CASE REPORT

IV Administration of *Erwinia*-Derived Asparaginase in Pediatric Patients with Acute Lymphoblastic Leukemia: Single-Centre Case Series

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INTRODUCTION

The survival of pediatric patients with acute lymphoblastic leukemia and lymphoblastic lymphoma has improved remarkably over the past 3 decades. This success has been due to improved risk stratification and optimization of treatment. Asparaginase is an important aspect of therapy for both conditions. Unfortunately, up to 30% of patients who receive the *Escherichia coli*–derived product will develop an allergy, which necessitates a switch to the antigenically distinct *Erwinia*-derived asparaginase (EA).[1,2] Although the intramuscular (IM) route of administration was used in dose-finding studies for EA, administration by the intravenous (IV) route is less painful. Furthermore, IV administration may reduce the requirement for platelet transfusions (which are sometimes needed before an IM injection), thus potentially reducing exposure to blood products and nursing workload. The authors' institution, the Children's Hospital, London Health Sciences Centre (LHSC), was one of the first pediatric centres in Canada to administer EA by the IV route. We present our initial experience with IV administration of this product.

CASE SERIES

This case series describes the first 7 consecutive children for whom IV EA therapy was initiated at the authors' institution (between April 2014 and June 2015) after publication of pharmacokinetic data showing efficacy and safety with IV administration.* Five patients had a diagnosis of precursor B-cell acute lymphoblastic leukemia (one of whom had the infant form of the disease), and 2 patients had precursor T-cell acute lymphoblastic leukemia (one of whom had experienced relapse). Demographic characteristics, the time and grade of patients' hypersensitivity reaction to pegaspargase, and the grade of nausea and vomiting with IV administration of EA are detailed in Table 1.

EA for IV administration was usually ordered in 100 mL normal saline. For all patients, the initial infusion was at least 1 h; however, for some children, the infusion was longer (up to 3 h) in an attempt to minimize nausea. All 7 children experienced nausea during the IV infusion, and 6 of the 7 experienced vomiting. Notably, 4 of the 7 patients had nausea and vomiting that persisted well after the end of the infusion, lasting up to 24 h, including one patient who experienced no nausea or vomiting during the infusion. All of the patients were given ondansetron in association with the EA therapy. The first patient to receive EA by the IV route (patient A in Table 1) was given diphenhydramine, as it was difficult to ascertain whether her intolerance of IV EA, despite administration of ondansetron, was potentially the result of a mild allergic reaction. Her nausea and vomiting resolved with the diphenhydramine, and she tolerated the remainder of her IV doses of EA. For the remaining 6 patients, multiple interventions, including premedication with diphenhydramine and serotonin antagonists, prolonged infusion times, and increased drug dilution, did not control their symptoms. One patient was admitted to hospital for treatment of dehydration secondary to severe vomiting with IV EA. Five of the 7 patients received at least one dose of EA by the IM route: 1 of these patients received the IM dose before IV administration and the other 4 patients received the IM dose after IV administration. One patient refused IM administration despite continued vomiting with IV administration. Of note, no significant nausea and vomiting were reported after IM administration.

None of the patients in this case series experienced signs of hyperglycemia, thrombosis, severe bleeding, or pancreatitis. The

*Verbal consent for publication was obtained from the patients' guardians. No ethics approval was required by the institution where care was provided.

Table 1. Demographic and Clinical Characteristics of Patients Receiving *Erwinia* Asparaginase

Patient ID	Sex	Age at Diagnosis	Diagnosis		Allergic Reaction to Pegaspargase*		Total No. of EA Doses	Symptoms with EA‡	Medications Before and/or After EA§	Grade of Nausea, Vomiting†
			B-ALL	T-ALL	Timing of Reaction (by Dose)	Grade of Reaction†				
A	F	22 mo	X		Dose 3	2	0 IM, 18 IV	Nausea, vomiting, retching	O, D	1, 1
B¶	M	6 yr		X	Dose 2**	2	38 IM, 2 IV	Nausea, vomiting	O, D	1, 1
C	M	9 yr	X		Dose 2	2	0 IM, 24 IV	Nausea, vomiting	O, D, L, N, G	2, 3
D	M	13 yr		X	Dose 4	2	6 IM, 6 IV	Abdominal pain, nausea	O	1, 0
E	M	8 mo	X		Dose 3††	2	4 IM, 2 IV	Nausea, vomiting, retching	O, D	2, 2
F	F	6 yr	X		Dose 3	2	4 IM, 2 IV	Nausea, vomiting	O	1, 2
G	M	5 yr	X		Dose 2	2	4 IM, 2 IV	Nausea, vomiting	O	2, 2

B-ALL = precursor B-cell acute lymphoblastic leukemia, EA = *Erwinia* asparaginase, IM = intramuscular, IV = intravenous, T-ALL = precursor T-cell acute lymphoblastic leukemia.
*Pegaspargase dose: 2500 units/m^2.
†Grading by Common Terminology Criteria for Adverse Events, version 4.0.[3]
‡EA dose: 25 000 units/m^2 by IV infusion.
§Medications administered by IV route before and/or after EA: O = ondansetron 5 mg/m^2, D = diphenhydramine 1 mg/kg, L = lorazepam 0.03 mg/kg, N = nabilone 1 mg, G = dimenhydrinate 1 mg/kg.
¶For patient B, the EA dose was 20 000 units/m^2 IV, as part of the modified UK MRC protocol for relapsed disease.[4]
**For patient B, the first dose was given by the IM route before initiation of IV administration.
††Patient E received 6 doses of native *Escherichia coli*–derived L-asparaginase before initiation of pegaspargase.

2 children with precursor T-cell acute lymphoblastic leukemia (patients B and D in Table 1) experienced transient transaminitis. In one of these patients, the transaminitis occurred during a course of EA therapy that overlapped with fluconazole and caspofungin therapy. The transaminitis resolved, despite further exposure to EA. In the second patient, marked transaminitis and hyperbilirubinemia were presumed to be secondary to voriconazole therapy for an invasive fungal infection. Both findings improved during the initial course of IV EA.

DISCUSSION

About 15% to 30% of patients receiving *E. coli*–derived asparaginase products will experience a hypersensitivity reaction, regardless of the route of administration, especially with repeated exposure.[2,5,6] Hypersensitivity rates at the authors' centre (unpublished data) approach the reported rate of up to 30%, with a median severity of grade 2 based on the Common Terminology Criteria for Adverse Events.[3] A large multicentre trial established the safety profile of EA in children with acute lymphoblastic leukemia or lymphoblastic lymphoma who had prior hypersensitivity reactions to *E.coli*–derived asparaginase products.[7] Substitution of EA into treatment regimens is critical to allow completion of planned asparaginase therapy. Importantly, decreased exposure to asparaginase because of intolerance has been associated with inferior outcomes in pediatric acute lymphoblastic leukemia.[5] Although in North America, most children receiving EA in the past have had administration via the IM route, a growing proportion receive this medication via the IV route. At the LHSC Children's Hospital, the most significant driving force for this change has been the change to IV administration in the most recent generation of Children's Oncology Group (COG) studies.[8]

At the authors' centre, EA is most commonly administered to patients who have experienced a hypersensitivity reaction to pegaspargase. Since spring 2014, EA has been administered by IV infusion on a Monday–Wednesday–Friday schedule, based on recommendations in current COG studies.[8] However, more recent pharmacokinetic data have suggested that this frequency may not be adequate to maintain nadir serum asparaginase activity (NSAA) levels, leading to inadequacy of sustained efficacy over the full 72-h period from Friday to Monday.[9] The hospital's practice will be re-evaluated as new pharmacokinetic data emerge on the efficacy of using this dosage regimen for IV administration.

Nausea and vomiting are common complaints with the administration of antineoplastic agents and can adversely affect quality of life.[10,11] Factors that influence the emetic risk include the chemotherapeutic agent, patient characteristics, frequency of administration, dosage of medication, and route of administration. Inadequate control of antineoplastic-induced nausea and vomiting can lead to anticipatory nausea and vomiting in 10% to 44% of patients.[11] Asparaginase is characterized as minimally emetogenic; however, the available products have not been differentiated in terms of their emetogenicity. Until recently, the classification of asparaginase products as having minimal emetogenic risk has accurately reflected our clinical experience; however, in our limited experience we have observed an increase in complaints of nausea and vomiting with introduction of the IV route of administration for EA.

Reported rates of nausea and vomiting with EA have varied widely. In a pharmacokinetic study of IV EA in 30 patients (1 to 30 years of age), the reported incidence of emesis was 20%, despite premedication with ondansetron.[9] In our limited experience with IV administration of EA, we have observed much higher rates of nausea (7/7 [100%]) and vomiting (6/7 [86%]). Of note, prolonging the infusion time did not provide any symptomatic relief. These observations indicate that IV EA should be classified as at least moderately emetogenic, requiring use of an antiemetic and potentially the addition of dexamethasone.[10-12] We continue to work toward optimizing antiemetic choices to better control antineoplastic-induced nausea and vomiting with IV administration of EA.

Asparaginase products are well known for causing several adverse effects regardless of the route of administration, including hyperglycemia, pancreatitis, transaminitis, hypersensitivity, and anaphylaxis.[2,7,13] In a review of 1368 patients who experienced hypersensitivity to *E. coli*–derived asparaginase and subsequently were switched to EA, a subgroup analysis comparing IV and IM administration suggested a trend for increased incidence of hypersensitivity reactions and hyperglycemia with the IV route (17.2% versus 11.7% and 6.9% versus 3.8%, respectively).[7]

At the LHSC Children's Hospital, all patients are asked about possible symptoms of hyperglycemia, such as polydipsia and polyuria, and biochemical laboratory markers such as bilirubin and transaminases are monitored periodically for evidence of hepatic dysfunction. Notably, measured laboratory values remained within normal ranges throughout treatment for most of the patients in this case series. Furthermore, none of the patients reported symptoms of hyperglycemia, and routine measurements showed that blood glucose levels were within the normal range. Two patients experienced transient transaminitis unrelated to administration of EA. Workup for possible pancreatitis in these 2 patients yielded negative results, with normal levels of serum amylase and lipase and normal abdominal ultrasonography findings.

As mentioned above, evidence in the literature is sparse comparing the IM and IV routes of EA administration in terms of incidence of adverse effects. Although it could be argued that the nausea and vomiting experienced by patients in this case series was caused by their concurrent chemotherapy rather than the IV administration of EA, these symptoms were also seen on days when EA was the only chemotherapeutic agent received. Furthermore, resolution of these symptoms with the change to IM injection suggests that nausea was related to the IV route of administration.

Currently available asparaginase products are derived from the bacteria *E. coli* (L-asparaginase and pegaspargase) and *Erwinia chrysanthemi* (*Erwinia* asparaginase). There is potential for development of antibodies against these agents, which might affect their efficacy in the patient. Although antibodies could present as a hypersensitivity reaction, some patients exhibit silent inactivation, defined as an unexpected and rapid decrease in L-asparaginase activity without the more typical clinical manifestations of hypersensitivity. In one study, event-free survival and overall survival were significantly lower among children who had developed anti-asparaginase antibodies.[14] The LHSC Children's Hospital currently does not measure NSAA levels or anti-asparaginase antibodies. It is uncertain whether administration of diphenhydramine before EA would decrease the clinician's ability to detect allergy and potential inactivation of asparaginase activity due to an immune response.

Given that the evidence and recommendations for IV administration of EA are fairly new, we have several recommendations for future studies to better guide the optimal use and administration of EA by the IV route. The impact of nausea and vomiting on the efficacy of EA should be evaluated, specifically whether the presence of these adverse effects correlates with NSAA levels and therefore reduced asparagine depletion. Although follow-up studies are under way,[9] the long-term comparative efficacy of IV versus IM administration of EA should continue to be assessed, given recent concerns that asparagine depletion may be suboptimal with IV administration on a Monday–Wednesday–Friday schedule.[9] Furthermore, it is possible that the nausea experienced by patients in the current series was a result of increased serum ammonia secondary to asparagine breakdown, as described by other investigators.[15,16] None of the current patients experienced lethargy or alteration in mental status suggestive of severe hyperammonemia, but systematic comparison of these results to symptoms seems justified. Finally, a direct comparison of the adverse effects experienced by patients with IM versus IV administration of EA should be performed.

CONCLUSION

In the authors' limited experience, delivery of EA by the IV route was moderately emetogenic, whereas little nausea or vomiting was seen when the drug was given by the IM route. We recommend that IV EA be reclassified as moderately to highly emetogenic and that patients receive suitable prophylaxis, including, at a minimum, a serotonin inhibitor and potentially other adjuvant agents.[10] For patients with inadequate control of nausea, IM administration of EA remains an option.

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ON THE FRONT COVER

Abraham Lake, Alberta

Abraham Lake is an artificial reservoir in southwestern Alberta. Its waters drain to the North Saskatchewan River, with levels being controlled by the Bighorn Dam. Methane gas that emerges from the lake bed forms bubbles that freeze within the winter ice. As the water level drops over the winter months, the ice collapses to form shoreline "icebergs". The ice is very clear: in most places, you can see the lake bottom and even the odd fish swimming by underfoot. This photograph was taken on February 13, 2010, by Jim Dobie, husband of CSHP member Terri Schindel. The photographer used a Canon EOS 5D Mark II camera, with Canon 17-mm TSE lens (f/16, shutter speed 0.5 second) and Singh-Ray circular polarizer.

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