Octreotide Therapy in Asparaginase-Associated Pancreatitis in Childhood Acute Lymphoblastic Leukemia

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Little is known about octreotide therapy in asparaginase-associated pancreatitis (AAP) in children. Of the 59 children with acute lymphoblastic leukemia (ALL) receiving *E. coli* L-asparaginase, 5 patients (8.5%) developed AAP. Octreotide was administered to four patients. Clinical and laboratory improvement were evident after octreotide therapy. There were no deaths and no severe adverse side effects were noted. No pseudocysts were detected; however, two of the four patients developed diabetes. One child without octreotide treatment developed chronic pancreatitis and pseudocyst. We conclude that octreotide therapy appears to be safe and potentially beneficial in the management of AAP in children. Pediatr Blood Cancer 2008;51:824–825.

Key words: acute lymphoblastic leukemia; L-asparaginase; octreotide; pancreatitis

INTRODUCTION

Asparaginase is an important anticancer drug in childhood acute lymphoblastic leukemia (ALL). However, the toxicity of asparginase is considerable and can lead to gastrointestinal disorders, coagulopathy, bone marrow dysfunction, hepatotoxicity, hyperglycemia, central nervous system disorders, and hypersensitivity reaction [1,2]. Asparaginase-associated pancreatitis (AAP) in children is not common but is a potential lethal complication [3].

Somatostatin suppresses pancreatic enzyme secretion and pancreatic islet release of insulin and glucagons [4]. Octreotide, a synthetic somatostatin analog, has been found to be effective for the treatment of acute pancreatitis in adults. However, little is known about its use in pediatric patients, especially in those with AAP.

MATERIALS AND METHODS

A total of 110 children (<18 years) in whom ALL was newly diagnosed from January 1996 and December 2007 at our medical center were enrolled in the study. Patients were stratified into three groups according to the Taiwan Pediatric Oncology Group (TPOG) protocol: standard-risk (SR), high-risk (HR), and very-high-risk (VHR) groups [5]. These patients were then treated according to the TPOG-ALL protocol [5]. *E. coli* L-asparaginase (Kyowa Hako Kogyo, Tokyo, Japan) was included in the chemotherapy protocols in the HR group and VHR group.

Pancreatitis was diagnosed based on typical symptoms and signs, biochemical parameters (serum amylase and lipase), hepatopancreatic ultrasonography, and abdominal CT scan. Management included discontinuation of chemotherapy, fluid resuscitation, nasogastric tube decompression, bowel rest, analgesics, and administration of systemic broad-spectrum antibiotics. Octreotide (Sandoz, Basle, Switzerland) was administered at an initial dose of 7.2 μg/kg/day by continuous intravenous infusion. When abdominal pain improved, octreotide was tapered to 3.6 μg/kg/day for 2 days and then to 1.8 μg/kg/day for the next 2 days. Octreotide was then discontinued. When pancreatitis resolved, chemotherapy was restarted and *E. coli* L-asparaginase was replaced with methotrexate.

RESULTS

Of the 110 patients with ALL, 51 patients (46%) were stratified into the SR group, 37 patients (34%) into the HR group and 22 patients (20%) into the VHR group. Of the 59 patients that received *E. coli* L-asparaginase in the chemotherapy protocols in the HR and VHR groups, 5 patients (8.5%) developed acute pancreatitis. The median onset of AAP after the last dose of L-asparaginase was 5.2 days (range, 2–14 days) and the median accumulated dose of L-asparaginase was 73,750 IU (range 30,000–155,000 IU).

Octreotide was administered i.v. to four of the five patients with AAP. After octreotide had been given to the four patients, the median duration of abdominal pain was 5 days (range 4–6 days). The median duration of abnormally elevated amylase and lipase was 7.5 days (range 4–11 days). The median duration of administration of octreotide was 5.3 days (range 4–7 days). After discontinuing octreotide, no abdominal pain and no elevated levels of amylase or lipase were observed. Furthermore, there were no severe adverse side effects associated with the use of octreotide. There was no pancreatitis-associated mortality among the 4 children receiving octreotide treatment. Insulin-dependent diabetes was diagnosed in two of the four patients after AAP. Leukemia was still in remission after AAP resolved and they restarted chemotherapy. At present, all four patients are alive and leukemia free.

The patient with AAP who did not receive octreotide treatment developed chronic pancreatitis and pseudocyst. Chemotherapy was delayed because of chronic pancreatitis and the patient died due to leukemia relapse. The characteristics of these five patients with AAP are shown in Table I.

DISCUSSION

ALL is the most common malignancy in children. Although asparaginase is effective in treating ALL, patients who receive

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TABLE I. The Characteristics of Patients With Asparaginase-Associated Pancreatitis

	Age (year)/ gender	Duration of octreotide treatment (days)	Duration of abdominal pain (days)	Duration of elevated amylase and lipase (days)	Complications	Outcome
1	8/M	6	5	10	DM	Alive, in remission
2	12/F	7	6	11	DM	Alive, in remission
3	13/F	4	4	4	Nil	Alive, in remission
4	3/F	4	5	5	Nil	Alive, in remission
5	16/M	Nil	268	278	Chronic pancreatitis; pseudocyst	Died to ALL relapse

M, male; F, female; DM, diabetes mellitus; ALL, acute lymphoblastic leukemia.

this antileukemic agent are at risk of developing pancreatitis. In the present study, the incidence of AAP was 8.5%, which is consistent with the incidence reported in previous studies [6–8]. Some cases of AAP are fatal [3], although the mechanism of AAP is still unclear and the occurrence of AAP is unpredictable [9]. Early diagnosis and treatment of this complication are important.

Other than supportive care, there is no standard therapy for pancreatitis. Most human clinical studies that have shown that somatostatin and its analog octreotide may be beneficial in the treatment of acute pancreatitis were conducted in adults [10–13]; few studies of the beneficial effects have been conducted in children [14,15]. In our study, clinical and laboratory improvement were evident after octreotide therapy in children with AAP. Furthermore, there were no significant adverse effects associated with octreotide treatment. Therefore, octreotide appears to be effective and safe in children with AAP.

One of the patients who developed AAP did not receive octreotide therapy because AAP was diagnosed 9 years ago and we were not familiar with octreotide treatment at that time. AAP in that patient resulted in chronic pancreatitis and pseudocyst. Chemotherapy was discontinued for a long period of time because of these complications. Consequently he died due to leukemia relapse. However, the four patients who received octreotide therapy were alive and leukemia-free at the most recent follow-up. Therefore, when AAP resolves quickly following octreotide treatment, chemotherapy can be restarted early to prevent leukemia relapse.

Pseudocyst (26.3%), encephalopathy and uremia (21.0%), and hyperglycemia (15.8%) were severe complications of AAP [16]. The mortality rate associated with AAP has been reported to be as high as 21% [16]. In our study, the patient with AAP who did not undergo octreotide treatment developed chronic pancreatitis and pseudocyst. Of the four patients who underwent octreotide treatment, no pseudocysts were detected and there were no mortalities. However, in two of these four patients, insulin-dependent diabetes persisted despite resolution of pancreatitis. We speculate that diabetes persisted because of AAP-related permanent damage to beta cells, which cannot be reversed by octreotide therapy.

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