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Severe Hypertriglyceridemia During Therapy For Childhood Acute Lymphoblastic Leukemia

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Abstract

Background—Asparaginase and steroids can cause hypertriglyceridemia in children with acute lymphoblastic leukemia (ALL). There are no guidelines for screening or management of patients with severe hypertriglyceridemia (>1000 mg/dL) during ALL therapy.

Patients and Methods—Fasting lipid profiles were obtained prospectively at 4 time-points for 257 children consecutively enrolled on a frontline ALL study. Risk factors were evaluated by the exact chi-square test. Details of adverse events and management of hypertriglyceridemia were extracted retrospectively.

Results—Eighteen of 257 (7%) patients developed severe hypertriglyceridemia. Older age and treatment with higher doses of asparaginase and steroids on the standard/high-risk arm were significant risk factors. Severe hypertriglyceridemia was not associated with pancreatitis after adjustment for age and treatment arm or with osteonecrosis after adjustment for age. However, patients with severe hypertriglyceridemia had a 2.5 to 3 times higher risk of thrombosis compared to patients without, albeit the difference was not statistical significant. Of the 30 episodes of

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severe hypertriglyceridemia in 18 patients, 7 were managed conservatively while the others with pharmacotherapy. Seventeen of 18 patients continued to receive asparaginase and steroids. Triglyceride levels normalized after completion of ALL therapy in all 12 patients with available measurements.

Conclusion—Asparaginase- and steroid-induced transient hypertriglyceridemia can be adequately managed with dietary modifications and close monitoring without altering chemotherapy. Patients with severe hypertriglyceridemia were not at increased risk of adverse events, with a possible exception of thrombosis. The benefit of pharmacotherapy in decreasing symptoms and potential complications requires further investigation.

Keywords

Hypertriglyceridemia; Childhood ALL; Asparaginase; Thrombosis

Introduction

In children with acute lymphoblastic leukemia (ALL), rational use of risk-adapted multidrug chemotherapy regimens and improved supportive care has led to 5-year survival rates of 90% or more [1, 2]. However, effective therapy can cause adverse interactions and complications. For example, co-administration of asparaginase and steroid can cause significant changes in serum lipid levels [3]. Cases of children with ALL have been reported with triglyceride and cholesterol levels as high as 20,600 mg/dL (normal: <130 mg/dL) and 1640 mg/dL (normal: <200 mg/dL), respectively [4].

Hypertriglyceridemia in children treated for ALL is believed to be under-diagnosed, but transient and generally benign [4]. However, triglyceride levels >1,000 mg/dL in the general population increases the risk of acute pancreatitis [5, 6]. In addition, hypertriglyceridemia-induced hyperviscosity syndrome can lead to thromboembolic events [7, 8]. Lipid derangements may also contribute to the development of steroid-induced osteonecrosis [9, 10]. Data on the prevalence, risk factors and complications of severe hypertriglyceridemia in children treated for ALL remain very limited and there is no consensus regarding the management of this condition.

Approximately 0.2% of healthy children in the United States have severe hypertriglyceridemia (>500 mg/dL) [11], but its prevalence can be as high as 8–16% in children with ALL (>1000 mg/dL) [3, 4, 12]. A study on children with ALL showed no association between triglyceride levels and age or gender [12]. However, a systematic evaluation of potential risk factors and complications has not been performed because of the small number of patients studied. There are no clear recommendations on screening patients for hypertriglyceridemia or for continuing asparaginase, steroids or their combination during severe hypertriglyceridemia [13, 14]. Occasionally, life-threatening emergencies have warranted plasmapheresis [15]. However, for asymptomatic patients or in those with milder symptoms, therapy has ranged from observation and dietary modification alone, [13] to steroid omission, [14] or pharmacotherapy with omega-3 fatty acids (FA), [16] fibrates, [12] statins, [17] heparin [12] or insulin [18].

In this study, we report the prevalence, describe the course and review the management of patients with severe hypertriglyceridemia. We also identify risk factors and potential complications associated with this condition in a large cohort of patients treated uniformly for ALL at a single institution.

Methods

Patients

From October 2008 through December 2011, 258 children with newly diagnosed ALL were consecutively enrolled on the Total Therapy XVI study (NCT00549848) at St Jude Children's Research Hospital, Memphis, TN [19]. All patients were prospectively screened for dyslipidemia except for 1 patient who died early during remission induction therapy. The study was approved by the institutional review board. Informed consent at enrollment from the parents or guardians and assent from patients, when appropriate, were obtained.

Treatment

In brief, therapy comprised of three phases: remission induction, consolidation and continuation which included two blocks of re-induction therapy (Figure 1). Table 1 provides details of steroid and asparaginase use in the study. Patients received 3000 units/m^2/dose of peg-asparaginase during induction and were randomized to receive 2500 units/m^2 or 3500 units/m^2/dose post-induction. During the continuation and re-induction phases, patients on the standard/high-risk arm received uninterrupted peg-asparaginase every other week for 29 weeks (cumulative dose 37,500–52,500 units/m^2) and patients on the low-risk arm received peg-asparaginase twice during each of the two re-induction phases (cumulative dose 10,000–14,000 units/m^2). Prednisone was used during induction and dexamethasone post-induction.

Lipid Screening

Fasting lipid profiles comprised serum triglycerides, cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels and were measured prospectively at diagnosis, start of re-inductions I and II and end of therapy. In patients with severe hypertriglyceridemia, additional measurements were obtained when clinically indicated and repeated at least weekly in most patients until <1000 mg/dL. Assays for measurement of triglycerides, cholesterol and HDL were performed on a Cobas 600 analyzer using enzymatic/colorimetric methods (Roche Diagnostics, Indianapolis IN). LDL cholesterol was calculated according to the Friedewald formula [20]. In this report, we focused on patients with severe hypertriglyceridemia defined as a fasting triglyceride level >1000 mg/dL (11.4 mmol/L) which corresponds to a grade 4 adverse event according to the Common Terminology Criteria for Adverse Events version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE). A recurrent episode of severe hypertriglyceridemia was defined as a triglyceride level >1000 mg/dL after reduction to ≤1000 mg/dL for ≥7 days.

Assessment of Risk Factors and Potential Toxicities of Severe Hypertriglyceridemia

Data on patient characteristics, details of therapy, adverse events and management of hypertriglyceridemia were extracted retrospectively from medical records and study

databases. For 2–19 year-old patients, body mass index percentiles were calculated and used to define obesity (www.cdc.gov/obesity/childhood). Dyslipidemia was classified according to the guidelines of the National Cholesterol Education Program [21, 22].

Statistical Analyses

To study risk factors associated with the development of severe hypertriglyceridemia, we compared data from patients with triglyceride levels >1000 mg/dL and all other patients using the exact chi-square test. Clinical factors significantly associated with risk of developing severe hypertriglyceridemia in univariate logistic regression models were subsequently included in multiple logistic regression models to identify independent risk factors. Data were analyzed by SAS v9.2 (SAS Institute Inc., Cary, NC).

Results

Patient Characteristics

Of the 257 children, 18 (7%) had at least one episode of severe hypertriglyceridemia. Table 2 shows clinical characteristics of these 18 patients (median age 11 years; range 7–18 years). Of the 14 patients for whom family history was available, 10 (71%) had a history of cardiovascular disease. At diagnosis, 4 (22%) patients were obese (BMI ≥95th percentile for age) and 4 (22%) were overweight (BMI 85th–94th percentile). Fifteen (83%) patients had elevated baseline triglyceride levels (≥130 mg/dL), 5 (28%) patients had elevated baseline total cholesterol (median 120 mg/dL; range 97–305 mg/dL), 3 (17%) patients had elevated LDL (median 73 mg/dL; range 39–199 mg/dL) and all patients had decreased HDL (median 19 mg/dL; range 7–35 mg/dL). Seventeen (94%) patients were treated on the standard/high-risk arm of their respective study.

Episodes of Severe Hypertriglyceridemia

The 18 patients had 30 isolated episodes of severe hypertriglyceridemia (Table 3). Twenty-eight (93%) episodes occurred within 2 weeks of receiving asparaginase and steroids concurrently, 1 episode after steroid alone and 1 after asparaginase alone. The most common symptoms were diarrhea (*N=7*), abdominal pain (*N=6*), fatigue (*N=6*), nausea/vomiting (*N=5*) and headache (*N=4*). One patient had transient blurred vision. No symptoms were reported for 15 (50%) episodes. Pseudohyponatremia and hepatic transaminitis (≥grade 2, i.e. ≥3 x normal) were noted during 19 and 10 episodes respectively. Evidence of a hemolyzed blood sample (hyperkalemia and elevated lactic dehydrogenase in a lipemic sample) was present in 11 episodes. In 21 of 30 (70%) episodes, triglyceride levels were measured at least weekly until <1000 mg/dL. The median duration of these 21 episodes was 7 days (range 1–42 days)

Management of Severe Hypertriglyceridemia

All patients were advised to follow a low-fat diet. Seven episodes were managed conservatively while 8 episodes were managed with omega-3 FA alone, one with fibrate alone (due to intolerance to omega-3 FA) and 12 with a combination of omega-3 FA and fibrate. For 5 of the latter 12 episodes, a fibrate was added after omega-3 FA did not lower triglyceride levels. One patient received cholestyramine (2 episodes).

Seventeen patients continued the planned asparaginase and/or steroids. Asparaginase was permanently discontinued after one additional dose for patient #11 because of recurrent conjugated hyperbilirubinemia (possibly related to the combination of asparaginase, doxorubicin and vincristine during induction and re-induction). One dose of peg-asparaginase was held for patients #14 and #15 during acute thromboembolic episodes. Eight patients had more than one episode of severe hypertriglyceridemia: 5 patients had 2 episodes, 2 patients had 3 episodes and 1 patient had 4 episodes. After completion of ALL therapy, triglyceride levels were available for 12 patients and had normalized in all.

Toxicities in Patients with Severe Hypertriglyceridemia

Significant toxicities possibly associated with severe hypertriglyceridemia were thromboembolism in 4 patients and pancreatitis in 2.

Thromboembolism—Four of 18 (22%) patients with severe hypertriglyceridemia developed thrombosis (including 2 patients with pulmonary embolism) compared to 17 of 239 (7.1%) patients without (P=0.02). However, this comparison did not reach statistical significance in multivariable analysis (P=0.1), possible due to small numbers. In analyses limited to patients treated on the standard/high-risk arm, the incidence of thrombosis was 2.4 times higher in patients with severe hypertriglyceridemia (4 of 17 patients; 23.5%) compared to the others (14 of 143 patients; 9.8%).

Triglyceride levels were measured at the time of the thrombotic event for patients #14 and #18 and were 2036 mg/dL and 637 mg/dL respectively. For patient #10, triglyceride levels was 611 mg/dL two days prior, and for patient #15, it was 521 mg/dL 10 days after the thrombotic event. Patients #15 and #18 were not taking lipid-lowering medications, patient #10 was taking omega-3 FA, and patient #14 had stopped taking omega-3 FA and fibrate one month before the event. Low-molecular weight heparin was initiated for all 4 patients and none of them developed further thromboembolic complications. One additional patient (#1) developed cerebral vasculitis attributed to asparaginase and intrathecal methotrexate therapy.

Pancreatitis—The incidence of pancreatitis did not differ between patients with triglyceride levels >1000 mg/dL (2 of 18 patients; 11%), or ≤1000 mg/dL (19 of 239 patients; 8%) (P=0.63). The 2 patients (#6 and #8; 8%) who developed pancreatitis had triglyceride levels of 444 mg/dL and 611 mg/dL respectively, at the time of the acute event. In both patients, acute pancreatitis developed 3 months after peak triglyceride levels (3730 mg/dL and 2709 mg/dL respectively). *Osteonecrosis:* Symptomatic osteonecrosis (≥ grade 2) developed in 7 of 18 (39%) patients with hypertriglyceridemia and in 27 of 239 (11%) without (P=0.0009). Results remained significant when adjusted for risk arm (P=0.01), but not for age (P=0.6).

Risk Factors for Severe Hypertriglyceridemia

Race or gender did not differ significantly between patients who developed severe hypertriglyceridemia (*N=18*) and those who did not (*N=239*) (Table 4). Baseline triglyceride, total cholesterol, LDL and HDL levels at diagnosis did not influence the

development of severe hypertriglyceridemia during therapy. Overweight/obesity was more prevalent in patients who developed severe hypertriglyceridemia compared to those who did not (44% versus 31% respectively), but the difference was not statistically significant (P=0.09). Age > 10 years and therapy on the standard/high-risk arm with higher cumulative doses of peg-asparaginase and dexamethasone, each significantly increased the risk of hypertriglyceridemia (P<0.0001 for age and P=0.0035 for therapy arm). The risk of severe hypertriglyceridemia was similar in patients randomized to receive 2500 units/m^2 or 3500 units/m^2/dose peg-asparaginase.

Discussion

This study reports the largest cohort of uniformly treated children with ALL who underwent prospective clinical screening for dyslipidemia during therapy. Older children and those treated with higher-risk therapy are at risk for severe hypertriglyceridemia. While severe hypertriglyceridemia is associated with major acute complications in the general population, this could not be confirmed in children with ALL. However, they may have higher rates of thromboembolic events which are already problematic in this vulnerable population.

Severe hypertriglyceridemia occurred in 7% of our patients with ALL and was temporally related to steroid and asparaginase administration as described previously [3, 12]. Corticosteroids increase triglyceride synthesis and also increase the activity of lipoprotein lipase, a key enzyme required for the hydrolysis of triglycerides. On the other hand, asparaginase can inhibit the activity of lipoprotein lipase[23]. When asparaginase and steroids are given together, it is likely that triglyceride-rich lipoproteins are rapidly formed but insufficiently cleared[23]. Patients with severe hypertriglyceridemia may be asymptomatic or develop non-specific symptoms, and thus a high index of suspicion must be maintained, especially during intensive asparaginase and steroid therapy. However, symptoms such as diarrhea, abdominal pain and fatigue can be caused by multiple chemotherapeutic agents and co-morbidities during ALL therapy and are difficult to attribute to hypertriglyceridemia alone. Hypertriglyceridemia should also be suspected in patients with transaminitis and/or hyponatremia of unclear etiology. As *ex vivo* hemolysis often occurs in lipemic blood samples [24], especially if tubes are not handled gently; samples should be carried by hand to the laboratory instead of using a pneumatic tube system.

Therapy on the standard/high-risk arm with higher doses of asparaginase and steroids and older age (two features that are highly correlated), were significantly associated with a higher risk of severe hypertriglyceridemia. It is recognized that older patients have delayed clearance and increased systemic exposure of steroids given the same dosages compared to younger patients; an observation which may partly explain the association between older age and the development of hypertriglyceridemia [25]. The majority of our patients (218 of 257 patients; 85%) had mild to moderate elevations in baseline triglycerides before chemotherapy was initiated, as reported in patients with ALL and other cancers [26, 27]. In contrast, only 10% of healthy children have triglyceride levels >150 mg/dL [11]. Because hypertriglyceridemia resolves after completion of ALL therapy, it has been speculated that

this lipid derangement is a manifestation of an acute phase or immunologic response [27, 28].

Although the association of hypertriglyceridemia with coronary artery disease is well known, [29] its association with venous thromboembolism is unclear and might be related to changes in the fibrinolytic system[30]. A few case reports describe thrombosis in ALL patients with hypertriglyceridemia [7, 12] but in our study, approximately 20% of patients with severe hypertriglyceridemia developed venous thromboembolism. The combination of asparaginase, steroids and triglycerides causes a hypofibrinolytic state in the setting of hyperviscosity which may explain the increased risk of thromboembolism. Whether lowering triglyceride levels with pharmacotherapy or interventions like prophylactic anticoagulants decreases the risk of thrombosis in these patients remains unclear, but the latter approach was advocated in one report and merits further investigation [12].

In adults, severe hypertriglyceridemia is a well-described risk factor for pancreatitis and fibrates are recommended as first-line therapy [5]. Similarly, expert guidelines for children recommend pharmacotherapy and referral to a lipid specialist to prevent pancreatitis [22]. Acute pancreatitis is a well-known complication of leukemia therapy due to the use of asparaginase, steroids and thiopurines [31, 32]. However, in our study and other reports of children with ALL, severe hypertriglyceridemia did not increase the risk of pancreatitis [3, 12].

The association of osteonecrosis with hypertriglyceridemia requires additional investigation. Although the incidence of osteonecrosis was high in patients with severe hypertriglyceridemia in our study, it was primarily related to age; patients ≥10 years old develop both osteonecrosis and hypertriglyceridemia more frequently than younger children. In an animal model of steroid-induced osteonecrosis, significant elevations in cholesterol, triglycerides and free fatty acids occurred concurrently with the onset of osteonecrosis, approximately 1 week after steroid injection and it was proposed that fat embolism contributed to the development of osteonecrosis [9]. In a clinical study of osteonecrosis during childhood ALL therapy, hypercholesterolemia (not hypertriglyceridemia) increased the risk of symptomatic osteonecrosis [10].

Our study has some limitations. The absence of a screening time-point during or at the end of remission induction therapy did not give us the opportunity to investigate the incidence and complications hypertriglyceridemia when patients were receiving prednisone instead of dexamethasone in combination with asparaginase. Since the majority of episodes of hypertriglyceridemia occurred after dexamethasone and asparaginase given together, it is plausible that dexamethasone may be more potent than prednisone in causing hypertriglyceridemia. The number of patients with adverse events is low, making it difficult to determine definite associations. Thus, additional studies are needed to investigate the contribution of hypertriglyceridemia in the development of toxicities such as thromboembolism. Also, the management of severe hypertriglyceridemia was not uniform and differed by treating physicians. Because of low patient numbers and lack of adequate information on duration of episodes, it is unclear whether pharmacotherapy, either single agent or in combination, could reduce symptoms and adverse events potentially related to

hypertriglyceridemia. Fibrates may help reduce triglyceride levels rapidly and decrease the risk of hypertriglyceridemia-associated complications [5, 33]. However, fibrates should be used with extreme caution in children with ALL because of their potential hepatotoxicity, especially in combination with other hepatotoxic chemotherapeutic agents. Randomized trials of early interventions, either dietary modifications in patients at risk, or pharmacotherapy in patients with severe hypertriglyceridemia are needed to study the benefit of these interventions.

In summary, severe hypertriglyceridemia, an untoward effect of asparaginase and steroid therapy can cause troublesome symptoms and laboratory abnormalities. Severe hypertriglyceridemia during ALL therapy is transient and rarely associated with significant acute complications other than a possible increased risk of thrombosis. Given the risk of the underlying malignancy, steroids or asparaginase should not be held for severe hypertriglyceridemia and can be continued under close observation. Although routine screening is likely not required in clinical practice, long-term follow up of patients with history of severe hypertriglyceridemia is recommended to better understand additional therapy-related risk factors for the development of metabolic syndrome and cardiovascular disease which are significant concerns in ALL survivors [34, 35].

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Highlights

1. Older age and higher doses of asparaginase are risk factors for hypertriglyceridemia
2. Hypertriglyceridemia can be adequately managed without altering ALL therapy
3. Hypertriglyceridemia was not associated with pancreatitis in children with ALL

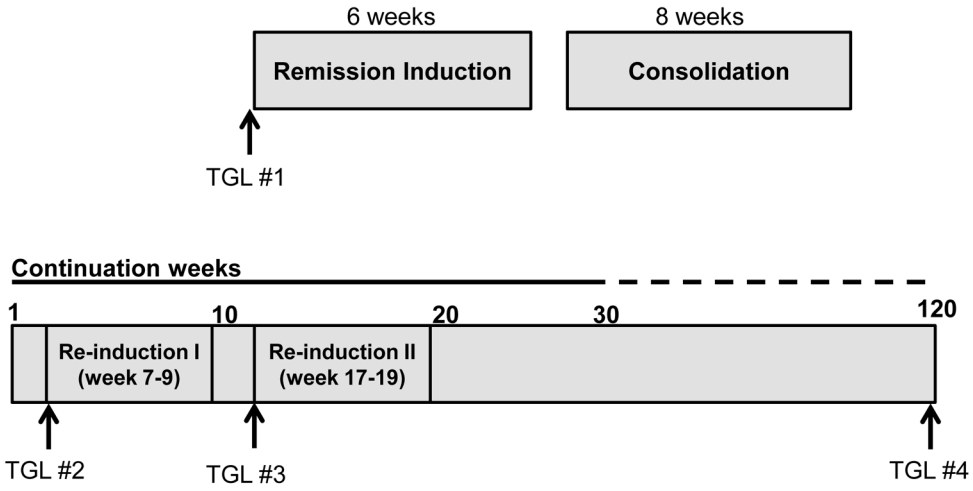

Figure 1.

Schematic representation of total XVI therapy.

Arrows represent the timing of screening triglyceride measurements.

Table 1

Steroids and asparaginase administered to patients enrolled on Total XVI

Treatment Phase	Drug	Low risk		Standard/high risk	
		Dose	**Total Dose**	**Dose**	**Total Dose**
Remission Induction	Prednisone	40 mg/m^2 for 28 days	1,120 mg/m^2	* Same	* Same
	Peg-asparaginase	3,000 units/m^2, 1 dose	3,000 units/m^2	3,000 units/m^2, 1–2 doses	3,000–6,000 units/m^2
Continuation (weeks 1–6 and 10–16)	Dexamethasone	8 mg/m^2/day for 5 days × 3 pulses	120 mg/m^2	12 mg/m^2/day for 5 days × 3 pulses	180 mg/m^2
	Peg-asparaginase	None	None	2,500 vs. 3,500 units/m ^{2}, 11 doses	27,500 vs. 38,500 units/m^2
Re-induction I (continuation weeks 7–9) and Re-induction II (continuation weeks 17–19)	Dexamethasone	8 mg/m^2 for 15 days	120 mg/m^2	8 mg/m^2 for 15 days	120 mg/m^2
	Peg-asparaginase	2,500 vs. 3,500 units/m^2, 4 doses	10,000 vs. 14,000 units/m^2	Same	Same
Continuation (Total XV weeks 21–28; Total XVI weeks 21–29)^	Dexamethasone	8 mg/m^2 for 5 days every 4 weeks	80 mg/m^2	12 mg/m^2 × 5 days every 4 weeks	120 mg/m^2
	Peg-asparaginase	None	None	2,500 vs. 3,500 units/m^2, 5 doses	12,500 vs. 17,500 units/m^2

*Patients with early T-cell precursor ALL received dexamethasone 10 mg/m^2/day from days 1–21, 2 mg/m^2/day from days 22–24 and 2 mg/m^2/day from days 25–28 (Total dose 230 mg/m^2).

#Second dose of peg-asparaginase was given if minimal residual disease was ≥ 1% on Day 15

^Subsequently, patients received 5-day pulses of dexamethasone every 4 weeks until week 100 of continuation.

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Table 2

Patient characteristics

Pt	Age(years)/Gender	Race	Cardiovascular disease in family	ALL subtype	Risk arm*	BMI at diagnosis kg/m^2 (percentile)	TGL at diagnosis (mg/dL)	Peak TGL (mg/dL)
1	7/M	W	Yes	B	Low	15.4 (25–50)	59	1619
2	14/F	W	Yes	B	Standard	24.4 (85–90)	492	1573
3	8/M	W	Yes	B	Standard	21.7 (>95)	151	6630
4	11/M	W	Yes	T	Standard	17.5 (50–75)	152	1146
5	8/F	W	No	B	Standard	15.2 (25–50)	81	4897
6	11/M	A	Yes	B	Standard	18.8 (75–85)	171	3730
7	18/M	W	Yes	T	Standard	24.8 (75–85)	288	5420
8	10/F	W	Unknown	T	Standard	20.27 (85–90)	239	2709
9	18/M	B	Yes	B	Standard	33.3 (>95)	160	1729
10	7/M	W	Yes	T	Standard	23.2 (>95)	658	1647
11	11/F	W	Yes	B	Standard	15.7 (10–25)	441	2399
12	15/M	B	Unknown	B	Standard	19.9 (50–75)	75	3578
13	8/F	W	No	B	Standard	15.4 (25–50)	204	1721
14	14/M	W	Yes	B	Standard	22.3 (75–85)	175	5489
15	12/M	W	Unknown	T	Standard	20.9 (85–90)	130	2066
16	7/M	W	No	B	Standard	15.5 (50–75)	202	2606
17	13/M	W	Unknown	T	Standard	28.1 (>95)	150	1982
18	13/M	W	No	T	Standard	22.1 (85–90)	153	1660

BMI: body mass index; TGL: triglyceride level, F: female; M: male; W: white; B: Black; A: Asian; NOS: not otherwise specified.

* For information on risk stratification, see reference 19

Table 3

Episodes of severe hypertriglyceridemia

Pt	Episode	Timing of therapy	Preceding steroid, asp	Peak TGL mg/dL	Days until TGL <1000 mg/dL	Symptoms	Abnormalities on laboratory tests	Adverse event (time from peak TGL)	Medications (duration in days)	Subsequent asparaginase
1	1st 2nd	Induction Day 24 Induction Day 32	Pred, peg-asp Pred	1619 1127	3 1	Headache None	HBS	Cerebral vasculitis (7 days pre)	Cholestyramine (12) Cholestyramine (continue)	Yes Yes
2*	1st	Re-induction I Day 1	Dex, peg-asp	1573	NA	Headache, nausea			–	Yes
3*	1st 2nd	Re-induction II Day 1 Continuation, Week 25	Dex, peg-asp Peg-asp	6630 1454	17 NA	Fatigue, diarrhea, nausea Fatigue, diarrhea	Transaminitis, hyponatremia HBS Transaminitis		O-3 FA (74), Fibrate (21) O-3 FA (continue)	Yes Yes
4	1st	Re-induction II Day 1	Dex, peg-asp	1146	NA	Diarrhea, abdominal pain			–	Yes
5	1st 2nd 3rd	Re-induction I Day 20 Continuation Week 14 Continuation Week 20	Dex, peg-asp Dex, peg-asp Dex, peg-asp	3937 4897 1282	22 36 NA	Fever, nausea, abdominal pain Abdominal pain None	Hyponatremia Hyponatremia		O-3 FA (7) Fibrate (30) –	Yes Yes Yes
6*	1st	Re-induction I Day 12	Dex, peg-asp	3730	4	Fatigue, headache	Transaminitis	Pancreatitis (56 days post)	–	Yes (stopped after pancreatitis)
7*	1st 2nd	Induction Day 24 Continuation Week 5	Pred, peg-asp Dex, peg-asp	5420 2062	16 2	Fatigue, emesis, diarrhea, abdominal pain Fatigue, diarrhea	Hyponatremia, transaminitis Transaminitis		O-3 FA (365), Fibrate (365) O-3 FA, Fibrate (continue)	Yes Yes
8	1st	Re-induction I Day 1	Dex, peg-asp	2709	19	Fatigue, diarrhea, abdominal pain, headache, blurred vision	Transaminitis, hyponatremia	Pancreatitis (75 days post)	O-3 FA (30)	Yes (stopped after pancreatitis)
9	1st 2nd	Re-induction I Day 8 Re-induction II Day 1	Dex, peg-asp Dex, peg-asp	1507 1729	42 7	None None			O-3 FA (350) O-3 FA (continue), Fibrate (180)	Yes Yes
10*	1st	Re-induction I Day 1	Dex, peg-asp	1647	7	None		Thrombosis: DVT (86 days post)	O-3 FA (7)	Yes
11	1st	Re-induction I Day 13	Dex, peg-asp	2399	7	Abdominal pain, fever	HBS		O-3 FA (14)	Only 1 dose (discontinued for hyperbilirubinemia)
12	1st 2nd	Re-induction I Day 1 Re-induction II Day 1	Dex, peg-asp Dex, peg-asp	3059 3578	NA NA	None None	HBS		O-3 FA (120) O-3 FA (continue)	Yes
13	1st	Re-induction I Day 1	Dex, peg-asp	1721	NA	None			–	Yes
14	1st 2nd 3rd	Re-induction I week 1 Continuation Week 22 Continuation Week 32	Dex, peg-asp Dex, peg-asp Dex, peg-asp	5489 2036 1790	17 25 7	None Fever Nausea, emesis	Hyponatremia, HBS Hyponatremia, HBS HBS	Thrombosis: DVT, PE (2 days pre)	O-3 FA (77), Fibrate (74) O-3 FA (153), Fibrate (153) O-3 FA, Fibrate (continue)	Yes Yes (held 1 dose) No (none due)
15	1st	Re-induction II Day 1	Dex, peg-asp	2066	NA	None		Thrombosis: DVT, PE (69 days pre)	–	Yes (held 1 dose)
16	1st 2nd 3rd 4th	Re-induction I Day 8 Continuation, Week 15 Re-induction II Day 14 Continuation Week 30	Dex, peg-asp Dex, peg-asp Dex, peg-asp Dex, peg-asp	1801 1169 1216 2606	42 7 5 7	None None None Fatigue, diarrhea, back pain	Transaminitis, hyponatremia HBS Transaminitis, HBS Transaminitis, hyponatremia, HBS		O-3 FA (180), Fibrate (90) O-3 FA, Fibrate (continue) O-3 FA, Fibrate (continue) O-3 FA (continue), Fibrate (35)	Yes Yes Yes No (none due)

Pt	Episode	Timing of therapy	Preceding steroid, asp	Peak TGL mg/dL	Days until TGL <1000 mg/dL	Symptoms	Abnormalities on laboratory tests	Adverse event (time from peak TGL)	Medications (duration in days)	Subsequent asparaginase
17*	1st	Re-induction II Day 1	Dex, peg-asp	1982	14	None	Transaminitis, HBS		O-3 FA (365), Fibrate (71)	Yes
18*	1st	Re-induction II Day 1	Dex, peg-asp	1660	NA	None		Thrombosis: cortical vein (70 days pre)	–	Yes

TGL: triglyceride; Pred: prednisone; Dex: dexamethasone; Asp: asparaginase; NA: not available; PE: pulmonary embolism; DVT: deep venous thrombosis; O-3FA: omega-3 fatty acids; HBS: hemolyzed blood sample

*Patients who developed symptomatic osteonecrosis during therapy

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Table 4

Risk factors for severe hypertriglyceridemia

Factor		Total number of patients (%)	Peak TG >1000mg/dL (%)	Peak TG ≤1000 mg/dL (%)	*P*-value
Age at diagnosis	<10 years	188 (73.2%)	6 (33.3%)	182 (76.2%)	<.0001
	≥10 years	69 (26.8%)	12 (66.7%)	57 (23.8%)	
Gender	Male	145 (56.4%)	13 (72.2%)	132 (55.2%)	0.16
	Female	112 (43.6%)	5 (27.8%)	107 (44.8%)	
Race	White	196 (76.3%)	15 (83.3%)	181 (75.7%)	0.76
	Black	39 (15.2%)	2 (11.1%)	37 (15.5%)	
	Other	22 (8.6%)	1 (5.6%)	21 (8.8%)	
Initial WBC	<50,000	211 (82.1%)	17 (94.4%)	194 (81.2%)	0.16
	≥50,000	46 (17.9%)	1 (5.6%)	45 (18.8%)	
BMI at diagnosis	Underweight/Healthy	139 (54.1%)	10 (55.6%)	129 (69.4%)	0.09
	Overweight/Obese	65 (25.3%)	8 (44.4%)	56 (30.6%)	
TGL at diagnosis*	Age Specific Normal	31 (12.1%)	2 (11.1%)	29 (12.6%)	0.38
	Age Specific Borderline High	42 (16.3%)	1 (5.6%)	41 (17.7%)	
	Age Specific High	176 (68.5%)	15 (83.3%)	161 (69.7%)	
LDL at diagnosis	Normal (<110 mg/dL)	215 (83.7%)	13 (81.3%)	202 (89.8%)	0.52
	Borderline High (110–129 mg/dL)	11 (4.3%)	1 (6.3%)	10 (4.4%)	
	High (>130 mg/dL)	15 (5.8%)	2 (12.5%)	13 (5.8%)	
HDL at diagnosis	Low (<40 mg/dL)	233 (90.7%)	18 (100.0%)	215 (93.1%)	0.51
	Borderline Low (40–45 mg/dL)	10 (3.9%)	0 (0.0%)	10 (4.3%)	
	Normal (> 45 mg/dL)	6 (2.3%)	0 (0.0%)	6 (2.6%)	
Total cholesterol at diagnosis	Normal (<169 mg/dL)	219 (85.2%)	13 (72.2%)	206 (89.2%)	0.09
	Borderline High (170–199 mg/dL)	20 (7.8%)	3 (16.7%)	17 (7.4%)	
	High (> 200 mg/dL)	10 (3.9%)	2 (11.1%)	8 (3.5%)	
Treatment arm	Low-risk	97 (37.7%)	1 (5.6%)	96 (40.2%)	0.0035
	Standard/High-risk	160 (62.3%)	17 (94.4%)	143 (59.8%)	
Peg-asparaginase randomization (LR arm)	2500 units/m^2	56 (56.6%)	1 (100.0%)	55 (56.1%)	0.38

Factor		Total number of patients (%)	Peak TG >1000mg/dL (%)	Peak TG ≤1000 mg/dL (%)	*P*-value
	3500 units/m^2	43 (43.4%)	0 (0.0%)	43 (43.9%)	
Peg-asparaginase randomization (SR/HR arm)	2500 units/m^2	91 (57.6%)	9 (52.9%)	82 (58.2%)	0.68
	3500 units/m^2	67 (42.4%)	8 (47.1%)	59 (41.8%)	

TGL: triglyceride; WBC: white blood cell count; BMI: body mass index; LDL: low-density lipoprotein; HDL: high-density lipoprotein; LR: low-risk; SR: standard-risk; HR: high-risk

*Normal TGL levels (mg/dL):

Age 0–9 years: Normal:

<75; Borderline High: 75–99; High: ≥100

Age 10–19 years: Normal: <90; Borderline High: 90–129; High: ≥130