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Original Article

Combination therapy of omega-3 fatty acids and acipimox for children with hypertriglyceridemia and acute lymphoblastic leukemia

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KEYWORDS:
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Omega-3 fatty acids;
Acipimox

BACKGROUND: Lipemic alterations are commonly seen in pediatric patients with acute lymphoblastic leukemia (ALL) treated with corticosteroids and L-asparaginase.

OBJECTIVE: In these children, hypertriglyceridemia rarely causes symptoms and mostly responds well to a low-fat diet. Only few patients demand further therapy, which is not clearly approved in the literature to date. Therefore, it may be important to compile generally accepted standard procedures for lipid-lowering therapy in the pediatric ALL population.

METHODS: We performed a study on 119 newly diagnosed pediatric patients with ALL, all treated according to the ALL-BFM 2000 protocol at our institution between the years 2000 and 2009, to evaluate the incidence of hypertriglyceridemia and the efficacy of a combination therapy with omega-3 fatty acids and acipimox in hypertriglyceridemic patients who did not respond to diet.

RESULTS: We observed hypertriglyceridemia in 34.5% of patients in this collective. In the majority, normalization of triglycerides was successfully managed by administration of a low-fat diet. However, 7.6% of patients (related to total study population) with hypertriglyceridemia did not show diminished lipid levels during diet and/or presented with symptoms such as abdominal pain, dyspnea, or anginal chest pain. In these cases, we performed a lipid-lowering combination therapy with omega-3 fatty acids and acipimox. We observed a prompt decline of serum triglycerides to normal values and an improvement of symptoms within days after onset of this therapy without occurrence of any side effects.

CONCLUSION: In summary, the combination treatment with omega-3 fatty acids and acipimox could represent an alternative to other reported lipid-lowering therapies without severe adverse reactions.

Introduction

Severe lipemic alterations are a common side effect of treatment with corticosteroids and L-asparaginase in pediatric patients with acute lymphoblastic leukemia (ALL). Both drugs are essential and widely used substances in

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induction chemotherapy of ALL (Fig. 1). The distinct mechanisms for lipid abnormalities during therapy with these cytoreductive agents are yet not fully understood. The nonessential amino acid asparagine, which is important for metabolic cellular processes, is depleted by L-asparaginase. In normal body cells, this is compensated by synthesis of L-asparagine from aspartic acid and glutamine by the asparagine synthetase. This enzyme shows reduced activity in malignant lymphoid cells, which explains the antileukemic effect of this therapeutic agent.[1,2] Side effects of L-asparaginase are caused by its effect on protein synthesis and include allergy, thromboembolic complications, altered liver enzymes, hyperglycemia, and severe pancreatitis.[3–5] Lipemic alterations, especially elevation of fasting triglycerides, are known during therapy with L-asparaginase and can be explained by an increase of endogenous synthesis of very low density lipoproteins (VLDLs).[6] Another suggested mechanism is decreased enzymatic activity of lipoprotein lipase, a key enzyme in the removal of triglyceride-rich lipoproteins from the plasma, resulting in decreased clearance and hypertriglyceridemia.[7] Corticosteroids are highly effective drugs during induction treatment of childhood ALL. They lead to lipemic alterations by increasing endogenous production of VLDLs[8,9] and of hepatic cholesterol synthesis.[10] Although hyperlipidemia is seen in about 10%[11] to 67%[12] of patients with ALL during therapy with corticosteroids and L-asparaginase, it is usually transient and benign[6,11] and not certainly associated with pancreatitis in this setting.[6,13] Despite this fact, hypertriglyceridemia may have devastating complications concerning central nervous system, coagulation, and cardiovascular system,[14–17] and all authors agree upon the importance of triglyceride screening during ALL induction therapy. However, treatment of hypertriglyceridemia during ALL therapy is discussed sparsely and controversially in the literature. To date, there is no commonly used guideline for the management of lipemic anomalies during therapy with L-asparaginase and corticosteroids.

This retrospective study presents an effective combination treatment with omega-3 fatty acids and acipimox with few side effects compared to the commonly used lipid-lowering management with fibrates.

Patients and methods

Patients

This retrospective study primarily comprised 122 children and adolescents (age >1 year to <18 years) with a newly diagnosed ALL at our institution between January 2000 and December 2009. Three patients were excluded from analysis: 1 child developing hypertriglyceridemia in line with a hemophagocytic lymphohistiocytosis and 2 patients dying before day 33 of induction therapy owing to severe infectious complications. Of the remaining 119 patients, 67 were male (56%) and 52 were female (44%). The mean age at diagnosis was 7.48 ± 4.65 years (range 1.7 to 17.34 years). All patients received chemotherapy according to the ALL-BFM 2000 protocol (Fig. 1, induction phase), stratified by risk group. Twenty-seven (22.6%) children were classified as standard-risk, 71 (59.7%) as medium-risk, and 19 (16%) as high-risk patients. High-risk status was defined by incomplete response to prednisone on day 8, incomplete remission on day 33, or detection of translocations t(9;22) or t(4;11). Two children (1.7%) died of septic complications before classification into a certain group.

Drug doses according to ALL-BFM 2000

L-asparaginase (*Escherichia coli*–asparaginase, 5000 IU/m^2/dose) from Medac (Wedel, Germany) was used as first-line L-asparaginase preparation in the induction phase (Fig. 1). In case of allergic reactions, pegylated asparaginase (Oncaspar, Medac) or Erwinia L-asparaginase (Erwinase, Speywood, London, United Kingdom) was recommended as a substitute. During induction therapy, prednisone was the corticosteroid of choice (60 mg/m^2/d). Only patients, who presented with T-ALL or were classified as high risk, were switched to dexamethasone (10 mg/m^2/d). High-risk patients received higher doses of dexamethasone (20 mg/m^2/d) and L-asparaginase (25,000 IE/m^2/dose). Further multiagent induction chemotherapy consisted of vincristine, daunorubicin, and intrathecal methotrexate (Fig. 1). All patients received subcutaneous low molecular weight heparin (enoxaparin) in a prophylactic

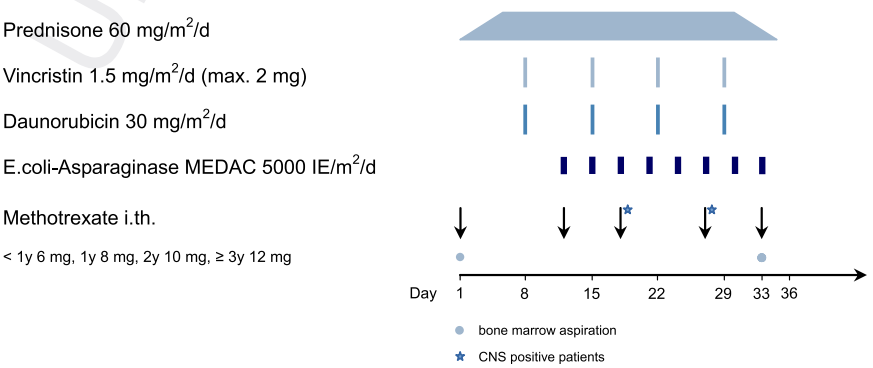

Figure 1 ALL-BFM 2000 induction therapy (protocol I).