A Retrospective study of L-asparaginase induced Thrombosis in Pediatric Acute Lymphoblastic Leukemia Patients

Thesis submitted for fulfillment of Master Degree in Pediatric Oncology

Submitted
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Omar Arafah.

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List of Abbreviations

6MP: 6- mercaptopurine

ACCP: The current American College of chest physicians

ADC: Apparent diffusion coefficient

ALL: Acute lymphoblastic leukemia

AML: Acute myeloid leukemia

AMP 21: Intrachromosomal amplification of AML 1 gene on chromosome 21

ANC: Absolute neutrophillic count

AP: Acute Pancreatitis

Ara-C: Cytosine Arabinoside

BCP phenotype: B cell precursor phenotype

BCSH: British Committee for Standards in Haematology

BFM: Berlin– Frankfurt–Munster

C.ALL: Common Acute lymphoblastic leukemia

CCSG: Children cancer study group

CD: Cluster of differentiation

CNS: Central nervous system

COG: Childern Oncology Group

CR: Complete remission

CSF: Cerebrospinal fluid

CTX: Cyclophosphamide

DDI: Double delayed intensification

DFCI: Dana-Farber consortium

DFS: Disease free survival

Dox: Doxorubicin

DTI: Direct Thrombin inhibitors

DWI: Diffusion weighted images

EFS: Event free survival

EMF: Electromagnetic field

ETGC: Endogenous thrombin generation capacity

FAB: French-American-British

FDA: Food & Drug Administration

FFP: Fresh frozen plasma

FISH: Fluorescence in situ hybridization

GST: Glutathione S transferase

HC II: Heparin cofactor II

HCT: Hematopoietic cell transplantation

HDMTX: High dose methotrexate

HIT: Heparin induced thrombocytopenia

HIV: Human immunedeficiency virus

HLA: Human leukocyte antigen

IgG: Immunoglobulin heavy chain

IL6: Interleukin 6

INR: International ratio

IPT: Immunophenotyping

IT: Intrathecal

IU: International Unit

L-ASP: L-asparaginase

LMWH: low molecular weight heparin

m TOR: mammalian target of Rapamycin

MLL: Mixed lineage leukemia gene

MRD: Minimal residual disease

MRI: Magnetic resonance imaging

MRV: Magnetic resonance venography

MTHFR: Methyl Tetrahydrofolate reductase

MTX: Methotrexate

NHL: Non Hodgkin lymphoma

OAT: Oral Anti-coagulant therapy

OS: overall survival

P value: Probability value

PAI-1: Plasminogen activator inhibitor 1

PARP: poly ADP ribose- polymerase

PCA: Procoagulant activity

PE: Pulmonary embolism

PEG –ASP: Poly ethylene glycol asparagines

POG: Pediatric Oncology Group

PRES: Posterior reversible encephalopathy syndrome

PROTEKT: PROphylaxis of ThromboEmbolism in Kids trial

PT: Prothrombin time

PTT: Partial Thromboblastin time

REVIVE: Reviparin in childhood venous thromboembolism

SAS: Statistical Analysis system

SHBG: Sex hormone binding globulin

SJCRH: San Jude Cancer Research Hospital

SR: Standard risk HR: High risk LR: Low risk

TAT: Thrombin-Antithrombin complex

TBG: Thyroxine binding globulin

TCR: T cell receptor

TE: Thromboembolism

TH: T helper

TLC: Total leukocytic count

TNFα: Tumor necrosis factor Alpha

t-PA: Tissue plasminogen Activator

UFH: Unfractionated heparin

UKCCS: United Kingdom Childhood Cancer Study

VCR : Vincristine

VKA: Vitamin K antagonist

vWF: Von Willebrand factor

WBCs: White blood cell count

Abstract

Background: Thromboembolism (TE) is a well-recognized serious complication in association with ALL leading to significant morbidity. Development of TE does interfere with the scheduled treatment plan for ALL and, thus, ultimate outcome from ALL. Concomitant administration of asparaginase and steroids is likely to be associated with higher incidence of TE, especially in children with at least one prothrombotic risk factor.

Aim: To study the incidence and outcome of asparaginase related coagulopathy and to assess biological, laboratory and clinical parameters affecting thromboembolic risk.

Methods: A retrospective study of 416 pediatric ALL patients who were treated at the Children's Cancer Hospital in Egypt (CCHE) during the time period between 7th of July 2007 and end of July 2009 and followed till end of may 2010. They received ALL protocol adopted from SJCRH study XV for low and standard/high risk.

Results: Twenty patients (4.8%) had coagulopathy related to L-asparaginase. CNS affection occurred in 12 patients (60%), DVT in neck and lower limbs in 8 patients (40%). The Majority of patients had thrombosis (55%), followed by cerebral haemorrhage (20%), cerebral thrombosis combined with haemorrhagic infarction (15%), cerebral Ischemia (5%) and cerebral infarction (5%). Seven patients (35%) occurred during induction, 3 (15%) post induction and 10 (50%) during maintenance. Four cases died as a complication to L-ASP induced coagulopathy events, all of them had CNS affection.

The total dosage of L-ASP and Dexamethazone were significantly higher in SR/HR than LR protocol. It was found that age, and risk stratification significantly increased the risk of L-ASP coagulopathy and only age retained its significance on multivariate analysis. Event free and overall survival were adversely affected in L-ASP positive patients, while disease free survival was not. Risk stratification and L-ASP coagulopathies were the only factors that independently affected event free survival and overall survival.

Conclusion: It can be concluded that combination of L-ASP and steroids increased the risk of coagulopathy in ALL pediatric patients especially in older ages, higher risk and higher doses of L-ASP. Mortality related to TE events affected outcome of patients.

Keywords: *Acute lymphoblastic leukemia, Asparaginase, Thromboembolism, Haemorrhage.*

Introduction and Aim of the work

L-asparaginase is a hydrolase that catalyzes the conversion of L-asparagine; an endogenous amino acid necessary for the function of some neoplastic cells, such as lymphoblasts. In most human cells, deficiency of L-asparagine can be compensated by alternative synthesis pathway through which L-asparagine is produced from aspartic acid and glutamine by asparagine synthethase. Depletion of L-asparagine from plasma by L-asparaginase results in inhibition of RNA and DNA synthesis with the subsequent blastic cell apoptosis.

Owing to the unique anti-cancer mechanism of action, L-asparaginase has been introduced to the multi-drug chemotherapy in children with acute lymphoblastic leukemia, which has contributed to significant improvement of therapy outcomes and to achieve complete remission in about 90% of patients.

Despite its high therapeutic efficacy, L-asparaginase can increase the risk of thrombosis. Inhibition of protein synthesis causes most complications observed during treatment with a native and pegylated form of L-asparaginase, including impaired functions of liver, kidneys or central nervous system. Thrombotic events occur as a result of inhibited synthesis of anticoagulant proteins (mainly antithrombin). **(Piatkowska-Jakubas et al., 2008)**

The occurrence of Thromboembolism (TE) seems to be emerging from the interaction of the disease, the therapy and possible genetic predisposition for hypercoagulibility, especially in children with ALL. Antileukemic therapy influences the haemostatic system either by direct effect of the chemotherapeutic agents or indirectly through the effect of supportive care, e.g. central venous line (CVL) or infectious complications secondary to immunosuppression **(Uma et al., 2003)**

Asparaginase and steroids are shown to induce hypercoagulable state by suppression of natural anticoagulants, especially AT and plasminogen, and by elevations in F VIII/vWF complex, respectively. In addition, steroid therapy causes hypofibrinolytic state by dose-dependent increase in plasminogen activator inhibitor 1 (PAI-1) levels.

Combination of these effects coupled with increased thrombin generation may be responsible for the increased incidence of TE observed with concomitant administration of asparaginase and steroids **(Athale et al., 2003).**

The reported incidence of TE in childhood ALL varies from 1.1% to 36.7% with an overall average of 3.2% **(Mitchell et al., 2003)** The wide variation in the reported incidence of TE seems to be related to the definition of TE (symptomatic versus asymptomatic), diagnostic methods used for detection of TE, study design (prospective versus retrospective analysis), and ALL treatment protocols. The studies designed to evaluate patients for asymptomatic TE (e.g. central venous line (CVL) related TE) have reported much higher incidence of TE compared to studies reporting only symptomatic TE.

Studies published prior to 1990 seem to report lower incidence of TE compared to more recent studies. The overall incidence of TE on studies conducted or reported prior to year 1990 is 1.8% (range, 1.1–14.2%) **(Priest et al., 1982)** ; whereas the same for studies or reports after 1990 is 4.7% (range, 1.7–36.7%) **(Mitchell et al., 2003).** Thus, it seems that incidence of TE has either increased over time or the apparent increase is related to the improved methods for detection.

Majority of thromboembolisms are venous and 5.0% of patients were reported to have multiple sites involved. Mitchell et al., reported CNS-TE in 65% and DVT in 16% of patients **(Mitchell et al., 1995)**. In contrast, **(Athale et al., 2003)** reported a much higher prevalence of DVT (43%)

Most of the Thrombotic complications occur during the induction phase of therapy. Lower doses of asparaginase (ASP) for long periods were associated with the highest incidence of thrombosis, as were anthracyclines and prednisone (instead of dexamethasone). The presence of central lines and of thrombophilic genetic abnormalities also appeared to be frequently associated with thrombosis **(Appel et al., 2008).**

The morbidity is usually reported for patients with CNS-TE. Approximately 15–20% of patients with CNS-TE are reported to have residual neurological deficits in the form of hemiparesis, aphasia or seizure disorder **(Ott et al., 1988).**

The overall mortality from TE in patients with ALL varies from 0 to 4.8%. However, amongst patients who develop TE, the case fatality ratio, based on individual series, could be 0–50%, with an average of 15%. With all cause mortality in children with ALL being approximately 15%, TE may be an important cause of mortality in children with ALL. Pulmonary embolism and CNS-TE are collectively responsible for majority of all TE-related deaths. An overall mortality related to CNS-TE is 21.1% **(Kankirawatana et al., 2002).**

During L-Asparaginase treatment the 11- to 16-year-old showed lower values in procoagulant and, even more, in anticoagulant factor levels compared to the younger children. Decreased synthesis of alpha2-antiplasmin and plasminogen during L-Asparaginase treatment resulted in less potential of clot lysis by plasmin in children older than 11 years of age. In conclusion, a more severe decline of anticoagulant and fibrinolytic parameters in children between 11 and 16 years of age underline that these children are at higher risk of thrombosis during ALL induction treatment **(Nowak-Göttl et al., 2002).** Age related risk may partly reflect the effect of ALL-risk stratification. Higher dose steroids combined with ASP may lead to an increased risk of TE in HR patients.

Management and prevention of venous thromboembolism (VTE) in cancer patients is challenging. Not only is the risk of VTE in cancer patients elevated compared to patients without malignancies, but also is standard treatment based on Vitamin K antagonists (VKAs) less effective and associated with an increased frequency of major bleeding.

Therapy with Low Molecular Weight Heparin (LMWH) is less sensitive to drug interactions, not hindered by a narrow therapeutic window and needs no monitoring. LMWH therapy therefore seems more practical and may also be more effective in cancer patients. Moreover a possible survival benefit has been suggested, the underlying mechanism of which is not yet unraveled **(Ten Cate-Hoek et al., 2008).**

For the long term treatment of venous thromboembolism in patients with cancer, LMWH compared to vitamin K antagonists reduces venous thromboembolism but not death **(Akl et al., 2008).**

Fresh frozen plasma administration for the prevention and treatment of acquired ATIII deficiency secondary to ASP has no demonstrable benefit on plasma levels of