Published in final edited form as:

Pediatr Blood Cancer. 2009 August ; 53(2): 162–167. doi:10.1002/pbc.22076.

Clinical Course and Outcome in Children with Acute Lymphoblastic Leukemia and Asparaginase-Associated Pancreatitis

Susan L. Kearney, M.D.¹, Suzanne E. Dahlberg, PhD², Donna E. Levy, M.S.³, Stephan D. Voss, M.D., PhD.^{4,5}, Stephen E. Sallan, M.D.^{4,6}, and Lewis B. Silverman, M.D.^{4,6}

¹ The Division of Pediatric Hematology, Oncology, Blood and Marrow Transplantation, University of Minnesota

² The Department of Biostatistics and Computational Biology, Dana Farber Cancer Institute, Boston

³ Rho Incorporated, Chapel Hill, NC

⁴ The Department of Pediatrics, Harvard Medical School, Boston

⁵ The Department of Radiology, Children's Hospital, Boston

⁶ The Division of Hematology/Oncology, Children's Hospital and Dana-Farber Cancer Institute, Boston

Abstract

Background—Asparaginase, an agent used in the treatment of acute lymphoblastic leukemia (ALL), is associated with the development of pancreatitis. The clinical course and long-term outcome of patients experiencing this complication has not been extensively detailed.

Procedure—We reviewed the clinical course for all children with ALL diagnosed with pancreatitis at the Dana-Farber Cancer Institute/Children's Hospital Boston between 1987 and 2003. The outcome of these patients was compared with that of patients with ALL who did not experience pancreatitis.

Results—Twenty-eight of 403 children (7%) were diagnosed with pancreatitis. Patients 10–18 years old at diagnosis had 2.4 times the risk of developing pancreatitis compared with younger patients. Pancreatitis typically occurred early in the course of therapy (median 4 weeks after first dose of asparaginase). Ninety-three percent of affected patients were hospitalized and 57% received parenteral nutrition. No patient developed chronic sequelae or died as a result of pancreatitis. Sixteen (57%) patients were retreated with asparaginase, 10 of whom had another episode of pancreatitis. No significant differences in event-free survival were observed when comparing patients with and without a history of pancreatitis.

Conclusion—Asparaginase-associated pancreatitis was more common in older children, and caused significant acute morbidity. It tended to occur after the first few doses of asparaginase, suggesting a predisposition to this complication rather than a cumulative drug effect. Re-treatment with asparaginase after an episode of pancreatitis was associated with a high risk of recurrent pancreatitis.

Address reprint requests to Susan Kearney, MD. 420 Delaware St. SE, Minneapolis, MN, 55455; email: kearn054@umn.edu; phone: 612-626 2778 fax: 612 626 2815;.

3 Preferred Reviewers: Kelly Maloney (The Children's Hospital, Denver CO; maloney.kelly@tchden.org), Eric Larsen (Maine Childrens Cancer Center; larsee1@mmc.org), Naomi Winick (UT Southwestern naomi.winick@utsouthwestern.edu)

Keywords

Asparaginase; Pancreatitis; Leukemia

INTRODUCTION

Asparaginase is a bacterially derived enzyme which is a universal component of all chemotherapeutic regimens for childhood acute lymphoblastic leukemia (ALL). Its unique mechanism of action, the depletion of asparagine, is thought to selectively kill leukemia cells that require external sources of the amino acid [1–3].

Asparaginase was first administered as a single agent to patients with ALL in the 1960's and was effective in inducing complete remission in up to 60% of cases [4]. Randomized clinical trials in the 1970's demonstrated improvement in event-free survival (EFS) for children with ALL when asparaginase was added to induction chemotherapy and/or post-remission consolidation.[5–7] Since 1981, all children with ALL treated on DFCI Childhood ALL Consortium protocols have received weekly asparaginase injections for 20–30 weeks immediately after achieving clinical remission [8–13]. The DFCI ALL Consortium Protocol 95-01 (1995–2000), which included 20 consecutive weeks of asparaginase during the consolidation phase, had a 5-year EFS rate of $82 \pm 2\%$ [13].

Asparaginase is associated with multiple toxicities. Allergic reactions, including erythema at the injection site, urticaria, bronchospasm and anaphylaxis have been reported to occur in 20–40% of children with ALL treated with E.coli L-asparaginase [8,14–16]. Other asparaginase-related toxicities include pancreatitis (observed in 5–18% of patients)[14,17–19], abnormalities of hemostasis (including central nervous system thromboses and hemorrhage, and peripheral deep venous thromboses in 2–4% of patients),[8,20–22] hyperglycemia[5,23–27], and abnormalities of lipid metabolism [8,28].

Asparaginase-associated complications also may impact anti-leukemic outcomes. We have previously reported that patients who experienced a dose-limiting toxicity to asparaginase (12% of all patients) had a significantly worse EFS than those who were able to tolerate all or nearly all of their intended doses (5-year EFS 73% versus 90%, $p < 0.01$) [12]. In a multivariate analysis, including covariates for age, presenting leukocyte count and leukemia immunophenotype, asparaginase intolerance was the only prognostically significant factor predicting EFS. Pancreatitis was the most common cause of asparaginase intolerance, observed in 39% of patients who stopped asparaginase prematurely.

Although pancreatitis has long been recognized as an important asparaginase-related complication, the clinical course of patients experiencing this toxicity (including the severity of the acute episode, as well as the risk of developing chronic sequelae and/or subsequent episodes of pancreatitis) has not been previously detailed. It is also not clear which, if any, imaging modalities are most helpful in evaluating children suspected of having asparaginase-associated pancreatitis. We report here the outcome of children with asparaginase-associated pancreatitis.

PATIENTS and METHODS

Patient Selection

Between November 1987 and October 2003, 1583 children (ages 0 to 18 years), with newly diagnosed ALL were enrolled onto four consecutive DFCI ALL Consortium protocols (protocols 87-01, 91-01, 95-01, 00-01) at 12 participating institutions (see supplemental

appendix for list of institutions). The Institutional Review Boards at these institutions approved each protocol prior to patient enrollment. Informed consent was obtained from parents or guardians before therapy started. Of the 1583 patients, 403 (25%) were enrolled at DFCI/Children's Hospital Boston.

Identification of cases of pancreatitis was performed prospectively. Pancreatitis was defined in each protocol as an elevation in the serum amylase level $> 3 \times$ normal associated with clinical signs and symptoms consistent with the diagnosis (such as abdominal pain). Of the 403 patients enrolled at DFCI/Children's Hospital Boston, 28 patients were diagnosed with pancreatitis while receiving therapy. Medical records and imaging studies of all 28 children with pancreatitis were reviewed to assess symptoms at presentation, peak amylase and lipase levels, radiographic findings, and clinical course (including number of days hospitalized, number of days without food or fluid by mouth, use of nasogastric tube, narcotics or parenteral nutrition or any surgical interventions). All radiographic studies performed at the time of diagnosis were re-analyzed by a pediatric radiologist (SDV) as part of the medical record review.

Therapy on DFCI ALL Consortium Protocols

Details of therapy on Protocols 87-01, 91-01, and 95-01 have been previously reported [9,11,12,13]. Each protocol consisted of four phases of treatment: remission induction (including 0–1 doses of asparaginase, depending on protocol), central nervous system treatment, consolidation (including 20–30 weeks of asparaginase), and continuation therapy. Treatment was stratified based on risk group assignment (standard or high risk), as previously reported [9,11,12,13]. The differences between each protocol with respect to asparaginase administration are listed in Table I. There were no differences in type or total doses of asparaginase on any protocol based on risk group.

Statistical Analysis

Event-time distributions were analyzed using the Kaplan-Meier method. Event-free survival (EFS) was defined as the time from registration to induction failure, induction death, first relapse, second malignancy, or death, whichever occurred first. Leukemia-free survival (LFS) was defined as the time from complete remission to death, relapse, or second malignancy, whichever occurred first. Overall survival (OS) was defined as the time from registration to death from any cause. Patients not experiencing any of these endpoints were censored at the date at which they were last known to be alive and disease-free. If a patient was removed from study for transplant in first complete remission, they were censored at this time point.

Demographics were compared using either Fisher's exact test or the Kruskal-Wallis test. Survival curves were compared using the log rank test whereas event summaries were compared using Fisher's exact test. Two sided tests at the 0.05 level were used throughout. Adjustments were not made for multiple comparisons.

Outcome data was reported for the entire study population ($n=403$). Presenting symptoms of ALL patients with or without pancreatitis was limited to those patients who completed the consolidation phase of therapy ($n=386$) so as to compare only those patients who had an equivalent opportunity to develop this complication.

RESULTS

Patients

Between November 1987 and October 2003, 403 children (aged 0–18 years) were enrolled on DFCI ALL Consortium protocols and treated at DFCI/Children's Hospital Boston. 28 of the 403 patients (7%) were diagnosed with at least one episode of acute pancreatitis during treatment phases which included asparaginase.

A comparison of the presenting features between patients experiencing pancreatitis and those who did not is provided in Table II. Patients with asparaginase-associated pancreatitis had a significantly higher median age at the time of diagnosis of ALL compared with patients who did not have pancreatitis (7.1 years versus 4.6 yrs; $p=0.003$). Results from logistic regression models indicate that patients 10–18 years at diagnosis had 2.4 times the risk of developing pancreatitis compared to younger children (95% confidence interval 1.1–5.5, $p<0.05$). No other presenting feature, including risk group, sex, race/ethnicity, presenting leukocyte count or immunophenotype, was associated with the development of pancreatitis. These findings were confirmed using the larger cohort of patients treated during the same time period and on the same protocols at the 10 other DFCI ALL Consortium institutions. In this data set, 74 of 1,155 patients (6.4%) developed pancreatitis. The age of patients experiencing pancreatitis was also significantly higher in this data set when compared with patients who did not have pancreatitis (8.5 years versus 4.5 years; $p < 0.001$).

Clinical Manifestations and Laboratory Findings

Asparaginase-associated pancreatitis generally occurred within the first few weeks of therapy. Five of the 28 (18%) children who developed pancreatitis did so following their first dose during the induction phase. During the post-induction consolidation phase, when patients received 20–30 weeks of asparaginase, the median number of weeks of asparaginase treatment prior to the first episode of pancreatitis was four (range 0 to 29). Of the 28 patients with pancreatitis, 79% were diagnosed within the first 10 weeks of the consolidation phase.

All patients with asparaginase-induced pancreatitis presented with abdominal or back pain and 89% also had nausea or vomiting. The median peak serum amylase was 553 u/l (range 111–1121) and the median peak lipase was 1143 u/l (range 42 to 12986). The degree of amylase or lipase elevation did not correlate with severity of pancreatitis as measured by number of days hospitalized or with number of days without food or fluid by mouth.

Radiographic Findings

Twenty-six of the 28 patients with asparaginase-associated pancreatitis were evaluated by ultrasound; 23 of these sonographic studies were available for retrospective review.

Twelve of the 23 patients also had computerized tomography (CT) scans performed within days of their ultrasound (US) examination. Nine of the 23 (39%) patients with acute pancreatitis had a normal US examination, 10 (44%) had findings suggestive of mild pancreatitis (pancreatic enlargement and decreased echogenicity) and 4 (17%) had findings of moderately severe pancreatitis (pancreatic enlargement, loss of pancreatic contours, associated free fluid and/or pseudocyst formation). Eleven of the 12 patients (92%) for whom both US and CT examinations were obtained had concordant findings with respect to evaluation of pancreatitis. In only one case of moderately severe pancreatitis was the extent of disease better delineated by CT.

Management and Complications

Table III summarizes the clinical course of patients after they were diagnosed with pancreatitis. Of the 28 patients with pancreatitis, 26 (93%) were hospitalized for a median of 10.5 days. Almost all of them were managed with complete bowel rest (median of 4 days), although in only 29% was a nasogastric tube placed. All patients received intravenous narcotics for pain control and 57% received total parenteral nutrition.

No patient died as a direct complication of acute pancreatitis. Five patients (18%) developed a pseudocyst, two of whom underwent surgical intervention. After recovery from the acute episode of pancreatitis, no patient developed chronic pancreatitis, long-term pancreatic exocrine insufficiency or an insulin requirement. Only 21% of the 28 patients with asparaginase-associated pancreatitis received at least 20 weeks of asparaginase compared with 71% in the group who did not experience this toxicity ($p<0.001$).

Re-challenge with Asparaginase after Recovery from Pancreatitis—After recovery from acute pancreatitis, patients were allowed by protocol to receive additional doses of asparaginase at the discretion of their treating physician if their initial episode of pancreatitis was considered mild based upon protocol-defined criteria (symptom resolution with 72 hours). Based on these criteria, 16 patients received additional doses of asparaginase after resolution of symptoms and normalization of pancreatic enzymes. Patients who were re-challenged with asparaginase were younger (median age 5.5 versus 8 years) and had received fewer doses of their planned asparaginase (median 4 versus 9.5 doses) prior to their first episode of pancreatitis compared with those who were not re-challenged. Five of the re-challenged patients had experienced pancreatitis following their first dose of asparaginase during the remission induction phase.

A median of 13 additional doses (range 1–28) were administered to patients re-challenged with asparaginase after recovery from a first episode of pancreatitis. Patients who were re-challenged received a median of 17 total doses of asparaginase (range 6–30) compared with a median of 9.5 (range 5–30) for patients who were not re-challenged. Ten of the 16 (63%) re-challenged patients experienced a second episode of pancreatitis. Nine of these second episodes self-resolved without significant complications, but one patient experienced a pseudocyst requiring surgical intervention as a result of the recurrent pancreatitis. No patient died as a result of an asparaginase-related complication after being re-challenged. Asparaginase was not administered again to any patient after a second episode of pancreatitis.

Outcome and Prognosis

Of the 403 patients treated at DFCI/Children's Hospital Boston, 384 (95%) achieved a complete remission (16 induction failures and 3 induction deaths). Eight of 28 (29%) patients with a history of asparaginase-associated pancreatitis subsequently relapsed compared with 50 of 356 (14%) patients without pancreatitis ($p=0.04$). There was a non-statistically significant trend toward inferior 5 year EFS in patients with a history of pancreatitis compared with other patients ($73.2 \pm 9\%$ vs $82.1 \pm 2\%$, $p=0.11$; median follow-up 6.6 years). An expanded analysis including the 1180 patients treated at other ten DFCI ALL Consortium sites during the same time period did not reveal any significant differences in rates of LFS ($p=0.55$) or EFS ($p=0.89$) comparing patients with and without a history of pancreatitis. The proportion of patients experiencing a relapse was similar in the larger cohort in those with and without a history of pancreatitis.

DISCUSSION

Asparaginase-associated pancreatitis is an important cause of morbidity in children with ALL. In previous studies, the incidence of asparaginase-associated pancreatitis ranged from 5–18%, [14,17–19] and pancreatitis-related mortality was reported to occur in up to 2–5% of cases [14,17,18]. In our series, the incidence of asparaginase-induced pancreatitis was 7%, consistent with these previous studies, and there were no cases of pancreatitis-related mortality, which may reflect improved supportive care measures.

While asparaginase-associated pancreatitis can affect patients of all ages, older children and adolescents were at higher risk for developing this complication. Although there is no clear explanation for this observation, other case series have reported similar age demographics [14,17–19]. Analysis of the other presenting characteristics did not reveal any other risk factors for the development of asparaginase-associated pancreatitis. We attempted to explore other potential predisposing factors, such as a history of gallstones or family history of pancreatitis, but this information was unavailable in most medical records.

In our series, patients who experienced pancreatitis had a significantly higher risk of relapse, although there was only a non-significant trend toward inferior LFS and EFS in these patients. Of note, we did not confirm a higher risk of relapse in children with asparaginase-associated pancreatitis when analyzing the larger cohort treated during the same time period on the same protocols at other DFCI ALL Consortium institutions. Thus, although we have previously reported that children who were unable to tolerate at least 26 weeks of asparaginase due to toxicity had an inferior EFS [12], we could not confirm in this expanded cohort that pancreatitis (the major cause of asparaginase intolerance on our protocols) was a significant predictor of outcome. Further studies with larger patient numbers are necessary to more definitively determine how pancreatitis and/or asparaginase intolerance impacts EFS.

The time to onset of pancreatic toxicity was notable. Previous studies have shown that pancreatitis can occur within days to weeks following a dose of asparaginase. Our study demonstrates that if pancreatitis is to occur, it generally does so within a few weeks following first exposure to asparaginase. Even though our regimen included 20–30 consecutive weeks of asparaginase during post-induction consolidation, nearly all patients were diagnosed with pancreatitis within the first 10 weeks of treatment. Our observation that pancreatitis tends to develop after the first few doses of asparaginase suggests that asparaginase-associated pancreatitis may occur as a result of an underlying predisposition rather than as a cumulative drug effect. Extensive ongoing research investigating the pharmacogenomics of chemotherapy-induced toxicities may help to identify patients at high risk of developing this complication.[29]

The diagnosis of asparaginase-induced pancreatitis is usually straightforward. Clinically, 100% of patients presented with abdominal or back pain and most also experienced nausea and/or emesis. In our series, the degree of elevation of amylase and/or lipase did not reflect the degree of morbidity that the patient experienced.

It is noteworthy that 39% of children with clinical and chemical pancreatitis did not have abnormalities detected by ultrasound; therefore, the diagnosis should not be dependent on radiographic confirmation. There was a high concordance between ultrasound and CT in detecting abnormalities, and so it may be reasonable to reserve the use of CT for those patients with persistence or worsening of clinical symptoms or laboratory findings in the setting of non-diagnostic ultrasonography..

The etiology of pancreatitis in this series was attributed to asparaginase; however, it should be noted that the majority of children were receiving additional medications that have been associated with pancreatitis, including corticosteroids, 6-mercaptopurine and trimethoprim-sulfamethoxazole. These medications were re-instituted following resolution of the acute episode, without recurrence of pancreatitis and were thus not thought to be the major contributor to pancreatic toxicity.

Children diagnosed with pancreatitis experienced significant acute morbidity. The majority of patients required prolonged hospital stays, and most received IV narcotics and total parenteral nutrition. Pseudocyst formation occurred in five (18%) patients. However, the need for surgical intervention was rare and long-term sequelae (such as chronic pancreatitis and pancreatic insufficiency) were not observed.

There is a paucity of published data regarding outcome after administration of additional doses of asparaginase following recovery from an episode of pancreatitis. Knoderer and colleagues reported a recurrence rate of 7.7% after additional asparaginase in 26 patients [19]. Our practice has been to re-introduce asparaginase in patients with relatively mild cases of pancreatitis. In this series, 16 patients were re-challenged with asparaginase. Although 63% of these patients experienced a second episode of pancreatitis, most were able to receive several doses of asparaginase (median 13 additional doses) before pancreatitis recurrence, suggesting that it may be feasible to administer some additional doses in children after an initial episode of pancreatitis. Therefore, until predisposing factors such as pharmacogenomic modifiers are identified, our experience suggests that one episode of mild pancreatitis may not be an absolute contraindication to the administration of more doses of asparaginase. 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported by Grant 5P01CA68484 from the National Cancer Institute

References

1. Broome JD. Studies on the mechanism of tumor inhibition by L-asparaginase. Effects of the enzyme on asparagine levels in the blood, normal tissues, and 6C3HED lymphomas of mice: differences in asparagine formation and utilization in asparaginase-sensitive and -resistant lymphoma cells. *The Journal of experimental medicine*. 1968; 127(6):1055–1072. [PubMed: 4871211]
2. Horowitz B, Madras BK, Meister A, et al. Asparagine synthetase activity of mouse leukemias. *Science (New York, NY)*. 1968; 160(827):533–535.
3. Haskell CM, Canellos GP. L-asparaginase resistance in human leukemia--asparagine synthetase. *Biochemical pharmacology*. 1969; 18(10):2578–2580. [PubMed: 4935103]
4. Tallal L, Tan C, Oettgen H, et al. E. coli L-asparaginase in the treatment of leukemia and solid tumors in 131 children. *Cancer*. 1970; 25(2):306–320. [PubMed: 4905155]
5. Rausen A. L-Asparaginase (L-ASP) in advanced childhood leukemia: comparative trial of drug schedules singly and in combination. *Proc Amer Assn Cancer Res*. 1970:137–144.
6. Jones B, Holland JF, Glidewell O, et al. Optimal use of L-asparaginase (NSC-109229) in acute lymphocytic leukemia. *Medical and pediatric oncology*. 1977; 3(4):387–400. [PubMed: 337095]

7. Sallan SE, Hitchcock-Bryan S, Gelber R, et al. Influence of intensive asparaginase in the treatment of childhood non-T-cell acute lymphoblastic leukemia. *Cancer research*. 1983; 43(11):5601–5607. [PubMed: 6352020]
8. Clavell LA, Gelber RD, Cohen HJ, et al. Four-agent induction and intensive asparaginase therapy for treatment of childhood acute lymphoblastic leukemia. *The New England journal of medicine*. 1986; 315(11):657–663. [PubMed: 2943992]
9. LeClerc JM, Billett AL, Gelber RD, et al. Treatment of childhood acute lymphoblastic leukemia: results of Dana-Farber ALL Consortium Protocol 87-01. *J Clin Oncol*. 2002; 20(1):237–246. [PubMed: 11773175]
10. Schorin MA, Blattner S, Gelber RD, et al. Treatment of childhood acute lymphoblastic leukemia: results of Dana-Farber Cancer Institute/Children's Hospital Acute Lymphoblastic Leukemia Consortium Protocol 85-01. *J Clin Oncol*. 1994; 12(4):740–747. [PubMed: 8151317]
11. Silverman LB, Decker L, Gelber RD, et al. Results of Dana-Farber Cancer Institute Consortium protocols for children with newly diagnosed acute lymphoblastic leukemia (1981–1995). *Leukemia*. 2000; 14(12):2247–2256. [PubMed: 11187916]
12. Silverman LB, Gelber RD, Dalton VK, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. *Blood*. 2001; 97(5):1211–1218. [PubMed: 11222362]
13. Moghribi A, Levy DE, Asselin B, et al. Results of the Dana-Farber Cancer Institute ALL Consortium Protocol 95-01 for children with acute lymphoblastic leukemia. *Blood*. 2007; 109(3):896–904. [PubMed: 17003366]
14. Haskell CM, Canellos GP, Leventhal BG, et al. L-asparaginase: therapeutic and toxic effects in patients with neoplastic disease. *N Engl J Med*. 1969; 281(19):1028–1034. [PubMed: 4898857]
15. Jaffe N, Traggis D, Das L, et al. L-asparaginase in the treatment of neoplastic diseases in children. *Cancer research*. 1971; 31(7):942–949. [PubMed: 4327086]
16. Nesbit M, Chard R, Evans A, et al. Evaluation of intramuscular versus intravenous administration of L-asparaginase in childhood leukemia. *The American journal of pediatric hematology/oncology*. 1979; 1(1):9–13. [PubMed: 295576]
17. Alvarez OA, Zimmerman G. Pegaspargase-induced pancreatitis. *Med Pediatr Oncol*. 2000; 34(3):200–205. [PubMed: 10696127]
18. Weetman RM, Baehner RL. Latent onset of clinical pancreatitis in children receiving L-asparaginase therapy. *Cancer*. 1974; 34(3):780–785. [PubMed: 4527863]
19. Knoderer HM, Robarge J, Flockhart DA. Predicting asparaginase-associated pancreatitis. *Pediatric blood & cancer*. 2007; 49(5):634–639. [PubMed: 16937362]
20. Gugliotta L, D'Angelo A, Mattioli Belmonte M, et al. Hypercoagulability during L-asparaginase treatment: the effect of antithrombin III supplementation in vivo. *British journal of haematology*. 1990; 74(4):465–470. [PubMed: 2189489]
21. Gugliotta L, Mazzucconi MG, Leone G, et al. Incidence of thrombotic complications in adult patients with acute lymphoblastic leukaemia receiving L-asparaginase during induction therapy: a retrospective study. The GIMEMA Group. *European journal of haematology*. 1992; 49(2):63–66. [PubMed: 1397242]
22. Leone G, Gugliotta L, Mazzucconi MG, et al. Evidence of a hypercoagulable state in patients with acute lymphoblastic leukemia treated with low dose of E. coli L-asparaginase: a GIMEMA study. *Thrombosis and haemostasis*. 1993; 69(1):12–15. [PubMed: 8446931]
23. Avramis VI, Sencer S, Periclou AP, et al. A randomized comparison of native *Escherichia coli* asparaginase and polyethylene glycol conjugated asparaginase for treatment of children with newly diagnosed standard-risk acute lymphoblastic leukemia: a Children's Cancer Group study. *Blood*. 2002; 99(6):1986–1994. [PubMed: 11877270]
24. Duval M, Suci S, Ferster A, et al. Comparison of *Escherichia coli*-asparaginase with *Erwinia*-asparaginase in the treatment of childhood lymphoid malignancies: results of a randomized European Organisation for Research and Treatment of Cancer-Children's Leukemia Group phase 3 trial. *Blood*. 2002; 99(8):2734–2739. [PubMed: 11929760]
25. Jaffe N. Diabetes mellitus secondary to L-asparaginase therapy. *The Journal of pediatrics*. 1972; 81(6):1220–1221. [PubMed: 4643049]

26. Land VJ, Sutow WW, Fernbach DJ, et al. Toxicity of L-asparaginase in children with advanced leukemia. *Cancer*. 1972; 30(2):339–347. [PubMed: 4626307]
27. Sutow WW, George S, Lowman JT, et al. Evaluation of dose and schedule of L-asparaginase in multidrug therapy of childhood leukemia. *Medical and pediatric oncology*. 1976; 2(4):387–395. [PubMed: 1004382]
28. Parsons SK, Skapek SX, Neufeld EJ, et al. Asparaginase-associated lipid abnormalities in children with acute lymphoblastic leukemia. *Blood*. 1997; 89(6):1886–1895. [PubMed: 9058708]
29. Weinstein JN. Searching for pharmacogenomic markers: the synergy between omic and hypothesis-driven research. *Disease markers*. 2001; 17(2):77–88. [PubMed: 11673654]

Table 1

Comparison of Asparaginase on DFCI ALL Consortium Protocols 1987–2003

Protocol	Investigational Window Asp	Induction (28days)	CNS treatment	Intensification	Continuation
87-01	Randomized to 1 dose of E. coli 25,000IU/m ² vs Erwinia 25,000IU/m ² vs PEG 2,500 IU/m ²	No Asp	No Asp	E. Coli Asparaginase 25,000 IU/m ² weekly for 20 weeks	No Asp
91-01	None	No Asp	No Asp	30 weeks of asparaginase; randomized to E.Coli Asp 25,000 IU/m ² weekly vs. PEG 2500 IU/m ² every 2 weeks	No Asp
95-01	None	Asp × 1 dose: Randomized to E. coli 25,000IU/m ² vs Erwinia 25,000IU/m ²	No Asp	20 weeks of asparaginase; Randomized to E.Coli Asp 25,000 IU/m ² weekly vs. Erwinia 25,000 IU/m ² weekly	No Asp
00-01	None	Asp × 1 dose: E. coli Asp 25,000IU/m ²	No Asp	30 weeks of asparaginase; Randomized to E.Coli Asp 25,000 IU/m ² vs individually dosed E.coli asparaginase (dose adjusted based on nadir asparaginase enzyme levels; maximum dose 25000 IU/m ²)	No Asp

Note: All asparaginase given intramuscularly. Abbreviations: ASP=asparaginase, PEG=polyethylene-glycosylated E.coli asparaginase

Table II

Presenting Features of DFCI ALL Patients with and without Pancreatitis

Number (%)	Pancreatitis	No Pancreatitis	p-value
N	28	356	
Protocol			
87001	10 (36)	71 (20)	0.29
91001	6 (21)	79 (22)	
95001	7 (25)	120 (33)	
00001	5 (18)	86 (24)	
Age (years)			
Median	7.1	4.6	0.003
(range)	2.6–17.4	0.36 – 17.9	
Age<1	0	5 (1)	0.11
Age 1–9.99	18 (64)	285 (80)	
Age ≥ 10	10 (36)	66 (19)	
Sex			
Male	13 (47)	191 (54)	0.56
Female	15 (54)	165 (46)	
Race			
White	26 (93)	305 (86)	0.75
Black	0 (0)	19 (5)	
Hispanic	1 (4)	17 (5)	
Asian	0 (0)	6 (2)	
Other	1 (4)	9 (3)	
DFCI Risk Group			
SR	11 (39)	170 (48)	0.44
HR	17 (61)	186 (52)	
WBC Day 0 ($\times 10^{-3}$ mm ³)			
Median	11.0	9.6	0.54
(range)	1.3–128.7	1.0 – 915.4	
WBC<20,000	20 (71)	239 (67)	0.62
WBC 20,000–49,999	5 (18)	53 (15)	
WBC ≥ 50,000	3 (11)	64 (18)	
AMM			
No	25 (89)	333 (94)	0.42
Yes	3 (11)	23 (6)	

Table III

Clinical Course of Patients With Pancreatitis

N	28
Hospitalized	26 (93%)
Days in Hospital (Median)	10.5 Days
Treatment of Pancreatitis	
Intravenous Narcotics	28 (100%)
Total Parental Nutrition (TPN)	16 (57%)
Naso-gastric Tube	8 (29%)
Days of Complete Bowel Rest (Median)	4 Days
Pseudocyst Formation	5 (18%)
Re-challenged with Asparaginase	16 (57%)
# of Doses of Asparaginase after Re-challenge (Median)	13
Second Episode of Pancreatitis after Re-challenge	10