



Acute pancreatitis following L-asparaginase in acute lymphoblastic leukemia

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is the most frequent malignancy in children, representing 25–30% of all childhood malignancies. Although treatment outcome has improved owing to advances in chemotherapy, there is still a group of patients who experience severe adverse events. L-Asparaginase is an effective antineoplastic agent used in chemotherapy of ALL. Despite its indisputable indication, it can cause various adverse effects, including acute pancreatitis (AP). Recently, an increase in the number of pediatric AP cases following L-Asparaginase in Acute Lymphoblastic Leukemia been reported. We presented a case of acute pancreatitis in children with ALL induced by administration of L-ASPA preparations.

1. Introduction

L-asparaginase is an essential drug in the treatment of acute lymphoblastic leukaemia (ALL). However, it is also known to induce several acute complications, such as acute pancreatitis and hypersensitivity reactions. Other side effects include liver dysfunction, coagulation defects and central nervous system depression. In patients with clinical symptoms such as abdominal pain, nausea and emesis, acute pancreatitis is suspected on the basis of elevated levels of serum amylase and/or lipase, along with abnormal findings on imaging studies. We report a case of a 15-year-old male patient who developed acute pancreatitis following L-asparaginase therapy.

1.1. Case report

A 15 years old boy with no particular history was treated with multidrug therapy for acute lymphoblastic leukemia phenotype T belonging to the high risk group, revealed one month before its hospitalization with associated complete bone marrow syndrome also with a syndrome tumor (lymphadenopathy and hepatosplenomegaly). Chemotherapy according to the Marall 2006 protocol was started by an induction cure combining vincristine, daunorubicin, prednisone with intrathecal methotrexate Ara-c and hydrocortisone. Following remission induction, therapy continues with a consolidation phase, intensification

1, interphase, intensification 2 and maintenance phase. Our child did not receive L-ASPA during induction therapy because it wasn't available. Chemotherapeutics during intensification 1 may include vincristine, Dexamethason, adriamycin, intrathecal chemotherapy, cyclophosphamide, Ara-C, mercaptopurine and L-Asparaginase. The latter was given on an alternate day amounting to a total of 6 doses. After the sixth IM asparaginase 6000 U/m²/day dose (The cumulative dose of 36,000 U/m²), the patient manifested severe abdominal pains. The pain was in the epigastric region. He also presented with pain radiating to the back and decrease in appetite, vomiting. He has been complaining of similar but milder pain for a week, which worsened with accumulative doses of asparaginase. The objective examination revealed a tenderness at palpation in the projection of the stomach, ascites, abdominal distension, normal peristaltics. Clinically, he was afebrile and haemodynamically stable, a blood-pressure of 110/60 mmHg, and an axillary temperature of 36.6 deg. The diagnosis of asparaginase-induced pancreatitis (AIP) was done on the elevation of amylasemia to 341 IU / L ($N < 86$ IU / L). Her blood-urea is 0.4 mg / L, her blood-sugar 0.8 g / L, creatinine 6.73 mg/L, sodium 129 mmol/L, C-reactive protein (CRP) 65 mg / l, hemoglobin 9.2 g/dL, neutrophilia of 4.22 cells/mm³. Transaminases and alkaline phosphatases Lacticodehydrogenases (LDH), Serum calcium was normal (93.3 mg/L). Computed tomography (CT) showed a swollen pancreas, with loss of physiological lobulation, associated with a significant infiltration of the adjacent fat including the

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duodeno-pancreatic groove with individualization of multiple castings necrosis. Pancreatitis was classified stage E of the classification Balthazar. This case represents a complication related to L-asparaginase treatment during the intensification 1 phase of treatment in a patient with ALLs. The patient was treated by antibiotherapy combining C3G, amikacin and metronidazole. This treatment evolution was good, infusion fluids, fasting, proton pump inhibitors (PPI) and analgesic. After five days of hospitalization abdominal pain diminished and laboratory results normalised. Treatment of his blood disease maligne was continued. the interphase happened without incident and then the child received cranial radiation therapy to treat spread to the spinal fluid. the child was admitted to pallor, fever and bleeding manifestations. He had hemoglobin of 6.1 g/dl, white blood cell of 800/ mm³, and platelet of 4000/ mm³. Blood smear has shown 47% of the blasts. Second intention chemotherapy has been established according to the protocol Hyper-CVAD course A . The patient died two months later.

2. Discussion

L-Asp has been widely used for the treatment of ALL since 1966. It is an important chemotherapeutic agent used in the treatment of hematological malignancies such as acute lymphoblastic leukemia [1,2]. There are currently three forms of asparaginase that are used in clinical practice: native and pegylated form derived from *Escherichia coli* (*E. coli*-ASP and PEG-ASP, respectively), and an enzyme isolated from *Erwinia chrysanthemi*, known as *Erwinia asparaginase* (*Erwinia*-ASP), antigenically distinct from *E. coli*-derived asparaginase forms [3]. The administration of asparaginase reduces plasma asparagine concentrations by catalyzing the deamination of asparagine into aspartic acid and ammonia [4]. At sufficient enzyme activity levels, asparaginase therapy results in the complete depletion of serum asparagine concentrations, depriving leukemic blasts of this amino acid [5], resulting in reduced protein synthesis and ultimately leukemic cell death. Although it has played an important role in increasing the survival rate of childhood ALL, it can cause adverse effects including hypersensitivity reactions, hypoproteinemia, abnormal liver function test results, acute pancreatitis (AP), hyperglycemia, hypertriglyceridemia, and thrombosis [2–6]. Pancreatic toxicity during L-asparaginase treatment has been reported with a prevalence of 16.2%, with an incidence of AP ranging from 2 to 18% [7,8]. The precise pathophysiology behind AAP is unknown [2-7, 9-11]. the reduction in protein synthesis resulting from asparaginase-induced depletion of asparagine has been implicated [12]. which leads to considerable toxicity particularly to organs associated with high protein production such as liver and pancreas [13]. this mechanism has been implicated for the development of pancreatic toxicity but it might not be the only one and may be genetic factors underlying predisposition and could be involved [7]. The association of L-asp treatment with other therapeutic agents like corticosteroids has been reported to induce toxicities [14]. Our children, received L-asp concomitant with Dexamethasone. In most of the cases clinical manifestations have been reported as mild and self-limited, and may start at anytime during treatment or even after the end of treatment [15]. The onset of pancreatitis was various, and more than 50% of patients occurred during the induction-remission treatment [12]. In our case, a patient developed L-AP during the intensification treatment although he didn't receive L-asparaginase in the induction-remission due to the unavailability of the product. L-AP is more common in older children or adolescents [2-7,12]. The dose of L-asp is not related to pancreatitis. Therefore, AP seems to be a side effect caused by hypersensitivity reactions rather than dose-related or dose accumulated reaction [9-12, 16-18]. The origin, formulation, or method of L-asp administration does not seem to influence the risk of L-AP [2-7,9-12]. His-Diagnosis is based on a combination of clinical, biochemical (amylase, lipase), and radiological evidence. Patients with AAP typically present with nausea, vomiting, and sudden abdominal pain, which is most commonly located in the epigastric region. Patients may also present with pain radiating to

the back or shoulders. Other symptoms include low grade fever, and pleural effusion [9–19]. Elevations in serum amylase and lipase are the most common biochemical characteristics of pancreatitis. Diagnostic imaging plays a crucial role in the evaluation of cases of AP and chronic pancreatitis in all age group [20]. Especially contrast-enhanced computed tomography (CT) is known to be the golden standard for staging severity and assessing complications. CT is also widely used in the follow-up examination [21]. CT findings include an increase in pancreatic size with ill-defined borders, peripancreatic fluid and possible areas of lower density or enhance after contrast, which may indicate necrosis. Besides these findings, one can find a diffuse enlargement of the gland with loss of lobular architecture, associated with isoor hypoattenuating parenchyma with narrowed or nondilated pancreatic ducts [22]. Our patient is diagnosed with definitive pancreatitis by the clinical symptoms, the subsequent elevation of serum amylase levels and evidence radiological. Treatment of acute pancreatitis is primarily supportive and aims to reduce symptoms and monitor potential complications. The most important therapeutic in the handling of AP are hydration, analgesia and nutrition [2-7,9-11]. Treatment of our patients included antibiotherapy combining C3G, amikacin and metronidazole, infusion fluids, fasting, proton pump inhibitors (PPI) and analgesic. Asparaginase therapy can be continued with mildly elevated amylase or lipase levels if clinical signs are absent; however, asparaginase treatment is generally discontinued in the case of severe pancreatitis [12]. Caution should be exercised, as recurrence of pancreatitis has been reported in up to 63% of patients following re-exposure to asparaginase [11].

3. Conclusion

L-Asp is an effective drug for the treatment of ALL, the administration of L-asp should require the monitoring of pancreatic toxicity. Early diagnosis may prevent to significant morbidity and mortality. There should be cessation of asparaginase once a diagnosis of pancreatitis is made. However, it is essential to balance, on a case-by-case basis, the relatively high risk of pancreatitis recurrence with the potential therapeutic benefit of this important chemotherapeutic agent. Predicting which patients will suffer from L-ASP toxicity and which type of toxicity will be developed is one of the challenges of modern medicine.

Informed consent

All members of the department have signed a consent to publish this work, and have taken the permission of the child's family to share this clinical case for scientific purposes

Declaration of Competing Interest

The authors declare there are no conflicts of interest.

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