Central Nervous System Relapse In Children With Acute Lymphoblastic Leukemia

Thesis submitted for partial fulfillment of master degree in pediatrics

Submitted
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6-MP	6-mercaptopurine
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
ANLL	Acute non-lymphoblastic leukemia
Ara-C	Cytarabine
BCR	Breakpoint cluster region
BFM	Berlin- Frankfurt-Munster
BM	Bone marrow
BMT	Bone marrow transplantation
CALLA	Common acute lymphoblastic leukemia antigen
CBC	Complete blood count
CCG	Children Cancer Group
CCR	Continuous complete remission
CDs	Clusters of differentiation
cm	Centimeter
CML	Chronic myeloid leukemia
CNS	Central nervous system
CR	Complete remission
CSF	Cerebrospinal fluid
CSI	Craniospinal irradiation
CTX	Cyclophosphamide
d	Day
DCLSG	Dutch Childhood Leukemia Study Group

DFCI	Dana-Farber Cancer Institute
Dox	Doxorubicin
EFS	Event-free survival
EORTC	European Organization for the Research and Treatment of Cancer
FAB	French-American-British
G-CSF	Granulocyte colony-stimulating factor
GVHD	Graft versus host disease
Gy	Gray
Hb	Hemoglobin
HCV	Hepatitis C virus
HDMTX	High dose methotrexate
HLA	Human leucocyte antigen
HR	High risk
HRG	High risk group
HSM	Hepatosplenomegaly
IM	Intramuscular
IPT	Immunophenotype
IQ	Intelligence quotient
IR	Intermediate risk
IT	Intrathecal
IU	International unit
IV	Intravenous
IVI	Intravenous infusion

Lab.	Laboratory
L-ASP	L-asparaginase
LENT	Late effects on normal tissues
LMN	Lower motor neuron
LNs	Lymph nodes
LP	Lumbar puncture
LR	Low risk
Max.	Maximum
MLL	Mixed lineage leukemia
MRD	Minimal residual disease
MRG	Medium risk group
MRI	Magnetic resonance imaging
MTX	Methotrexate
MTXPGs	Methotrexate polyglutamates
NCI	National Cancer Institute
PB	Peripheral blood
PCP	Pneumocystis carinii pneumonia
PGR	Prednisone good responders
Ph	Philadelphia
Plt	Platelets
PNCI	Protocol of National Cancer Institute
PO	Per oral
POG	Pediatric Oncology Group
PPR	Prednisone poor responders

PR	Partial remission
RER	Rapid early response
RTOG	Radiation Therapy Oncology Group
SOMA	Subjective, Objective, Management, and Analytical components
SC	Subcutaneous
SR	Standard risk
SRG	Standard risk group
T-ALL	T-cell acute lymphoblastic leukemia
TdT	Terminal deoxynucleotidyl transferase
TGNs	Thioguanine nucleotides
TIT	Triple intrathecal
TLC	Total leucocytic count
TLP	Traumatic lumbar puncture
TMP-SMX	Trimethoprime-sulfamethoxazole
UMN	Upper motor neuron
VM-26	Teniposide
VP-16	Etoposide
VS	Versus
VZIG	Varicella zoster immunoglobulin
WBCs	White blood cells
WCI	Whole cranial irradiation
XRT	Radiotherapy

ABSTRACT

Introduction: Despite steady improvement in therapy of lymphoblastic leukemia, 20-25% of patients still experience a relapse. CNS relapse in children with ALL became clinically apparent as bone marrow remissions became more durable. Although the frequency of isolated meningeal relapse is currently only 5% or less in most studies, it remains a significant problem with regard to definition, treatment, or outcome. The main factors determining the success rate for patients with CNS relapse include whether the relapse occurred more than or less than 18 months (83% and 46% EFS respectively) from the initial diagnosis and whether the patient received CNS directed irradiation during the initial treatment regimen.

Objective: The aim of the current study is to assess the implemented rationale for CNS prophylaxis and CNS treatment in newly diagnosed pediatric patients with acute lymphoblastic leukemia (ALL) in the period between January 2005 and June 2006.

Patients and methods: During this period, 151 cases presented with ALL. In attempt to identify the factors associated with treatment failure, the clinico-pathological characteristics of patients with maintained complete remission will be compared with those of patients showed relapse. Data of patients who experienced CNS relapse during the period of the study, whether isolated or combined with systemic relapse, will be analyzed to identify the risk factors that may be associated with CNS relapse.

Abstract

Results: The study included 151 patients with ALL, 83 were males and 68 were females. CNS disease at presentation was reported in 8 patients (5.3%). According to age, initial total leucocytic count, CNS status & immunophenotype (as T-cell ALL is considered high risk), patients included in the current study were stratified into low risk; 75 patients (49.6%), and high risk; 76 patients (50.4%). The induction mortality rate was 2.6%. Complete remission by the end of induction was present in 99.4%. Out of these 151 patients, 12 patients were excluded (6 of them because of early deaths, and the other 6 patients lost follow up). Out of the 139 evaluable patients, 24 patients had relapse (Relapse Rate 17.3%). CNS relapse was observed in 16 patients (11.5%). Statistical difference was found in patients with initial high TLC, T-cell ALL, CNS disease at presentation, high risk group patients, and patients who did not receive different modalities of CNS prophylaxis and treatment.

Conclusion: Egyptian patients are usually presented with poor prognostic factors. This can partly be explained by biologically more aggressive tumor and/or late diagnosis of disease in Egypt. The only factors that independently affect CNS relapse were whether the case is T-cell vs progenitor B-cell and having CNS disease at presentation vs not.

Keywords: Acute lymphoblastic leukemia, CNS prophylaxis, CNS preventive therapy, isolated CNS relapse.

Introduction
&
Aim Of The Work