European Journal of Cancer (2014) xxx, xxx–xxx

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Severe hypertriglyceridaemia during therapy for childhood acute lymphoblastic leukaemia ☆

Deepa Bhojwani [a,f,*], Rashid Darbandi [b], Deqing Pei [c], Laura B. Ramsey [d], Wassim Chemaitilly [e], John T. Sandlund [a,f], Cheng Cheng [c], Ching-Hon Pui [a,f], Mary V. Relling [d], Sima Jeha [a,f], Monika L. Metzger [a,f]

[a] *Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN, USA*
[b] *Department of Biochemistry, St. Jude Children's Research Hospital, Memphis, TN, USA*
[c] *Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, TN, USA*
[d] *Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN, USA*
[e] *Department of Pediatrics, St. Jude Children's Research Hospital, Memphis, TN, USA*
[f] *Department of Pediatrics, University of Tennessee Health Sciences Center, Memphis, TN, USA*

Received 14 April 2014; received in revised form 7 June 2014; accepted 30 June 2014

KEYWORDS
Hypertriglyceridaemia
Childhood ALL
Asparaginase
Thrombosis

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

Patients and methods: Fasting lipid profiles were obtained prospectively at four 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 hypertriglyceridaemia were extracted retrospectively.

Results: Eighteen of 257 (7%) patients developed severe hypertriglyceridaemia. Older age and treatment with higher doses of asparaginase and steroids on the standard/high-risk arm were significant risk factors. Severe hypertriglyceridaemia was not associated with pancreatitis after adjustment for age and treatment arm or with osteonecrosis after adjustment for age. However, patients with severe hypertriglyceridaemia had a 2.5–3 times higher risk of thrombosis compared to patients without, albeit the difference was not statistically significant. Of the 30 episodes of severe hypertriglyceridaemia in 18 patients, seven were managed conservatively while the others with pharmacotherapy. Seventeen of 18 patients continued to receive

☆ *Funding:* This work was supported by the National Institutes of Health grant GM92666 (MVR), P30-CA021765 and the American Lebanese Syrian Associated Charities (all authors).

* *Corresponding author at:* Department of Oncology, MS 260, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105, USA. Tel.: +1 901 595 3519; fax: +1 901 521 9005.
E-mail address: deepa.bhojwani@stjude.org (D. Bhojwani).

http://dx.doi.org/10.1016/j.ejca.2014.06.023

asparaginase and steroids. Triglyceride levels normalised after completion of ALL therapy in all 12 patients with available measurements.

Conclusion: Asparaginase- and steroid-induced transient hypertriglyceridaemia can be adequately managed with dietary modifications and close monitoring without altering chemotherapy. Patients with severe hypertriglyceridaemia 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.

1. Introduction

In children with acute lymphoblastic leukaemia (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].

Hypertriglyceridaemia in children treated for ALL is believed to be under-diagnosed, but transient and generally benign [4]. However, triglyceride levels >1000 mg/dL in the general population increase the risk of acute pancreatitis [5,6]. In addition, hypertriglyceridaemia-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 hypertriglyceridaemia 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 hypertriglyceridaemia (>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 hypertriglyceridaemia or for continuing asparaginase, steroids or their combination during severe hypertriglyceridaemia [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 hypertriglyceridaemia. 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.

2. Methods

2.1. 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 dyslipidaemia except for one patient who died early during remission induction therapy. The study was approved by the institutional review board. Informed consent at enrolment from the parents or guardians and assent from patients, when appropriate, were obtained.

2.2. Treatment

In brief, therapy comprised of three phases: remission induction, consolidation and continuation which included two blocks of re-induction therapy (Fig. 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 randomised 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.

2.3. Lipid screening

Fasting lipid profiles comprised serum triglyceride, cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels and were measured prospectively at diagnosis, start of re-inductions I and

Please cite this article in press as: Bhojwani D. et al., Severe hypertriglyceridaemia during therapy for childhood acute lymphoblastic leukaemia, *Eur J Cancer* (2014), http://dx.doi.org/10.1016/j.ejca.2014.06.023