

## RESEARCH ARTICLE

# Incidence and Management of Toxicity Associated with L-Asparaginase in the Treatment of ALL and NK/T-Cell Lymphoma: an Observational Study

Shu Hui Yeang<sup>1\*</sup>, Alexandre Chan<sup>2</sup>, Chuen Wen Tan<sup>3</sup>, Soon Thye Lim<sup>2</sup>, Heng Joo Ng<sup>3</sup>

### Abstract

**Background:** L-asparaginase (ASNase) is commonly used in the treatment of acute lymphoblastic leukemia (ALL) and natural killer (NK)/T-cell lymphoma. This study was designed to describe the incidence of toxicity associated with ASNase in Asian adults. Secondary objectives were to investigate the management and impact of toxicity on subsequent ASNase use, and to compare the actual management against current recommendations. **Materials and Methods:** In this retrospective, multi-center, observational study, Asian patients  $\geq 18$  years old who received  $\geq 1$  dose of the native *E. coli* ASNase from 2008 to 2013 were included. Patients were excluded if they did not receive ASNase. Endpoints of this study were development of specific toxicities, whether ASNase was discontinued or re-challenged, and development of recurrent toxicity. All data analyses were performed using SPSS version 20.0. **Results:** A total of 56 patients were analyzed. Mean ( $\pm$ SD) age was 36.2 ( $\pm$ 15.2) years old, with 62.5% being males, 55.4% with ALL and 28.6% with NK/T-cell lymphoma. Hypersensitivity (12.5%) was associated with the highest incidence of toxicity (6 out of 7 patients had Grade 3 and 4 toxicity), followed by 10.7% for hepatic transaminitis, 3.6% for non-CNS thrombosis and 1.8% each for hyperbilirubinemia and pancreatitis. Hypersensitivity recurred in the 3 patients who were re-challenged with *E. coli* ASNase. **Conclusions:** ASNase is associated with a wide range of toxicities, with hypersensitivity being the most commonly observed among Asian adult patients.

**Keywords:** L-Asparaginase - ALL - NK/T cell lymphoma - treatment - toxicity - hypersensitivity

*Asian Pac J Cancer Prev*, 17 (7), 3155-3160

### Introduction

L-asparaginase (ASNase) is an anti-cancer agent commonly used for the treatment of acute lymphoblastic leukemia (ALL). It is also used in combination with other chemotherapeutic agents for the treatment of natural killer (NK)/T-cell lymphoma (Yong et al., 2003; Yamaguchi et al., 2008; Yamaguchi et al., 2011). The use of ASNase in ALL is well-established and it has been the mainstay of pediatric ALL regimens since the 1960s. Today, ASNase is included in selected treatment regimens of adult ALL (Stock et al., 2011). The mechanism of action of ASNase involves its rapid depletion of extracellular asparagine by irreversibly hydrolyzing L-asparagine to L-aspartic acid and ammonia (Asselin et al., 2011). Leukemic lymphoblasts have characteristically low asparagine synthetase activity and hence, are dependent on exogenous asparagine for protein synthesis to support their malignant proliferation and survival (Narta et al., 2007). The action of ASNase leads to deficiency in asparagine, which culminates in the death of the leukemic lymphoblasts

(Kafkewitz and Bendich, 1983). Healthy cells, on the other hand, have sufficient amounts of asparagine synthetase, and thus, are able to synthesize asparagine de novo (Asselin et al., 2011).

ASNase is associated with a wide range of adverse events including hypersensitivity, coagulation disorders, hepatotoxicity and pancreatitis among both pediatric and adult populations (Oettgen et al., 1970). The frequency of these adverse events in the published literature is wide-ranging, depending on the formulations of ASNase used and the age group studied. Hypersensitivity has been reported to occur in about 15% of patients (Stock et al., 2011). Coagulation disorders and hepatotoxicity may occur in about 30% of patients while pancreatitis is less common, occurring in up to 2% of patients (Earl, 2009). Other toxicities, such as fever, nausea, vomiting and anorexia were observed in the earlier adult trials and attributed to the presence of other bacterial proteins and impurities in the native *Escherichia coli* (*E. coli*)-derived drug (Oettgen et al., 1970). Recent improvements in the purity of the native *E. coli* ASNase and the availability

Department of Pharmacy, <sup>1</sup>Singapore General Hospital, <sup>2</sup>National Cancer Centre Singapore, <sup>3</sup>Department of Haematology, Singapore General Hospital, Singapore \*For correspondence: yeang.shu.hui@sgh.com.sg

of Erwinia ASNase, a product isolated from *Erwinia chrysanthemi*, as well as the introduction of longer-acting pegylated ASNase have resulted lower rates of adverse events and a renewed interest in the use of ASNase in the adult population (Stock et al., 2011).

Recommendations on the prevention and management of ASNase-associated toxicities in adults and older adolescents have recently been incorporated in clinical practice guidelines including those from the National Comprehensive Cancer Network (NCCN) (Stock et al., 2011; Alvarnas et al., 2012). These recommendations allow clinicians to better manage patients who manifest toxicities, as well as guide the subsequent use of ASNase but are mainly based on Western populations. Toxicity data is emerging from Asian studies on adult patients receiving ASNase for NK/T cell lymphoma but less so in adult ALL patients. We sought to investigate the incidence of the various toxicities associated with ASNase and its management in our cohort of adult ALL and NK/T cell lymphoma patients and compare our management against current recommended guidelines.

## Materials and Methods

This was a retrospective, two center, observational study, which was conducted at Singapore General Hospital (SGH), a tertiary referral center with a comprehensive haematology service and National Cancer Centre Singapore (NCCS), a specialty cancer centre. The study protocol was approved by our Centralized Institutional Review Board. Informed consent from patients was waived because of the retrospective observational design.

Patients aged  $\geq 18$  years old who received at least one dose of the native *E. coli* ASNase or the Erwinia ASNase in accordance to institutional chemotherapy protocols from January 2008 to September 2013 were included in the study. The latter formulation was usually given to patients who developed toxicities to ASNase. Demographic, clinical and radiological data were extracted from the institution databases and electronic archives. The chemotherapy protocols and doses of ASNase administered were obtained from medical records.

The primary endpoint was the proportion of patients who developed any of the following toxicities associated with ASNase: hypersensitivity, pancreatitis, hepatic transaminitis, hyperbilirubinemia, thrombosis, bleeding, hypertriglyceridemia and hyperglycemia. Toxicities were graded using the Common Terminology Criteria of Adverse Events version 4.0 (CTCAEv4.0), which classifies each toxicity from Grades 1 to 5 with unique

clinical descriptions of severity for each toxicity (National Cancer Institute, 2009).

Specific measures in the management of patients who developed toxicities associated with the native *E. coli* ASNase were obtained from medical records. The management of toxicities was then compared with that recommended by the NCCN Guidelines Panel (Stock et al., 2011; Alvarnas et al., 2012; Alvarnas et al., 2015).

The secondary endpoint was the proportion of patients who discontinued ASNase therapy because of toxicities and the proportion developing recurrent toxicity. The management strategy for these individuals was also investigated.

## Statistical Analysis

Descriptive statistics were performed for baseline characteristics. Inferential statistics for correlation were performed using Spearman correlation test. All data analyses were performed using SPSS version 20.0.

## Results

A total of 56 patients received at least one dose of the native *E. coli* ASNase. The mean ( $\pm$ SD) age was 36.2 ( $\pm 15.2$ ) years old and 62.5% were males. The majority of them were treated for ALL (55.4%) and NK/T-cell lymphoma (28.6%). The study population was mostly made up of patients with Chinese descent (64.3%) followed by races of other origin (25.0%). All patients received the full unit dose based on their body surface areas, as defined in the institution-based chemotherapy protocols (Table 1).

Thirty-six patients (64.3%) received more than one cycle of chemotherapy that contained ASNase. A total of 462 doses of ASNase were intended for all the patients, out of which 399 doses (86.4%) were administered. Reasons for not completing all the intended doses of ASNase included occurrence of toxicities associated with ASNase and the development of severe medical complications including sepsis that necessitated the cessation of chemotherapy. The baseline characteristics of the study population are shown in Table 2.

The incidence of each toxicity associated with *E. coli* ASNase is shown in Table 3, with breakdown of the grades of toxicity. The proportion of patients who had their ASNase therapy discontinued and the incidence of recurrent toxicity are also shown in Tables 3 and 4.

## Hypersensitivity

Seven patients (12.5%) developed hypersensitivity reactions attributed to the native *E. coli* ASNase, all of

**Table 1. Doses of L-aspa Based on Institution-Based Chemotherapy Protocols**

Diagnosis	Protocol	L-aspa dose	L-aspa test dose	Days (D)
NK/T-cell lymphoma	SMILE	IV 6000 units/m <sup>2</sup> every other day	SC 2 units on D8	D8, 10, 12, 14, 16, 18 and 20
ALL	HCVAD Maintenance Month 9	IV 10000 units/m <sup>2</sup>	SC 2 units on D1	D1, 3 and 5
ALL	HCVAD Maintenance Month 12	IV 10000 units/m <sup>2</sup>	SC 2 units on D1	D1, 3 and 5
ALL	BFM Salvage Relapse 1	IV 25000 units/m <sup>2</sup> at 11am	SC 2 units at 10am on D6	D6
ALL	HKSG ALL 97- Induction Phase IA High Risk and Intermediate Risk	5000 units/m <sup>2</sup> every 3 days	SC 2 units on D12	D12, 15, 18, 21, 24, 27, 30 and 33

which manifested during the first full dose of ASNase (Tables 3 and 4). Six out of 7 patients developed Grades 3 or 4 toxicities. All of them were managed with intravenous (IV) hydrocortisone, IV diphenhydramine and oral (PO) chlorpheniramine. Three of them (1 patient with Grade 3 and 2 patients with Grade 4 toxicities) required IV adrenaline and/or fluid resuscitation in addition to steroids and antihistamines.

The seventh patient developed Grade 2 toxicity during his first cycle of the SMILE regimen. It was managed symptomatically with PO hydroxyzine and topical mometasone cream for the erythematous macular rash on his thigh. The patient subsequently developed Grade 3 hypersensitivity during the first ASNase infusion of his

**Table 2. Baseline Characteristics (n=56)**

Characteristic	
Age – years	
Mean	36.2 ± 15.2
Range	18 - 78
Sex – no. (%)	
Male	35 (62.5)
Race – no. (%)	
Chinese	36 (64.3)
Malay	5 (8.9)
Indian	1 (1.8)
Others	14 (25.0)
Type of cancer – no. (%)	
ALL	31 (55.4)
NK T-cell lymphoma	16 (28.6)
Others	9 (16.1)
No. of cycles containing <i>E. coli</i> ASNase received – no. (%)	
1	20 (35.7)
2	27 (48.2)
3	6 (10.7)
4	3 (5.4)
Chemotherapy regimen in cycle 1 – no. (%)	
SMILE	18 (32.1)
HCVAD Maintenance Month 9 or 12	12 (21.4)
BFM Salvage Relapse 1	10 (17.9)
HKSG ALL 97 – Induction Phase 1A (IR and HR)	7 (12.5)
Others	9 (16.1)
Route of <i>E. coli</i> ASNase in cycle 1 – no. (%)	
Intravenous (IV)	44 (78.6)
Subcutaneous (SC)	12 (21.4)

second cycle of SMILE. It necessitated the temporary cessation of ASNase infusion. The patient was treated with IV diphenhydramine and PO chlorpheniramine. The ASNase infusion was resumed two hours after it was stopped and this infusion was completed uneventfully. Subsequently, one dose of IV diphenhydramine and IV hydrocortisone was administered prior to every ASNase infusion. The patient completed his second cycle of the SMILE regimen uneventfully.

ASNase was re-challenged in 2 of the 7 patients. One of them was re-challenged within the same chemotherapy cycle while the other was re-challenged during the next chemotherapy cycle. Both of these patients developed recurrent hypersensitivities. Four out of the 7 patients were switched to Erwinia ASNase and none of them developed recurrent hypersensitivity reactions.

*Pancreatitis*

One patient (1.8%) was diagnosed with pancreatitis secondary to the native *E. coli* ASNase (Table 3). This is a 35 year-old patient with NK/T-cell lymphoma who had tolerated cycle 1 of the SMILE regimen. During her second cycle of treatment, she complained of abdominal pain and ASNase was temporarily held off. Further workup revealed elevated amylase and lipase levels at 117 U/L and 87 U/L respectively. However, radiological findings were not indicative of pancreatitis and ASNase therapy was continued in this patient. The patient's amylase and lipase levels, which were monitored closely, ranged from 78 – 137 U/L and 62 – 94 U/L respectively. The patient continued to complain of abdominal pain throughout cycle 2 of the SMILE regimen and was eventually diagnosed with infected pancreatic pseudocyst and ASNase-induced latent onset pancreatitis. By that time, she had received five doses of ASNase. ASNase was discontinued and the patient underwent open pancreatic cystogastrostomy.

*Hepatic transaminitis*

Six patients (10.7%) developed hepatic transaminitis secondary to the native *E. coli* ASNase (Table 3). Five out of 6 patients developed toxicity after completion of ASNase therapy during cycle 1 of their chemotherapy regimen. None of the 6 patients had underlying hepatic

**Table 3. Incidence of Toxicities Associated with *E. coli* ASNase (n = 56)**

Types of toxicity	Incidence of toxicity (%)	Grades of toxicity (%)					Impact of ≥ Grade 1 toxicity on subsequent doses of ASNase (%)
		1	2	3	4	5	
Hypersensitivity	12.5	0	1.8	7.1	3.6	0	Refer to Table 4
Pancreatitis	1.8	0	0	1.8	0	0	DC: 1.8
Hepatic transaminasemia	10.7	1.8	1.8	7.1	0	0	DC: 1.8 CM: 8.9
Hyperbilirubinemia	1.8	0	0	1.8	0	0	CM: 1.8
Central nervous system (CNS) thrombosis	0	0	0	0	0	0	-
Non-CNS§ thrombosis	3.6	0	3.6	0	0	0	C: 1.8; recurrence CM: 1.8
CNS bleeding	0	0	0	0	0	0	-
Non-CNS§ bleeding	0	0	0	0	0	0	-
Hypertriglyceridemia	3.6	0	0	0	3.6	0	DC: 1.8 CM: 1.8
Hyperglycemia	0	0	0	0	0	0	-

C: continued, DC: discontinued, CM: course of native *E. coli* ASNase was completed when diagnosis of toxicity was made; §Non-CNS thrombosis/bleeding refers to thrombosis/bleeding located outside of the CNS

**Table 4. Proportion of Patients Who Received Test Doses and Developed Hypersensitivity, the Proportion Whose ASNase Was Discontinued or Re-Challenged, and the Proportion Who Developed Recurrent Hypersensitivity (n = 56)**

Test doses performed	100%
Negative ID test doses	100%
Hypersensitivity despite negative test doses	12.50%
No. of ASNase doses given in current cycle prior to hypersensitivity	
1	100% (7/7)
≥ 1	0% (0/7)
No. of exposures to ASNase prior to current cycle	
0	25% (2/8)
1	62.5% (5/8)
2	12.5% (1/8)
Impact of hypersensitivity	
Continued ASNase	28.6% (2/7)
Switched to Erwinia ASNase	57.1% (4/7)
Discontinued ASNase	14.3% (1/7)
Recurrence of hypersensitivity	
After continuing ASNase	100% (2/2)
After switching to Erwinia ASNase	0% (0/4)

**Table 5. Grades of Hypofibrinogenemia Associated with *E. coli* ASNase as well as Age Range and No. of ASNase Doses Required for Patients with Incomplete Fibrinogen Monitoring**

Grade of hypofibrinogenemia (n = 56)	No. of patients (%)
Grade 1	7 (12.5)
Grade 2	10 (17.9)
Grade 3	14 (25.0)
Grade 4	1 (1.8)
Grade 5	0 (0)
Unknown due to incomplete monitoring	24 (42.9)
Patients with incomplete monitoring (n = 24)	No. of patients (%)
Age range	
≥ 18 – 20	9 (37.5)
> 20 – 30	5 (20.8)
> 30 – 40	6 (25)
> 40	4 (16.7)
No. of ASNase doses required	
1	14 (58.3)
2	0 (0)
3	3 (12.5)
4	3 (12.5)
≥ 5	4 (16.7)

dysfunction, but they were concurrently receiving other potentially hepatotoxic drugs including itraconazole, fluconazole, etoposide, gemcitabine, 6-mercaptopurine and/or methotrexate. The transaminase levels improved after ASNase was discontinued or completed. One patient was given a second cycle of ASNase after his initial Grade 1 toxicity had resolved. He developed another episode of Grade 1 toxicity and ASNase therapy was subsequently discontinued.

Monitoring of hepatic transaminases, alanine transaminase (ALT) and aspartate transaminase (AST), was done for all 56 patients pre-, during and post-ASNase administration.

*Hyperbilirubinemia*

One patient (1.8%) developed Grade 3 hyperbilirubinemia and concurrent Grade 3 hepatic transaminitis after completion of the first cycle of the native *E. coli* ASNase (Table 3). This patient’s liver function tests eventually improved over time. Monitoring of serum bilirubin was done for all 56 patients pre-, during and post-ASNase administration.

*CNS and non-CNS thrombosis*

None of the patients developed CNS thrombosis, whereas 2 patients (3.6%) experienced non-CNS thrombosis associated with the native *E. coli* ASNase (Table 3). The first patient was a 19 year-old with ALL receiving induction chemotherapy with the HK SG ALL 97 IA (IR) protocol. His magnetic resonance imaging showed right arm thrombosis in the basilic, brachial and axillary veins after two doses of SC ASNase. Intermediate doses of enoxaparin were started and continued on discharge, with doses titrated based on the degree of his concomitant thrombocytopenia. Five additional doses of SC ASNase were given while he was being treated for his thrombosis. The patient was subsequently diagnosed with thrombosis of his left cephalic vein and right subclavian vein three months later during his second chemotherapy cycle, while he was still on intermediate-dose enoxaparin therapy. Only a single dose of IV ASNase was required for the second chemotherapy cycle and the decision was made to proceed with the dose. Erwinia ASNase was substituted for subsequent cycles, and the patient was not documented to have recurrent thrombosis.

The second patient was a 20 year-old with ALL who was diagnosed with subacute right subclavian and axillary thrombosis four months earlier. During continuation of treatment with the HK SG ALL Reinduction phase IIA (IR) regimen, she developed new right upper limb venous thrombosis approximately one week after the fourth dose of IV ASNase. This occurred in the presence of peripherally-inserted central catheter.

*Bleeding*

None of the patients experienced clinically overt bleeding events associated with the native *E. coli* ASNase. Hypofibrinogenemia was common among all the patients. Twenty-four patients (42.9%) were given prophylactic cryoprecipitate which was administered when fibrinogen levels were below 1 g/L. A mean of 32.0 (10-100) units of cryoprecipitate was administered for the 24 patients to maintain fibrinogen levels at > 1 g/L.

Monitoring of fibrinogen was considered complete if fibrinogen levels were obtained pre- and post-ASNase, as well as prior to each dose of ASNase for every chemotherapy cycle containing ASNase. Complete monitoring of fibrinogen was observed in 32 patients (57.1%). The severity of hypofibrinogenemia is shown in Table 5.

Monitoring of baseline activated partial thromboplastin time (aPTT) and prothrombin time (PT) was done for all patients prior to the first dose of ASNase.

#### *Hypertriglyceridemia*

Two patients (3.6%) developed hypertriglyceridemia attributed to the native *E. coli* ASNase (Table 3). Both of them did not have elevated amylase levels or clinical symptoms of acute pancreatitis.

The first patient was a 36 year-old male on cycle 2 of the SMILE regimen NK/T-cell lymphoma. An unquantifiable fibrinogen assay due to lipemia, taken prior to his final dose of ASNase, led to the discovery of a fasting triglyceride (TG) level of 49.24 mmol/L. Fenofibrate was initiated for his Grade 4 toxicity and his TG levels gradually returned to baseline. He completed his third cycle of the SMILE regimen without recurrence of hypertriglyceridemia.

The second patient was a 53 year-old male on the SMILE regimen with a past medical history of hyperlipidemia that was well-controlled with simvastatin and fenofibrate. Both drugs were withheld to avoid possible drug interactions with his SMILE regimen. His lipid levels were not monitored during this time. A lipemic blood sample for fibrinogen assay led to the finding of a serum TG level of 40.75 mmol/L during the third cycle of SMILE. TG levels gradually returned to normal after management with diet control, fenofibrate and omega-3-fatty acids (Seah et al., 2012).

Monitoring of TG levels was not performed prior to the start of each course of ASNase for all 56 patients.

#### *Hyperglycemia*

None of the patients experienced hyperglycemia due to the native *E. coli* ASNase and monitoring of serum glucose specifically for possible hyperglycemia due to ASNase was not done for all 56 patients.

## **Discussion**

This study describes the incidence of toxicities associated with the native *E. coli* ASNase, as well as evaluated the management strategies and impact of these toxicities on subsequent ASNase therapy in a cohort of Asian adults. The incidence of toxicities was generally low, with the highest incidence being that of hypersensitivity, followed by hepatic transaminitis. Although this was a retrospective study with a small sample size, a number of potentially practice-changing observations was evident in this study.

Firstly, intradermal (ID) test doses did not predict for hypersensitivity as all the clinically significant reactions occurred despite negative test doses. None of our patients tested positive in the first instance, calling into question the value of this test. The incidence of hypersensitivity observed in our study is similar to the estimated incidence of 10% to 15% reported in the literature (Stock et al., 2011). Majority of the hypersensitivities in our study occurred in patients who were not ASNase-naïve, suggesting that prior exposure to ASNase increases the risk of development of hypersensitivity. Arising from

this finding, a review should therefore be carried out to reassess the necessity of this practice in our institution.

Secondly, hypersensitivity to ASNase should mandate a switch to Erwinia ASNase rather than a rechallenge. The hypersensitivities were mostly of Grades 3 and 4 severity. These clinically significant hypersensitivities, which necessitated temporary cessation or discontinuation of ASNase therapy, developed despite negative ID test doses. The recent NCCN guidelines recommend the discontinuation of the native *E. coli* ASNase or peg-ASNase and switching to the use of Erwinia ASNase in patients who develop hypersensitivities of Grades 1 and above (Alvarnas et al., 2015). This is because hypersensitivities associated with the native *E. coli* ASNase arise from the production of anti-ASNase antibodies and cross-reactivity between these neutralizing antibodies have been reported for peg-ASNase but not for Erwinia ASNase (Wang et al., 2003; Zalewska et al., 2009; Liu et al., 2012; Alvarnas et al., 2015). Reactions such as hypertriglyceridemia and venous thrombosis in which there are preventive interventions however, may not necessarily mandate a switch to the more expensive option.

Severe hypofibrinogenemia occurred frequently among our patients and were managed with prophylactic cryoprecipitate infusion. Despite this, there were no reported bleeding events in our patients. This may be attributable to replacement with cryoprecipitate in some of our patients. It is however uncertain if there is indeed a need to replace cryoprecipitate as the alternative problem of thrombosis seems more common albeit with low incidence. Indeed, many centres give venous thrombosis prophylaxis to their patients because of the substantial risk of venous thrombosis caused by a decline in natural anticoagulants which occurs in concert with the reduction in clotting factors. Given the substantial exposure to blood donors with cryoprecipitate infusion, there is again a need to review this practice with a view to refine and limit transfusion to as few patients as possible. This can be achieved by either further lowering the limits for which transfusion is given or eliminating fibrinogen monitoring altogether.

Cases of hepatic transaminitis and hyperbilirubinemia documented in our study were asymptomatic and self-limited with discontinuation of exposure. The concurrent use of other hepatotoxic agents, as part of the chemotherapy regimen or as anti-fungal prophylaxis in treatment of ALL and NK/T-cell lymphoma can make differentiating the exact cause of the toxicities difficult (Stock et al., 2011). A prudent approach is to closely monitor liver function tests to allow for early management of toxicity by limiting exposure to the most likely incriminating agents.

ASNase therapy has been associated with an acquired deficiency of antithrombin, as well as concurrent depletion of hemostatic proteins. In addition, external prothrombotic factors like immobility, corticosteroid use and increased age may also contribute to increased thrombotic risk. To date, the exact mechanism of thrombosis related to the use of ASNase is not defined (Truelove, Fielding and Hunt, 2013). In terms of thrombosis management, there is no clear indication from the literature whether subsequent

doses of ASNase should be discontinued in adults. However, it has been shown in a study that ASNase can be restarted if repeat imaging demonstrates clot stabilization or improvement and resolution of thromboembolic symptoms. This is in conjunction with close monitoring of anticoagulation (Grace et al., 2011). Based on this study, the typical time frame for ASNase to be restarted is about four weeks from the time of venous thromboembolism (VTE) diagnosis (Grace et al., 2011). These findings are reflected in the NCCN guidelines (Alvarnas et al., 2012). In the study, recurrence of VTE occurred only in those patients restarted on ASNase. 11 out of the 33 patients restarted on ASNase after VTE experienced a recurrence of VTE (17% of pediatric patients vs. 47% of adults,  $P = 0.07$ ) (Grace et al., 2011).

In our 19 year-old patient who was restarted on the native *E. coli* ASNase after initiation of anticoagulation, recurrent thrombosis was observed. The management of therapeutic anticoagulation was complicated as it had to be balanced with the bleeding risks due to his thrombocytopenia. Furthermore, no repeat imaging was done to assess the status of his thrombosis prior to restarting ASNase.

Hypertriglyceridemia associated with ASNase is possibly related to increased synthesis of very low density lipoproteins, decreased activity of lipoprotein lipase that removes TG from the blood circulation, and increased exogenous chylomicrons in the blood (Steinherz, 1994; Parsons et al., 1997). As in our patients, hypertriglyceridemia associated with ASNase reported in the literature were typically discovered when patients manifested with symptoms of acute pancreatitis or when turbid serum or blood samples were drawn (Kfoury-Baz et al., 2008; Nakagawa et al., 2008). Among the various toxicities of ASNase, this appears to be the one that is least likely to be monitored. Regular monitoring of amylase and lipase levels is thus important to prevent progression to and manifestation of acute pancreatitis. Amylase monitoring, although instituted in our chemotherapy protocols, was not done for our study population prior to the first dose of ASNase. A baseline TG level should be obtained prior to the first dose of ASNase to allow for observation of trends in cases of hypertriglyceridemia or pancreatitis.

Our study represents a comprehensive review of the incidence and management of toxicities associated with ASNase in an Asian adults population. Its findings confirms the wide range of toxicities associated with ASNase although event rates were low. Nonetheless, this study will provide supporting data for the institution of measures to reduce the occurrence such toxicities and manage them accordingly. Additionally, it may help institutions refine their strategies for monitoring patients receiving ASNase as part of their chemotherapy protocols.

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