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Clinical case

Pancreatitis during therapy of acute myeloid leukemia: Cytarabine related?*

L. H. McGrail,[1] L. H. Sehn,[2] R. B. Weiss,[1] M. R. Robson,[1] J. H. Antin[2] & J. C. Byrd[1,3]

[1]*Walter Reed Army Medical Center, Washington DC and Uniformed Services and Health Science University, Bethesda, MD;* [2]*Brigham and Women's Hospital, Boston, MA;* [3]*Division of Hematologic Malignancies, Johns Hopkins Oncology Center, Baltimore, MD, USA*

Summary

Background: Acute pancreatitis in acute myeloid leukemia (AML) has been rarely associated with cytarabine therapy. This report attempts to characterize this toxicity.

Patients and methods: Criteria for pancreatitis was prospectively defined. Seven patients with pancreatitis were identified from an AML database and a clinical study at two tertiary care centers (n = 134). Their records were retrospectively reviewed.

Results: Seven patients with pancreatitis complicating AML therapy were identified. Median age was 36 (range 25–73) years. Median amylase was 184 (range 77–552) U/l and median lipase was 1026 (range 630–6087) U/l. The patients had received high dose bolus cytarabine (2 g/m^2 i.v. bolus every 12 hours; n = 2), and continuous infusion cytarabine followed by high-dose cytarabine (100 mg/m^2 i.v. CI days 1–7 then 2 g/m^2 i.v. bolus every 12 hours days 8–10; n = 2), or standard dose continuous infusion cytarabine (200 mg/m^2/d; n = 3) prior to developing pancreatitis. Pancreatitis occurred at a median of 10 days following day one of cytarabine administration with resolution at a median of 11 days after initial diagnosis. Six patients did not suffer major complications. One patient died of causes unrelated to pancreatitis. Five of six patients was rechallenged and all remained free of pancreatitis. One patient subsequently did develop pancreatitis on a later rechallenge.

Conclusions: Pancreatitis in the setting of AML therapy may be an infrequent and self-limited toxicity of cytarabine. A schedule dependent toxicity with cytarabine was not identified.

Key words: acute myeloid leukemia, cytarabine, pancreatitis

Introduction

Cytarabine is the single most effective agent in the treatment of AML. While effective, it has a well characterized toxicity profile including myelosuppresion, cutaneous rash, drug-related pulmonary edema, mucositis, neurotoxicity, and neutrophilic hydranitis [1–6]. Rare reports of cytarabine-associated pancreatitis have also been described but lack sufficient data regarding the frequency of occurance and consequence of cytarabine re-challenge [7–10].

Despite the fact that the majority of these established extramedullary toxicities occur more frequently with increased dose intensity, sequential cytarabine treatment at high intensity is an acceptable curative therapy for a subset of young patients having good [t(8;21) and inv(16)] or intermediate [normal] karyotype [11]. Additionally despite a clear consensus on appropriate post-induction therapy in elderly AML patients, cytarabine is commonly utilized by many for this purpose. Given cytarabine's expanded clinical efficacy, it is increasingly important to better define its toxicity profile. The clinical features and outcome with rechallenge of even rare toxicities such as pancreatitis associated with cytarabine is of interest to the practicing oncologist.

This report describes the clinical characterisitcs and outcome of what we believe to be the largest cohort of patients developing pancreatitis following cytarabine administration and reviews the literature experience on this topic.

Patients and methods

Definition of pancreatitis

The definition of pancreatitis was determined prospectively by the investigators. Requirements included physical, laboratory and radiographic data. All patients had to have abdominal pain, and radiographic data suggestive of pancreatitis or amylase and/or lipase levels three times the upper limit of normal [4, 12–15]. The range of normal values for Brigham and Women's Hospital are amylase 31–90 U/l and lipase 7–65 U/l and for Walter Reed Army Medical Center the values are amylase 30–110 U/l and lipase 5–90 U/l.

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Table 1. Patient characteristics.

Pt	Age/sex	Dx	FAB	Time of pancreatitis	Dose of ara-C	Number of prior ara-C Rx	Other risk factors for pancreatitis	Abdominal pain	X-ray findings	Pk amylase/ lipase	Major complications	Days until pancreatitis resolution
A	25/F	AML	M3	Induction	SDAC + HDAC	0	No	Yes	Yes	367/1954	No	11
B	36/M	AML	M4	Induction	SDAC + HDAC	0	No	Yes	No	358/1399	No	15
C	36/F	AML	M5	Induction	SDAC	0	No	Yes	No	122/630	No	8
D	73/F	CML-B	NA	Induction	HDAC	0	No	Yes	No	116/725	No	NA
E	26/M	AML	M0	Relapse	HDAC	1	No	Yes	Yes	184/726	No	35
F	29/F	AML	M3	Induction	SDAC	0	No	Yes	No	176/907	No	11
G	36/M	AML	M5	Induction	SDAC	0	No	Yes	Yes	77/1026	No	10
				Re-induction	IDAC	2	No	Yes	Yes	552/6087	No	32

Abbreviations: NA – not applicable; Dx – diagnosis; ara-C – cytarabine; AML – acute myeloid leukemia; CML-B – chronic myelogenous leukemia in blast crisis; SDAC – cytarabine 200 mg/m^2/day by infusion × 7 days; HDAC – 2–3 g/m^2 i.v bolus Q12 hours × 3–7 days; IDAC – cytarabine 500 mg/m^2/day on 1–3 and 7–10 of Rx.

Patient selection

The cases of pancreatitis were identified from an AML database at Walter Reed Army Medical Center 1990–1995 (n = 44) and from a clinical study performed at Brigham and Women's Hospital 1987–1993 (n = 93).

Data collection

The respective hospital and outpatient records of those patients fulfilling the criteria for pancreatitis were retrospectively reviewed (n = 7). Risk factors for other causes of pancreatitis such as: biliary disease, alcohol use, hypertriglyceridemia, hypercalcemia, prior history of pancreatitis, and prior L-asparaginase exposure were evaluated [7, 12–15]. In addition the following data was assessed: medications administered prior to the development of pancreatitis, sex, age, race, cytarabine administration schedule, temporal relationship to cytarabine therapy, radiographic studies, treatment modalities, complications, and outcome with rechallenge.

Results

Pre-pancreatitis characteristics

Of the 137 patients, seven (5.1%) had clinically diagnosed pancreatitis complicating the therapy of AML. Four patients were female and three were male. One patient was African-American and the others were Caucasian. The median age was 36, with a range of 25–73 years. Six patients had AML and one patient had CML (chronic myeloid leukemia) in myeloid blast crisis. Six patients developed pancreatitis during initial induction with cytarabine, and one patient was in relapse. At the time pancreatitis was diagnosed patients had received high dose bolus cytarabine (2 g/m^2 i.v. bolus every 12 hours; n = 2), continuous infusion cytarabine followed by three days of high-dose (100 mg/m^2 i.v. CI days 1–7 then 2 g/m^2 i.v. bolus every 12 hours days 8–10; n = 2) standard dose continuous infusion cyarabine (200 mg/m^2 i.v. CI QD × 7 days; n = 3). No patients in this cohort had a history of L-aspariginase exposure or alcohol abuse. All patients had normal calcium levels. Four patients had normal triglyceride levels, one had a mildly elevated value and two patients did not have levels checked at the time pancreatitis was diagnosed.

Clinical features of pancreatitis

All patients suffered from abdominal pain and had amylase or lipase values at least three times the upper level of normal. The median amylase was 184 (range 77–552) U/l and median lipase was 1026 (range 630–6087) U/l. Pancreatitis occurred at a median of 10 days following the first day of cytarabine administration. Six patients were receiving antibiotics and five patients were receiving amphotericin B (Fungizone Intravenous) at the time pancreatitis was diagnosed. However, none of the medications which these patients received are known to be associated with pancreatitis [16]. Additionally six of seven patients had right upper quadrant ultrasounds which failed to demonstrate evidence of biliary or gallbladder disease. All patients had radiographs during the workup of abdominal pain and three were found to be consistent with pancreatitis. These included two computed axial topography scans showing peripancreatic inflammation and edema, and one abdominal radiograph showing a sentinel loop (Table 1).

Outcome and rechallenge

All patients received aggressive supportive care for pancreatitis, and four patients required total parenteral nutrition. In six of seven patients pancreatitis spontaneously resolved without chronic pain or pseudocyst, and complete resolution was noted at a median of 11 days after initial diagnosis. One patient with CML in blast crisis died as a consequence of disease progression without clinical sequeale of pancreatitis. None of the patients suffered secondary complications related to pancreatitis.

Of the seven patients, five continued to received cyta-

Table 2. Cycles of cytarabine received after resolution of cytarabine associated pancreatitis.

Patient number	DAC	Inter-DAC	HiDAC	Recurrent pancreatitis
1	2	0	2	No
2	2	0	1	No
3	0	4	1	No
4	_[a]	_[a]	_[a]	_[a]
5	_[b]	_[b]	_[b]	_[b]
6	1	0	2	No
7	0	1	1	Yes

Key: DAC = 100–200 mg/m^2
Inter-DAC = 400–500 mg/m^2
HiDAC = 2–3 mg/m^2

[a] Patient died prior to rechallenge.

[b] Patient received bone marrow transplant without rechallenge.

rabine after resolution of pancreatitis, one died prior to receiving another dose of cytarabine and one patient went to stem cell transplant without receiving further cytarabine. Of the five patients who were rechallenged, each received varying doses of cytarabine (Table 2), and only one developed recurrent pancreatitis. As was previously described, this patient initially developed pancreatitis during induction and then was consolidated with high-dose bolus cytarabine (3 g/m^2 i.v. bolus for three doses) without recurrent pancreatitis [9]. However, in preparation for a bone marrrow transplant he received a regimen which included cytarabine 500 mg/m^2 continuous infusion and with this he did develop recurrent pancreatitis. He was treated aggressively with supportive care to include analgesia and transvenous parenteral nutrition, and did well. He subsequently proceeded to allogenic transplant.

Discussion

To our knowledge this report describes the largest cohort of patients to develop cytarabine associated pancreatitis during AML therapy. There are few previous reports to support a causal relationship between cytarabine and pancreatitis. Altman et al. reported a patient with ALL who developed pancreatitis while receiving cytarabine on two separate administrations and who had previously been exposed to L-asparaginase. He was receiving maintenance therapy with cytarabine (160 mg by continuous infusion) when pancreatitis was first diagnosed. This episode resolved spontaneously within two days but recurred a year later when he received another course of cytarabine. As no previous reports of cytarabine related pancreatitis had been described and no pre-clinical data suggested an etiology of such toxicity the authors concluded that pancreatitis complicating cytarabine therapy was related to previous L-asparaginase exposure. Additionally they postulated that prior treatment with L-asparaginase, a drug well known to cause pancreatitis, may some how render the pancreas more susceptible to damage by cytarabine [16].

Seimers et al. subsequently described pancreatitis following high dose cytarabine administration in 2 of 30 patients with leukemia or lymphoma. Pancreatitis resolved within 22–25 days from the initiation of high-dose cytarabine without clinical sequelae. Seimers et al. concluded that there was an association between pancreatitis and high-dose cytarabine, however, they could not prove a definitive causal relationship.

Combining our cohort of seven patients and a review of the literature as outlined above, a temporal relationship between pancreatitis and cytarabine is further substantiated. However a definitive causal relationship between the two is difficult to prove given multiple confounding factors to include severity of underlying illness, comorbidities, and lack of data regarding possible infectious etiologies.

We observed that six of seven patients in this cohort developed pancreatitis during induction therapy suggesting that initial exposure to cytarabine may be more toxic to the pancreas. The clinical consequence of the cytarabine related pancreatitis was limited, as six of seven patients improved with supportive measures and one died of causes unrelated to pancreatitis. Most importantly, five of the six patients who were rechallenged did not develop recurrent pancreatitis, and the one patient who did, tolerated this repeat episode well. Given the small number of patients, firm clinical decisions regarding safty of rechallenge can not be made. This study was unable to demonstrate a dose dependent or schedule dependent toxicity, as was postulated in an earlier case report from our institution [9].

This retrospective analysis thus raises several interesting questions. Given that we reviewed only those cases in which elevated pancreatic enzymes were discovered in response to evaluation of clinical abdominal pain, we are unable to compare our cohort with those patients who did not have enzyme levels checked for lack of clinical cause. It could be postulated that cytarabine may cause a chemical pancreatitis and that there may be underlying predisposing factors which cause a small subset of patients to develop clinical pancreatitis. Such predisposing factors could be; age, performance status, comorbidities, concurrent infection, coadministration of an antibiotic or antifungal medication, or underlying malignancy. These retrospective findings have prompted a prospective evaluation of this at our institution.

We conclude that pancreatitis may be an infrequent toxicity of cytarabine administration. There appears to be no schedule or dose dependent toxicity, and pancreatitis in this setting is self-limited. This study demonstrates that readmistration of cytarabine to patients with AML and a history of treatment related pancreatitis may be safe, however given this small number of patients and the limitations of retrospective analysis the results of a larger prospective study is needed to confirm this observation.

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Correspondence to:
J. C. Byrd, MD
Hematology-Oncology Service, Ward 78
Walter Reed Army Medical Center
Washington, DC 20307
USA