vomiting, shortness of breath, dehydration. Laboratory evidence of acute pancreatitis includes elevations of the amylase and lipase. Mild pancreatitis occurs when there is no organ dysfunction, moderate pancreatitis is associated with one organ dysfunction, and severe pancreatitis is complicated by multiple organ dysfunction. Hypotension, hypocalcemia, or anemia suggest a more severe course of the pancreatitis. In some instances, the pancreatitis may be an adverse reaction to the therapy being given. However, other causes such as hypercalcemia, hypertriglyceridemia, cholelithiasis, and underlying malignancy must be ruled out before ascribing pancreatitis to a specific drug. To date, two classifications systems have been proposed by Trivedi¹ and Badalov² to evaluate the degree to which a drug is responsible for pancreatitis (Table 1). Furthermore, Naranjo and colleagues have proposed a more general method of assessing the causal relationship between drugs and adverse events.³ The Naranjo algorithm is not specific for pancreatitis. Jones and colleagues⁴ reported that 0.1%-2% of acute pancreatitis cases were owing to drugs. In 2015, they listed the older chemotherapy agents associated with pancreatitis. However, more recently, many new agents have been approved for the management of cancers. The newer classes of antineoplastic agents including proteasome inhibitors, immune-modulating agents, tyrosine kinase

inhibitors, monoclonal antibodies against programmed cell death-1 (PD-1) and its ligand PD-L1 and antibody-toxin conjugates are now associated with acute pancreatitis.

Methods

We conducted a search in PubMed, Google Scholar, and Micromedex for pancreatitis related to antineoplastic agents, including proteasome inhibitors, immune checkpoint inhibitors, monoclonal antibodies, immune-modulating agents, drug-induced pancreatitis. Terms used for the searches included each specific agent and *pancreatitis*, *immunotherapy* and *pancreatitis*, *tyrosine kinase inhibitors* and *pancreatitis*, *auto immune pancreatitis*, and *toxicities of molecular target therapies*. Reference lists from the identified manuscripts were reviewed for further studies of pancreatitis as a result of antineoplastic therapy. The most recent search date was February 15, 2017.

The degree to which each agent was associated with inducing pancreatitis was evaluated using the Badalov classification system² in addition to the Naranjo Adverse Drug Reaction (ADR) Probability Scale.³ The Naranjo scale consists of 10 questions with values assigned to each answer. Total scores range from -4 to 13, where 13-9 indicates the reaction is considered definitely attributable to the drug; 8-5, probably attributable; 4-1, possibly attributable; and ≤0, doubtful if attributable.

A total of 67 manuscripts and abstracts were identified. Four manuscripts and 3 abstracts were excluded because they had insufficient information about possible pancreatitis or there was a presence of

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TABLE 1 Classification systems for drug-induced pancreatitis

Trivedi ¹	Badalov ²
Class I At least 20 reported cases of acute pancreatitis At least 1 case with positive rechallenge	Class Ia At least 1 case report with positive rechallenge, excluding all other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs Class Ib At least 1 case report with positive rechallenge; however, other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs were not ruled out
Class II >10 but <20 reported cases of acute pancreatitis with or without positive rechallenge	Class II As least 2 cases in the literature Consistent latency (≥75% of cases)
Class III All medications implicated in pancreatitis, ie, Class I, Class II, and those with ≤10 reported cases or unpublished reports in pharmaceutical or FDA files	Class III At least 2 cases in the literature No consistent latency among cases No rechallenge Class IV Drugs not fitting into the previously described classes, single case report published in medical literature, without rechallenge

FDA, US Food and Drug Administration;

multiple other agents or conditions that might have caused pancreatitis. In total, 60 publications met inclusion criteria and were evaluated.

Results

Immune checkpoint inhibitors

In a review of toxicities of anti-programmed cell death-1 (PD-1) therapy, pancreatitis was reported to occur in about 1.8% of patients who received nivolumab or pembrolizumab.⁵ The 9 patients with pancreatitis attributed to an immune etiology were treated with corticosteroids. Pancreatitis was grade 2 in 3 patients (1.5-2 times upper limit of normal [ULN]), grade 3 in 4 patients (>2-5 ULN), and grade 4 (>5 ULN) in 2 patients.

In asymptomatic individuals, pancreatitis has been detected on a positron-emission tomography-computed tomography (CT) scan after anti-PD-1 therapy.⁵ By contrast, there was a case report of a patient treated with nivolumab for lung cancer who developed anorexia, vomiting, and back pain on day 18 of therapy with an elevation of the amylase and lipase levels, but a negative CT.⁶ Later the patient developed a swollen pancreas on CT. Autoimmune

pancreatitis comes in two forms. The most common relates to elevated levels of immunoglobulin G4 (IgG4; normal, 135 mg/dL ULN)⁷ The mechanism of immune pancreatitis associated with anti-PD-1 therapy is unknown.

Ipilimumab (an anti-CTLA4 antibody) has been approved by the US Food and Drug Administration (FDA) for the treatment of melanoma. Pancreatitis occurred in 1 patient in a phase 1 trial in pediatric patients.⁹ In a summary of 14 phase 1-3 trials of ipilimumab in advanced melanoma, pancreatitis was reported in fewer than 1% of the patients.¹⁰ In management guidelines for therapy with ipilimumab, pancreatitis may present as an asymptomatic increase in the levels of amylase and lipase, or with fevers, malaise, or abdominal pain. Oral prednisone or dexamethasone were given for the immune pancreatitis, but the decline in enzymes was slow, often taking months.¹¹ In a preclinical model of autoimmune pancreatitis due to the blocking of CTLA4, there was suppression of regulatory T-cell function. The autoimmune pancreatitis responded to cyclosporin or rapamycin but there are no clinical data for these agents.¹² The anti-PD-L1 agent atezolizumab has been associated with acute pancreatitis in 2 of 1,978 patients (0.1%).¹³ A review by Champiat and colleagues on dysimmune toxicities related to immune checkpoint inhibitors includes pancreatitis as an autoimmune complication of such therapies.¹⁴

Blinatumomab is an anti-CD19-directed CD3 T-cell engager that has been approved by the FDA for refractory B-cell acute lymphoblastic leukemia. In August 2016, the maker of the drug, Amgen, advised hematologists and oncologists that since February 2016, 10 patients out of more than 2,000 treated with blinatumomab had developed pancreatitis.¹⁵ Other medications the patients were receiving such as high-dose steroids might have caused or contributed to the pancreatitis. In one case, the pancreatitis improved with stopping blinatumomab but worsened with re-challenge. It is possible that the mechanism of the associated pancreatitis relates to a change in immune checkpoint inhibition. CD19-positive, CD24-high, CD27-positive regulatory B cells are decreased in autoimmune pancreatitis.¹⁶ Treatment with blinatumomab may decrease the CD19-positive cells.

Molecularly targeted agents, including TKIs

Molecularly targeted agents such as tyrosine kinase inhibitors (TKIs) or other kinase inhibitors have been associated with pancreatitis.^{17,18} In a retrospective study by Tiruman and colleagues,¹⁹ the investigators found 91 patients with pancreatitis on imaging, of whom 15 were receiving molecularly target drugs. The pancreatitis was asymptomatic in 2 patients, but 13 had abdominal pain, many with nausea. Four of the patients also had gallstones, but the drug was deemed to be the cause of the pancreatitis. In 4 of the 9 patients in whom a rechallenge was done with the TKI, the pancreatitis relapsed. The pancreatitis resolved in 14 of the

15 patients; 1 patient died because of progressive cancer before the pancreatitis resolved. The pancreatitis was mild, 7 of the 15 patients had normal pancreatic enzymes and the pancreatitis was diagnosed by radiology.

Ghatlia and colleagues¹⁷ performed a meta-analysis of trials of TKI. They found 9 cases of pancreatitis in patients on sunitinib therapy. Of those, 4 patients were on sunitinib alone, and 5 were on other chemotherapy agents in combination with sunitinib. Eight cases of pancreatitis due to sorafenib were found. Three of the patients were on sorafenib alone, and 5 were on other chemotherapy including 1 on transcatheter embolization (TACE). Three cases of pancreatitis were associated with vandetanib; 2 of those patients had other concurrent chemotherapy. One case of axitinib induced pancreatitis was described.

Pancreatitis was reported in the phase 1 trials of sorafenib and sunitinib. In all, 3 of 69 patients treated with sorafenib had grade 3 pancreatitis and asymptomatic elevations of amylase and lipase levels were present in about 5% of patients receiving sunitinib.^{18,19}

Other TKIs associated with pancreatitis include pazopanib,^{20,21} axitinib,²² and nilotinib.²³ Pezzilli and colleagues²⁴ described 5 patients with pancreatitis on sorafenib, 3 on sunitinib, 6 on nilotinib. It is possible that some of these cases appeared in other reviews. Ibrutinib, an inhibitor of Bruton's tyrosine kinase, caused a single case of pancreatitis in 9 patients.²⁵

Vemurafenib, a BRAF kinase inhibitor, was associated with pancreatitis in one case. In this case, the pancreatitis resolved on stopping the medication but recurred when vemurafenib rechallenge was attempted.²⁶ There is a report of dabrafenib being associated with pancreatitis in 1 patient.²⁷

Agents that inhibit the TKIs associated with BCR-ABL in chronic myelogenous leukemia are associated with acute pancreatitis. Imatinib-induced pancreatitis was reported in a small number of cases.²⁸ Nilotinib has caused amylase/lipase elevations with and without symptomatic pancreatitis.^{29,30} Ponatinib, an inhibitor of BCR-ABL tyrosine kinase, is associated with pancreatitis.³¹ Pancreatitis occurred in 11 of 81 patients treated with ponatinib, and in 8 patients it was described as serious. Further elevation of amylase or lipase levels without clinical pancreatitis was noted in 7 other patients.

Proteasome inhibitors

In 2010, Elouni and colleagues³² reported a case of IV bortezomib-induced pancreatitis, which recurred on rechallenge with bortezomib. This same patient was also reported in an abstract in 2009.³³ In 2009, there was an editorial comment which was added to the end of the abstract that the World Health Organization Adverse Drug Reaction database had 11 reports of bortezomib associated pancreatitis. Talamo and colleagues³⁴ reported a case of bortezomib-induced pancreatitis due to bortezomib that had been administered sub-

cutaneously. At that time, they also summarized 7 previous reports of bortezomib-associated pancreatitis. The mechanism of bortezomib-induced pancreatitis is not known.³⁵⁻³⁷

Fotouh and colleagues reported a patient with myeloma who had elevated triglyceride levels after bortezomib therapy.³⁸ In one case of bortezomib-associated pancreatitis, the patient had an elevated triglyceride level, but it was not extremely high.³⁹ Multiple myeloma itself may be associated with hyperlipidemia but only rarely.⁴⁰ Gozetti and colleagues reported a patient who developed hyperlipidemia after two courses of bortezomib;⁴¹ stopping bisphosphonates may be associated with a rise in triglycerides. There was one case of carfilzomib causing pancreatitis during a phase 1 trial.⁴²

Older chemotherapy agents

Reviews of drug-induced pancreatitis have listed many chemotherapy agents which may cause pancreatitis.^{1,43} The agent most frequently associated with acute pancreatitis has been asparaginase,⁴⁴ with 2%-16% of patients undergoing asparaginase therapy developing pancreatitis. Asparaginase-related pancreatitis is grade 3 or 4 in 5%-10% of patients, and recurs in 63% of patients on rechallenge. Other chemotherapy agents associated with pancreatitis include: mercaptopurine, cytosine arabinoside, cisplatin, interferon alfa-2b, doxorubicin, tamoxifen, gefitinib, vinorelbine, oxaliplatin, levamisole, methotrexate, azathioprine, 5-fluorouracil, capecitabine, ifosfamide, paclitaxel, and all-trans retinoic acid.

Oxaliplatin carries a 0.1%-2% incidence of drug-induced pancreatitis. In one series of 6 patients, cessation of the agent allowed for resolution of symptoms and decrease in serum lipase and amylase levels.⁴⁵ With capecitabine there are 2 case reports of pancreatitis.⁴⁶ Cases of pancreatitis associated with trifluridine or tipiracil were not present in the literature.

Thalidomide caused severe pancreatitis in a patient when it was used to treat chronic graft-versus-host disease.⁴⁷ This patient suffered recurrent pancreatitis on retreatment with the thalidomide. The authors further referenced two other suspected cases of thalidomide-induced, acute pancreatitis. However, in view of the extensive use of thalidomide for multiple myeloma before the development of lenalidomide, thalidomide-associated pancreatitis would be <1% of patients.

Agents that cause hypertriglyceridemia may cause pancreatitis. This mechanism has been reported as the cause of pancreatitis for everolimus⁴⁸ and tamoxifen.^{49,50-52} Everolimus causes elevated triglycerides in 30%-50% of patients. There are case reports and a review of tamoxifen-associated pancreatitis caused by elevated triglycerides.⁵² There has also been a case of temsirolimus-associated pancreatitis,⁵³ another agent that elevates triglycerides.

Pancreatitis associated with hepatic embolization or hyperthermic intraperitoneal chemotherapy

TACE leads to symptomatic acute pancreatitis in 0.4%-2%

of patients, but nonselective TACE (into the hepatic artery and not just feeder vessels), may lead to elevated amylase levels in 15%-40% of patients.⁵⁴⁻⁵⁶ The risk of pancreatitis would depend on which chemotherapy drug is being infused into the liver. It would also be greater if the chemotherapy has to be infused into a larger part of the liver than into a small portion of the liver. In one patient, severe pancreatitis secondary to TACE occurred after two previous embolizations; prior embolization may have led to occlusion of the previously infused vessels.⁵⁷ Radioembolization with 90Y microspheres was associated with one case of pancreatitis in 112 consecutive patients.⁵⁸ The postembolization syndrome in the first 24 hours after the procedure may involve fever, abdominal pain, nausea, and vomiting due to acute pancreatitis in some instances.

Acute pancreatitis has also been described as a complication of hyperthermic intraperitoneal chemotherapy (HIPEC).^{59,60} Two of 13 patients receiving HIPEC for gastric cancer developed pancreatitis.⁵⁹ In 25 patients with colon cancer who were treated with HIPEC, 1 patient had pancreatitis.⁶⁰

Antibody-drug conjugates

Muzaffar and colleagues reported a patient with acute pancreatitis 3 days after starting therapy with ado-trastuzumab emtansine.⁶¹ Urru and colleagues⁶² reported a patient who developed acute pancreatitis after brentuximab vedotin therapy. Ghandi and colleagues⁶³ identified 2 cases of fatal acute pancreatitis with brentuximab vedotin and 6 cases of nonfatal pancreatitis. Two of the nonfatal patients were rechallenged, and 1 developed recurrent pancreatitis. Because abdominal pain may occur in up to 18% of patients receiving brentuximab vedotin, the incidence of pancreatitis may be underestimated with this agent.⁶⁴

In Table 2, ado-trastuzumab emtansine and brentuximab vedotin are listed with incidence and level of association given by the Baldavo² and Naranjo.³ With greater awareness, the incidence of pancreatitis associated with these agents may rise or fall as more data is accumulated. In many instances, there are insufficient numbers of reported cases or insufficient information in single-case reports to complete the entire table.

Discussion

Acute pancreatitis is an uncommon complication of tyrosine kinase inhibitors, other kinase inhibitors, proteasome inhibitors, monoclonal antibody-drug conjugates and anti-PD-1 immunotherapies. As nausea, abdominal pain, emesis are common in patients with cancer on antineoplastic therapy, some patients may have acute pancreatitis which is undiagnosed. It is not clear whether a patient with pancreatitis secondary to a TKI can be safely switched to a different TKI. As more molecularly targeted agents and more monoclonal antibodies targeting PD-L1 and PD-1 are

under development, screening for amylase and lipase levels during phase 1/2 testing may prove helpful.

The natural history of cancer-drug-associated pancreatitis may depend on which agent is the cause. Although there are descriptions of the course of autoimmune pancreatitis, these studies have not included pancreatitis associated with anti-PD-L1 or -PD-1 therapies.⁶⁵ It is possible that once an autoimmune pancreatitis has developed, simply stopping the inciting anti-PD-L1 or -PD-1 antibody may not lead to immediate resolution. Therapy with combined immune checkpoint blockade agents (eg, nivolumab and ipilimumab) may cause a higher incidence of pancreatitis than therapy with a single agent.⁶⁶

In a report of 119 patients with melanoma who were treated with nivolumab and ipilimumab, there were 2 cases of acute pancreatitis, though 20% of patients had a grade 3 or higher amylase level, and just over 6% had a grade 3 or higher lipase.⁶⁷ Stopping this type of immunotherapy early for grade 1,2, or 3 rises in pancreatic enzymes might prevent symptomatic pancreatitis from developing, but would stop potentially curative therapy for many patients who would have never developed clinically serious pancreatitis. Patients who suffer immune toxicities with anti-PD-1 therapies may be more apt to obtain some clinical benefit. The development of immune-related toxicities in patients treated with ipilimumab (an anti CTLA4 antibody) seemed to correlate the tumor regression.⁶⁸ This has also been suggested by the fact that the development of vitiligo correlates with clinical response in melanoma patients treated with nivolumab.⁶⁹ Although clinically significant pancreatitis might be averted by stopping immune therapies earlier, stopping before it is deemed necessary might prevent cancer patients from receiving life-prolonging therapy.

Acute pancreatitis in general is severe in about 25% of cases and is associated with a significant risk of death. Scoring systems such as Ranson criteria and Apache 2 are used to assess the severity of pancreatitis although their utility is debated.⁷⁰ Asparaginase is the chemotherapy agent most frequently associated with pancreatitis. It has been used to treat acute lymphoblastic leukemia for more than 30 years. This allowed for a study of 5,185 children and young adults who received asparaginase to determine what clinical factors and genomic factors were associated with the development of acute pancreatitis in 117 individuals.⁷¹ Further information gathered from programs such as the FDA and the adverse drug reaction program at Northwestern University in Chicago, coupled with the publication of other cases of pancreatitis associated with newer cancer agents may provide more insight into the mechanism causing pancreatitis due to a specific agent. With more cases being published, it may also become possible to determine if there are specific predisposing factors based on the clearance or metabolism of the offending agent or any genetic predisposition for drug-related pancreatitis.

TABLE 2 Pancreatitis secondary to new anticancer therapy using Badalov criteria and Naranjo algorithm

Agent	Incidence	Level of evidence		Notes
		Badalov	Naranjo score (n)	
Immunotherapy				
Nivolumab	cases/total patients (<1%)	Class 2	Probable (1)	
Ipilimumab/nivolumab	cases/total patients (6%)	Class 2	ID	
Pembrolizumab	cases/total patients (<1%)	Class 2	ID	
Ipilimumab	cases/total patients (1.3%)	Class 2	ID	
Blinatumomab	10/>2,000	Class 3	ID	
Atezolizumab	2/1,978 (<1%)	Class 4	ID	
Tyrosine kinase inhibitors				
Sunitinib	cases/total patients (4.3%)	Class 2	ID	No rechallenges reported
Sorafenib	cases/total patients (<1%)	Class 1	ID	
Pazopanib	cases/total patients (<1%)	Class 1	Probable (4)	
Nilotinib	8 case reports	Class 1	Probable (1)	
Axitinib	ND	Class 4	Probable (1)	
Ibrutinib	ND	Class 4	ID	
Vemurafinib	cases/total patients (<1%)	Class 1	Definite (1)	1 case with rechallenge
Dabrafenib	cases/total patients (<10%)	Class 4	ID	
Ponatinib	11/81 (14%)	Class 2	ID	
Proteasome inhibitors				
Bortezomib	cases/total patients (<1%)	Class 1	Possible (2) Probable (4)	3/6 rechallenge
Carfilzomib	1 case report	Class 4	ID	
Other				
Oxaliplatin	cases/total patients (<1%)	Class 2	Probable (2)	No rechallenge
Thalidomide	1 case report	Class 1	Probable (1)	
Everolimus	ND	Class 4	Probable (1)	
Tamoxifen	5 case reports	Class 4	Probable (1)	
Temsirolimus		Class 4	Possible (1)	
TACE		Class 2	ID	
Radioembolization	3/193 (2%)	Class 3	ID	
HIPEC	2 case reports	Class 4	ID	
Ado-trastuzumab emtansine	1 case report	Class 4	Probable (1)	
Brentuzimab vendotin	8 case reports	Class 1		2 rechallenge; 1 recurrence

HIPEC, hyperthermic intraperitoneal chemotherapy; ID, insufficient data; ND, not documented; TACE, transcatheter arterial chemoembolization

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