Ain Shams University
Institute of Post-Graduate Childhood Studies
Department of Medical Studies

Impact Of Hepatitis B and C Virus Infection In Treatment Of Acute Lymphatic Leukemia

Thesis

Submitted for the fulfillment of PhD in Childhood Studies
(Child Health and Nutrition)
Department of Medical Studies

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جامعة عين شمس
معهد الدراسات العليا للطفولة
قسم الدراسات الطبية

تأثير الإلتهاب الكبدى الفيروسى بى وسى على علاج الأطفال المصابين بسرطان الدم (اللوكيميا الحادة)

رسالة

مقدمة للحصول على درجة دكتوراه الفلسفة فى
دراسات الطفولة (قسم الدراسات الطبية)

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ABSTRACT

This prospective study include (120) newly diagnosed acute lymphoblastic leukemia patient, the age between (2-12) years who presented to the pediatric oncology department at Abu El-Reesh Student Health Insurance Hospital within a period of (12) months period from March 2006 to March 2007. There were classified into (2) groups. First group newly diagnosed group acute lymphoblastic leukemia before start chemotherapy, second group (6) months after chemotherapy according to immunophenotypes was common acute lymphoblastic leukemia 41-67% followed by T-cell 30%, pre B 28.33% P-value 0.971 not significant, bone marrow aspiration D15 (M1) 81.67%, (M2) 10% (M3) 2.5%, not detected 5.83% statistically significant with P-value <0.001, bone marrow aspiration in day 45 was M1 (82.5%), M2 (3.37%), M3 (0.83%), not detected (13.3%) statistically significant with P-value <0.001. There was statistically significant difference in HBVAg between before and after chemotheraphy, where Z equal 2.23 at P-value <0.05. There was statistically signfiacnt difference in HBV DNA between before and after chemotheraphy, where Z waual 2.24 at P-value <0.05. There was statistically signfacint difference in HCV antibody between before and after chemotheraphy, where Z equal 4.58 at P-value <0.01. There was statistically significant difference in HCV RNA between before and after chemotheraphy, where Z equal 4.59 at P-value <0.01. There was statistically significant difference in lymph nodes between before and after chemotheraphy, where Z equal 7.8 at P-value <0.01. There was statistically significant difference in cerebrospinal fluid between before and after chemotheraphy, where Z equal 4.12 at P-value <0.01, blood urea and creatinine was

significant change between before and after chemotheraphy with P-value <0.001, liver function tests (SGOT, SGPT) was significant change before and after chemotheraphy with P-value <0.001.

The end result to our work 90/120, 13 died, 10 lost, 7 off, therapy when correlated with BFS multivariate analysis showed independent prognostic factors.

It's concluded that infection with HCV and HBV not only delay chemotherapy and alter the prognosis of malignant diseases but also worsens the outcome of successfully treated pediatric oncology patients or progression to cirrhosis and risk of hepatocellular carcinoma.

Keywords: Acute lymphoblastic leukemia, Cerebrospinal fluid, Deoxyribo-nucleic acid, Hepatitis B virus, Hepatitis C virus, Hepatitis C virus ribonucleic acid.

Contents

List Of Abbreviations

μg	Microgram
6-MP	6-Mercaptopurine
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
ANLL	Acute non-lymphoblastic leukemia
Anti-HBc IgG	Anti hepatitis B core immunoglobulin G
Anti-HBc IgM	Anti hepatitis B core immunoglobulin M
Anti-HBeAg	Antibody to HBe antigen
Anti-HBsAg	Anti hepatitis B sirface antigen
Ara-C	Aracytine-cytarabine
BM d15	Bone marrow day 15
BFM	Berline-Franfurt-Munster
BMT	Bone marrow transplantation
C-ALL	Common ALL
CDC	Center for disease control
CIFN	Consensus interferon
Cig	Cytoplasmic immunoglobulin
CNS	Central nervous system
CP	Cyclophosphamide
CR	Complete remission
CSF	Cerebro-spinal fluid
CT	Computed tomography
Cyt	Cytoplasmic
DFCI	Dana farber cancer institute
DNA	Branched chain DNA
DNA	Deoxyribonucleic acid
ELA1	First generation ELISA tests
ELA2	Second generation ELISA tests
ELA3	Third generation ELISA tests
EMF	Electromagnetic fields
ETR	End of treatemnt response
F	Female
FAB	French-American-British
FLT3	FMS-like tyrosine kinase
GCT	Germ cell tumor

GM CSF	Granulocyte macrophage colony stimulating factor
HBcAg	Hepatitis B core antigen
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDMTX	High dose methotrexate
HIV	Human immunodeficiency virus
HLA	Humal leucocytic antigen
HSC	Hematopoietic stem-cell transplantation
IARC	International agency for research on cancer
IFN	Interferon
IFN/RIE	Interferon + ribavirin
Ig	Immunoglobulin
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-12	Interleukin 12
ITs	Intrathecals
L-ASP	L'Asparaginase
LDA	Lactate dehydrogenase
M	Male
M1	<5% blasts in bone marrow
M2	5-25% blasts in bone marrow
M3	>25% blasts in bone marrow
MDR1	Multi-drug resistance gene
MI	Milliliter
MRI	Magnetic resonance imaging
MU	Million units
N/C ratio	Nuclear/cytoplasmic ration
NANBH	Non-A non-B hepatitis
NCI	National Cancer Institute
NHANES	National Health and Nutritional Examination Survey
NRs	Non-responders
PAN	Polyarteritis nodosa
PB	Peripheral blood
PCR	Polymerase chain reaction
PDN	Prednisone

PEG	Pegylated interferon
PEG/RIB	Pegylated interferon + ribavirin
RIBA	Recombinant immunoblot assay
RNA	Ribonucleic acid
SEER	Surveillance, epidemiology and end results
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvate transaminase
SJCRH	St. jude children's research hospital
Sig	Surface immunoglobulin
SR	Sustained response
STD	Sexually transmited disease
TAH-C	Transfusion assocaited hepatitis C
TCR	T-cell receptor
TdT	Terminal deoxynucleotidyl transferase
TLC	Total leucocytic count
TPMT	Thiopurine methyltransferase
VCR	Vincristine
VP-16	Vepeside-etoposide
WBC	White blood cells


قَالُوا سُبْحَانَكَ
لاَ عِلْمَ لَنَا
إِلاَّ مَا عَلَّمْتَنَا
إِنَّكَ أَنتَ
الْعَلِيمُ الْحَكِيمُ
صدق الله العظيم
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INTRODUCTION

Survival of children with cancer has improved dramatically in correlation with advances in therapy. These children require multiple transfusion during intensive therapy and are a increased risk for blood transmittable infections such as HBV, HCV and HIV infections *(Kebudi et al., 2007)*.

Although the HBV contact rate is similar both in multiply transfused children with benign hematological disorders and in cancer; the HBs Ag positivity was found to be much higher in children ith cancer. Survivors treated before adequate blood donor screening for hepatitis c virus (HCV) was intitiated in the early 1990s, are at risk for chronic liver disease *(Castellino et al., 2004)*.

Prevalence of circulating HCV-RNA in acute lymphoblastic leukemia (ALL) patients treated before 1990 ranges from 6.6-49%, with an unknown and likely sizable percentage of survivors never having been tested or awarew of their risk *(Strickland et al., 2006)*.

Aggressive chronic HCV infection has also been observed in survivors co-infected with hepatitis B and in those treated with hematopoietic stem cell transplantation *(Peffault et al., 2004)*. Reports of childhood cancer survivors with chronic HCV suggest that this population is at increased risk of liver-related morbidity and mortality *(Castellino et al., 2004)*.

Patients treated for pediatric malignancy are at a high risk for parent rally transmitted viral hepatitis *(Kebudi et al., 2005)*. Hepatitis continues to result from blood transfusions in children with cancer. The pathophysiology and the natural history of hepatitis are probably similar to those in other transfusion recipients, but in view of the concomitant immunodepression due to chemotherapy and the hepatotoxicity os some anti neoplastic agents, the potential exists for serious chronic liver disease *(Paul ct al., 2006)*.

During the last two decades, screening blood donors for hepatitis R virus (HBV) has resulted in a remarkable reduction of post transfusion B virus hepatitis *(Fanning et al., 1999)*. Thus non-A, non-B hepatitis virus has become the major cause of the

parent rally transmitted hepatitis *(Actor et al., 1993, Iwarson et al., 1994)*.

The successful cloning of hepatitis C virus (HCV) genome and the development of serologic markers of HCV infection showed that HCV was responsible for 85% to 90% of parent rally transmitted non-non-B hepatitis *(Xiong et al., 1998)*.

Studies indicated that HCV plays a significant role in the etiology of chronic hepatitis in leukemic patients and that persistent anti-HCV activity correlates with a more severe chronic liver disease which could jeopardize the final prognosis of children cured of leukemia *(Alocasciulli et al., 1991)*.

The Prognosis of chronic HCV is a matter of controversy. HCV could worsen the out come of successfully treated pediatric oncology patients because a progression rate to cirrhosis of 20% has been documented in 29yrs follow-up studies in HCV infected adults with no other disease *(Tong et al., 1995; Davis et al., 1999)*.

Furthermore, recent studies have shown that HCV infections is a risk factor for hepatocelular carcinoma *(Donald et al., 2000)*.

On the other hand *Seef et al. (1992)* after an average follow-up of 18yrs, reported a low incidence of deaths related to chronic HCV infection acquired from blood transfusion.