Asparaginase-associated pancreatitis during therapy for pediatric acute lymphoblastic leukemia

Approximately 90% of children with acute lymphoblastic leukemia (ALL) become long-term survivors utilizing asparaginase-containing regimens.[1,2] However, asparaginase-associated pancreatitis (AAP) occurs in 1-7.4% of ALL patients during therapy.[3,4] AAP occurs early in therapy (after a median of 3-5 doses),[5,6] and most cases are severe: approximately two-thirds meet systemic inflammatory response syndrome (SIRS) criteria acutely[7] or progress to pancreatic necrosis or pseudocyst as the AAP resolves. Pseudocyst developed in up to 60% of patients, with an overall average of 26% across multiple groups in a large international study.[8] One recent study demonstrated that 17 of 43 patients (39.5%) with AAP developed organ failure or pancreatic necrosis, including necrosis within the first week in 12 (27.9%).[9]

Understanding AAP is critical for clinical decision-making in the context of ongoing leukemia-directed therapy. Re-exposure to asparaginase is frequently desired, as asparaginase truncation can increase the risk of relapse.[10] Re-exposure is generally only considered in patients whose pancreatic enzymes rapidly normalize and who do not develop either a pseudocyst or pancreatic necrosis.[11] Despite this, recurrent pancreatitis occurs in half of patients.[8]

To understand predictors and consequences of severe AAP, we retrospectively reviewed patient-level data in patients treated for newly diagnosed ALL on the Total Therapy XVI trial (clinicaltrials.gov NCT00549848).[1] Children <19 years of age at diagnosis received 1-2 doses of PEG-asparaginase during induction. Patients subsequently received 4 (low-risk) or 15 (standard/high-risk) post-inductions doses of PEG-asparaginase during the first 30 weeks of continuation therapy. Infants <1 year of age at diagnosis received modified therapy and were excluded from the current study. All patients and/or their families provided informed consent/assent in alignment with the Declaration of Helsinki. The institutional review board approved all studies.

The protocol adverse events database was reviewed to identify patients who experienced symptomatic pancreatitis (Common Terminology Criteria for Adverse Events [CTCAE] v3 grade 2 or higher, equivalent to CTCAE v5 grade 3 or higher). Pancreatitis required at least 2 of 3 diagnostic criteria: imaging evidence of pancreatic inflammation, amylase and/or lipase ≥3 times the laboratory upper limit of normal (ULN), and pain characteristic of pancreatitis. Pancreatitis was categorized as AAP if it occurred within 35 days of asparaginase therapy. All patients with computed tomography (CT) or ultrasound (US) available after the incident pancreatitis episode had imaging reviewed by a single pediatric radiologist (MBM).

Statistical analyses were performed in R. The cumulative incidence of pancreatitis was calculated using the Kalbfleisch-Prentice method with the first episode as an event and non-pancreatitis toxic death, relapse, and second malignancy considered as competing risks. In analysis of AAP risk, other pancreatitis episodes were treated as non-events. The impact of pancreatitis on event-free survival (EFS) was calculated using Cox proportional hazard regressions with survival censored at last follow-up.

Pancreatitis occurred in 57 of 586 patients (9.7%), who experienced a total of 80 discrete episodes. The first episode of pancreatitis occurred a median of 195 days into therapy (interquartile range: 112-236 days) with 1-year and 3-year cumulative incidences of 9.4% and 9.7%, respectively. Forty-seven (59%) episodes were classified as grade 2, 27 (34%) as grade 3, 5 (6%) as grade 4, and one resulted in death (grade 5). This fatality followed a prolonged hospitalization with multiorgan failure and was discovered post-mortem; pancreatitis was diagnosed >35 days from this patient's 5th dose of asparaginase therapy. In 5 additional patients, the first episode of pancreatitis occurred >35 days after 1-17 doses of asparaginase treatment. Among patients with pancreatitis, 42 patients experienced a single episode, 10 had 2 episodes, 2 experienced 3 episodes, and 3 had 4 episodes. Recurrent pancreatitis occurred in 5/35 patients who received no asparaginase after their first AAP compared to 11/16 rechallenged with asparaginase after a mean of 5 additional doses (range: 1-12). Seven patients experienced a higher-grade pancreatitis after an initial grade 2 AAP episode, although the overall grade of first and subsequent pancreatitis was similar (P=0.6). All 6 patients with non-AAP had only a single episode without known prior AAP and none recurred. Four of these patients experienced their episode of pancreatitis during mercaptopurine therapy, one patient experienced pancreatitis following high-dose dexamethasone containing reintensification II therapy, and the final patient, noted above, was more than 35 days from reinduction 1 asparaginase.

Asparaginase-associated pancreatitis (N=51) occurred more frequently in older patients (*Online Supplementary Table S1*), in those receiving standard/high-risk therapy (*Online Supplementary Figure S1A*), in children of Hispanic ancestry (*Online Supplementary Figure S1B*),[4] and in children with elevated body mass index (Table 1). There was no significant difference in AAP according to sex, leukemia immunophenotype, randomized asparaginase dose,[1] Down syndrome, or in other ancestral groups. In multivariable analyses, standard/high-risk therapy and mixed/other ancestry were associated with AAP (Table 1).

Asparaginase-associated pancreatitis was frequently severe. Patients were hospitalized for a median of ten days and 11

required intensive care. TPN was required in 30 cases for a median duration of 23 days (range: 3-153). Serial pancreatic enzymes were available for 47 patients and remained ≥3 times ULN 72 hours after pancreatitis onset in 22 patients. Among 39 patients with follow-up imaging after the diagnosis of AAP, 22 (56% of patients with imaging, 43% of all patients with AAP) had imaging sequalae of severe pancreatitis after their first episode, including pancreatic necrosis (N=4), pseudocyst (N=8), or both (N=10) (*Online Supplementary Figure S2*). Among 48 patients with evaluable follow-up pancreatic imaging (N=1), enzymes (N=18), or both (N=29), 30 met published criteria for severe AAP.[8] Severe AAP was due to imaging identification of sequalae of severe pancreatitis (N=8), prolonged pancreatic enzyme elevation (N=8), or both (N=14).

To identify risks for severe pancreatitis, cases with severe AAP were compared to all other patients. Older age (Odds Ratio [OR] 1.16, 95% Confidence Interval [CI]: 1.01-1.17 per year) and standard/high-risk therapy (OR 2.74, 95% CI: 1.2-7), but not other features, were associated with severe AAP. There were no differences between patients with severe AAP and other patients with AAP (*P*>0.2 for all features).

Because AAP interrupts early leukemia therapy and thus may compromise treatment efficacy, we assessed the impact

Table 1. Patient characteristics and associations with asparaginase-associated pancreatitis.

	No AAP N=535	Grade ≥2 AAP N=51	3-year CIN of grade ≥2 AAP %	Odds Ratio (95% CI; *P*) Univariate	Odds Ratio (95% CI; *P*) Multivariate
Sex					
Female	225	17	7	-	-
Male	310	34	9.9	1.5 (0.8-2.72; 0.23)	-
Age at diagnosis of ALL, years					
Mean	7.2	9.90	-	-	-
Median (Min, Max)	5.62 (1.07, 18.9)	10.1 (1.86, 18.5)	-	1.1 (1.05-1.18; 0.0002) per 1 year increase	1.04 (0.98-1.12; 0.18) per 1 year increase
Age <10 years	398	25	5.9	-	-
Age ≥10 years	137	2	16	3 (1.68-5.43; 0.0002)	-
Leukemia immunophenotype					
B-lineage	446	37	7.7	-	-
T-lineage	89	14	13.6	1.9 (0.96-3.58; 0.06)	-
Risk group					
Low	251	9	3.5	-	-
Standard or high	284	42	12.9	4.1 (2.06-9.2; 0.0002)	3.7 (1.62-9.25; 0.003)
Down syndrome					
Absent	524	50	8.7	-	-
Present	11	1	8.3	0.95 (0.05-5.05; 0.96)	-
BMI at diagnosis					
Mean BMI percentile	0.59	0.69	-	-	-
Median BMI percentile (Min, Max)	0.64 (0.01, 1)	0.76 (0.07, 1)	-	3.17 (1.14-9.56; 0.03) per 1 unit increase	2.39 [0.85-7.27; 0.11) per 1 unit increase
Healthy weight (5-85%)	338	29	7.9	Reference	-
Underweight (<5%)	23	0	0	-	-
Overweight (85-95%)	60	8	11.8	1.56 (0.64-3.42; 0.3)	-
Obese (>95%)	66	12	15.4	2.11 (0.996-4.28; 0.04)	-
Null	48	2	4	0.49 (0.08-1.68; 0.33)	-
Genetic ancestry					
Asian	4	0	0	-	-
Black	72	9	11.1	1.8 (0.77-3.91; 0.15)	1.18 (0.47-2.7; 0.7)
Hispanic	52	10	16.1	2.8 (1.21-5.98; 0.01)	2.37 (0.96-5.49; 0.05)
Other or mixed	43	7	14	2.4 (0.9-5.52; 0.06)	2.8 (1.03-6.93; 0.03)
White	362	25	6.5	Reference	Reference
Missing	2	0	0.0	-	-

AAP: asparaginase-associated pancreatitis; ALL: acute lymphoblastic leukemia; BMI: body mass index; CI: Confidence Interval; CIN: cumulative incidence; Max: maximum; Min: minimum; N: number. BMI data is NULL for patients age <2 years at diagnosis or in children with Down syndrome. *P* values calculated using logistic regression. When testing multivariable models, continuous variables for age and BMI z-score were preferred to discrete categories.

of pancreatitis on both asparaginase delivery and EFS of patients treated on this trial. Patients with AAP received 5.2 fewer doses of asparaginase after adjusting for treatment arm (P<0.001) and had inferior EFS compared to those without AAP (5-year EFS without AAP 90.4% *vs*. 80.7% in those with pancreatitis (Hazard Ratio [HR] 2.14 [1.09-4.2]; P=0.028) (Figure 1A). In multivariate analysis including treatment group, patients with AAP had a non-significant trend toward inferior EFS in both low- and standard/high-risk treatment groups (HR 1.52 [0.77-3]; P=0.22) (Figure 1B). Results were similar when also adjusting for age at diagnosis and ancestry (P=0.3 for association of AAP and EFS in this model). Causes of failure differed in patients who experienced AAP with more extramedullary relapse (EM) in those with AAP (5-year cumulative incidence of EM 7.1% *vs*. 1.4%; P=0.012) (Figure 2) with a trend in multivariate analysis including treatment risk group (P=0.08). Five-year overall survival was 92% in those with *versus* 95% in those without AAP (P=0.2), consistent with high salvage rates for patients experiencing EM.

Pancreatitis is among the most feared complications of ALL therapy because complications such as pseudocyst, pancreatic necrosis, abdominal pain, and endocrine or exocrine pancreatic insufficiency can persist after therapy, with lifelong morbidity.[7,8] Pancreatitis also interrupts therapy and often necessitates early discontinuation of asparaginase,

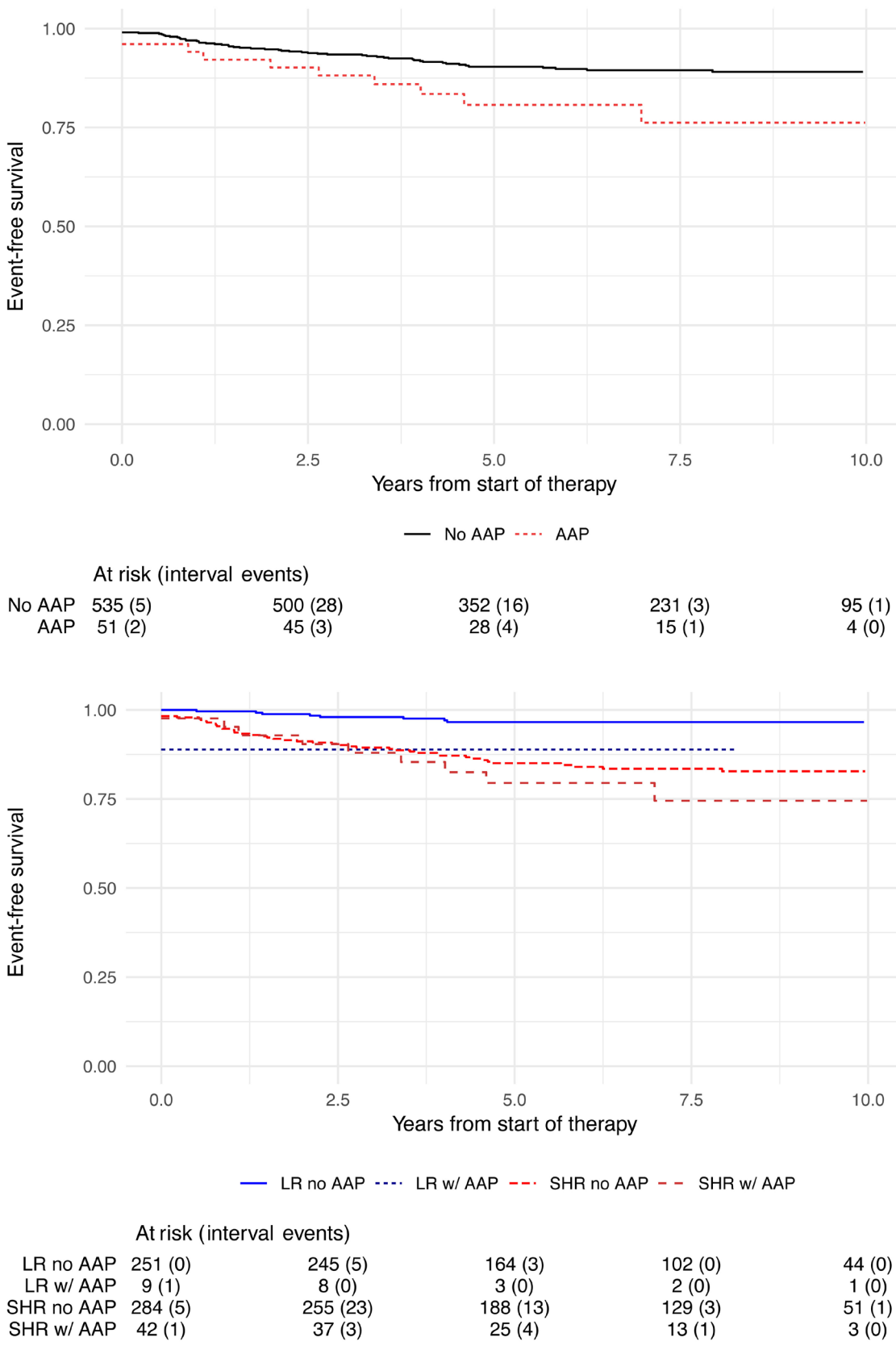

Figure 1. Event-free survival. Event-free survival was associated with the occurrence of asparaginase-associated pancreatitis (AAP). (A) In univariate analysis, the 5-year event-free survival (EFS) was 80.7% in those with AAP and 90.4% in those without AAP (P=0.028). (B) While this difference was not statistically significant after adjusting for treatment arm (P=0.22), 5-year EFS was lower in patients with AAP in both treatment arms. Events for EFS analysis included death from any cause, failure to achieve remission, relapse, and second cancer. LR: low risk; SHR: standard/high risk; w: with.

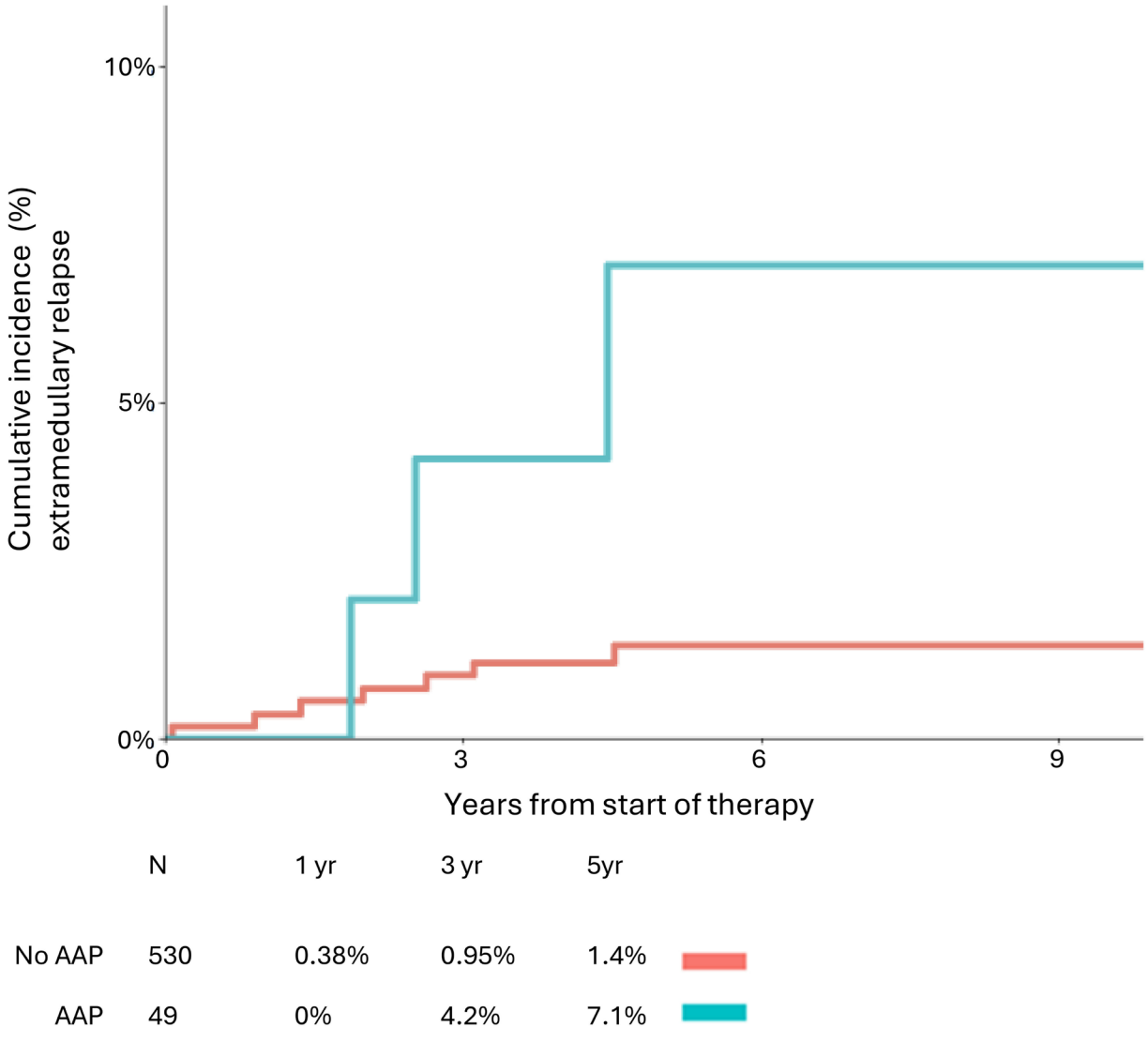

Figure 2. The 5-year cumulative incidence of extramedullary relapse. The 5-year cumulative incidence of extramedullary relapse (isolated or combined) was greater in patients experiencing asparaginase-associated pancreatitis (AAP) (7.1%, 3 events) than in other patients (1.4%, 7 events, *P*=0.012, Gray's test). Adjusting for risk group, there remained a trend toward increased risk in those with AAP (*P*=0.08, Hazard Ratio 3.4, Fine and Gray's test). Competing events in these analyses include medullary relapse without extramedullary involvement, death, and second malignancy. N: number; yr: years.

possibly increasing the risk of relapse.[10,12] Thus, it is critical to understand not only the frequency of pancreatitis, but also the frequency of these severe complications.

This cohort validated previously identified risk factors for AAP, including older age,[6,13] prolonged asparaginase exposure,[4] obesity,[13] and Hispanic ancestry.[4] Four of the 6 patients who developed pancreatitis unassociated with asparaginase therapy were also Hispanic, suggesting that the risk imparted by Hispanic ancestry applies throughout therapy and is not just limited to AAP, consistent with prior genomic studies.[4]

More than 40% of patients in this study who developed AAP had radiographic severe pancreatic injury, and only 18 of 48 evaluable patients met criteria for rechallenge.[11] Patients with AAP also trended toward more EM relapses than other patients (5-year cumulative incidence rate 7.1% *vs*. 1.4%). It has previously been shown that truncation of asparaginase therapy increases the risk of relapse in Dana Farber and Children's Oncology Group trials.[10,14] Data from our earlier Total 15 study demonstrated that anti-asparaginase antibodies which reduces asparaginase exposure increased the risk of central nervous system but not systemic relapse.[15] We thus hypothesize that AAP may increase the risk of extramedullary relapse by both terminating asparaginase therapy early and interrupting other leukemia therapy, compromising extramedullary control.

Study limitations include a lack of follow-up imaging in some patients and the relatively intensive asparaginase regimen used. In a prior meta-analysis of pancreatitis, the incidence of pancreatitis was linked to asparaginase therapy duration.[4] Longer-acting asparaginase formulations or alternative ALL regimens using less asparaginase may impact rates of AAP in other populations.

Because our data demonstrate that patients who developed severe AAP cannot be differentiated from other patients with AAP, therapies to mitigate AAP should be studied in all patients and not just in those with severe early symptoms. These data also highlight the urgent need to mitigate the severity of AAP. Ongoing investigations are seeking to address this critical need.

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Contributions

SEK designed the study. MBR, RR, HDS, HI, SJ, SEK and CHP provided data and/or supervised the clinical trial. SEK, EA and CC performed analyses and interpreted the data. SEK drafted the manuscript which was finalized with input from all authors.

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Data-sharing statement

Reasonable requests for deidentified data will be considered pending completion of appropriate data-sharing agreements; please contact the corresponding author.

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