# ROLE OF RIBAVIRIN MONOTHERAPY IN NORMALISING TRANSAMINASES IN HCV INFECTED PATIENTS UNDER CHEMOTHERAPY

Thesis

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## ABSTRACT

**Background:** The prevalence of HCV infections in children with cancer is 54.3% with the highest rate among patients with leukemia. HCV could worsen the outcome of successfully treated pediatric oncology patients. Due to concerns that antineoplastic therapy produces prolonged decrease in immune function, options other than combination of peginterferon alfa and ribavirin should be studied in pediatric cancer patients while on chemotherapy. The role of ribavirin monotherapy and it's effect on transaninases is discussed in these patients. ***Subjects and Methods:*** The present study was a retrospective case cohort of 65 pediatric hematological cancer patients on chemotherapy; 23patients with HCV and on ribavirin monotherapy, 19 patients with HCV recieving no therapy and 23 patients not infected with HCV. ALT level was measured every 3 months for 2 years of follow up and at every phase of chemotherapy, viral load, total bilirubin level, number of hepatitis flares and hemoglobin level were compared between the three groups and pre – and during ribavirin therapy in group I and also effect of HDMTX on ALT level was studied. ***Results:*** There was a significant decrease of ALT level and number of hepatitis flares during ribavirin therapy compared to before therapy. Viral load decreased after therapy compared to before therapy but the difference did not reach a significant level. No significant decline in hemoglobin level post ribavirin therapy was found and total bilirubin levels significantly increased after therapy. ALT level was significantly high in HCV infected patients treated with HDMTX compared to those who were not receiving HDMTX in the second year of follow up. ***Conclusions:*** Ribavirin as a monotherapy has a significant role in normalizing ALT level in HCV infected pediatric cancer patients on chemotherapy. But it's effect on the decrease in HCV viral load is not reliable.

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# LIST OF ABBREVIATIONS

| Abbrev. | Meaning |
|---|---|
| 6MP | : 6 mercaptopurine |
| ALF | : Acute liver failure |
| ALL | : Acute lymphoblastic leukemia |
| ALP | : Alkaline phosphatase |
| ALT | : Alanine aminotransaminase |
| AML | : Acute myeloid leukemia |
| Anti-HBc | : Antibody to hepatitis B core antigen |
| Anti-HBs | : Antibody to hepatitis B surface antigen |
| AST | : Aspartate aminotransaminase |
| CAHC | : Chronic active hepatitis C |
| CMV | : Cytomegalovirus. |
| CYP | : Cytochromes P-450 |
| EBV | : Epstien –Barr virus |
| FHF | : Fulminant hepatic failure |
| GGT | : Gamma-glutamyl transpeptidase |
| GOT | : Glutamic-oxaloacetic transaminase = AST |
| GPT | : Glutamic-pyruvic transaminase = ALT |
| GST | : Glutathione S-transferase |
| HAV | : Hepatitis A virus |
| HbeAg | : Hepatitis B e antigen |
| HbsAg | : Hepatitis B surface antigen |
| HBV | : Hepatitis B virus |
| HCC | : Hepatocellular carcinoma |
| HCV | : Hepatitis C virus |
| HDV | : Hepatitis D virus |
| HEV | : Hepatitis E virus |
| HGV | : Hepatitis G virus |
| HHV-6A & HHV-6B | : Human herpesvirus 6 variants A and B |
| HHV-7 | : Human herpesvirus 7 |
| HR | : High risk group |
| HSCT | : Hematopoietic stem cell transplantation |
| HSV | : Herpes simplex virus |
| HVOD | : Hepatic veno – occlusive disease |
| IFN – γ | : Interferon gamma |
| IL- 1, IL -6, IL -12 | : Interleukin 1 , 2, 12 |

# LIST OF ABBREVIATIONS (Cont...)

| Abbrev. | Meaning |
|---|---|
| IMPDH | : Inosine monophosphate dehydrogenase |
| ISC: | : Interferon secreting cell |
| LDH: | : Lactic dehydrogenase |
| LE: | : Leukoencephalopathy |
| LR: | : Low risk group |
| LT | : Liver transplantation |
| MALT | : Mucosal- associated lymphoid tissues |
| MBL | : Mannan-building lectin |
| MOF | : Multiorgan failure |
| MTHFR C677T | : Methylenetetrahydrofolate reductase C677T |
| MTX | : Methotrexate |
| NHL | : Non hodgkin lymphoma |
| NK cells | : Natural killer cells |
| OLT | : Orthotopic liver transplant |
| PCR | : Polymerase chain reaction |
| PD-1 | : Programmed death 1 |
| PEG-IFN | : Pegylated interferon |
| PGE-1 | : Prostaglandin E 1 |
| PMN | : Polymorphic nuclear cells |
| PTLD | : Posttransplant lymphoproliferative disease |
| RBV | : Ribavirin |
| RFC1 G80A | : Reduced folate carrier 1 G80A |
| RMP | : Ribavirin 5′-monophosphate |
| RSV | : Respiratory syncytial virus |
| RTP | : Ribavirin 5′-triphosphate |
| SARS | : Severe acute respiratory syudrome |
| SCT | : Stem cell transplantation |
| SOS | : Sinusoidal obstructive syndrome |
| SOT | : Solid organ transplant |
| SVR | : Sustained virologic response |
| TGF-β | : Transforming growth factor β |
| TNF – α | : Tumor necrosis factor alpha |
| TPMT | : Thiopurine methyl transferase |
| UGT1A1 | : Uridine diphosphate glucuronosyltransferase |
| VEGF | : Vascular endothelial growth factor |
| VZV | : Varicella – zoster virus |

# INTRODUCTION

Patients treated for pediatric malignancy are at high risk of parentrally transmitted viral hepatitis ***(Kebudi et al., 2000).*** Blood product transfusions are the major risk factors. Moreover, when compared with immunocompetent patients, the immunodepression caused by chemotherapy increases the chronicity rate of viral hepatitis ***(Simone et al., 2000).***

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

The prognosis of chronic HCV is a matter of controversy. HCV could worsen the outcome of successfully treated pediatric oncology patients because a progression rate to cirrhosis of 20% has been documented in follow up studies of up to 29 years in HCV infected adults with no other disease ***(Davis, 1999)***.

An Egyptian study found that the seropositivities for HBV and HCV were 3.6% and 0.9% respectively among the patients were proved to have pediatric malignancies. The seropositivities for HBV and HCV infection after six months of chemotherapy increased significantly to 18.2%

and 13.1%, respectively ***(Mostafa et al., 2003)***. Furthermore, a three year prospective survey has shown an incidence rate of 79% for HBV and 62% for HCV in children with hematological malignancies and severe outcome of liver disease in HBV and HBV/HCV infected children ***(El-Sayed et al., 2003).***

Ribavirin, a nucleoside analogue, was one of the first drugs shown to reduce the ability of viruses to reproduce. Ribavirin is effective against many different types of viruses, particularly RNA viruses such as HCV ***(Dorny, 1999).*** A systematic review of ribavirin monotherapy identified 13 randomized trials including 594 patients with chronic hepatitis C. The review found that ribavirin versus placebo/no intervention had no significant beneficial effect on virological response and liver morbidity, but may improve biochemical and histological response. Ribavirin, however, increased the risk of anemia ***(Brok et al., 2005).***

# AIM OF THE WORK

1- To evaluate the role of ribavirin monotherapy in normalising transaminases in hepatitis C virus (HCV) infected pediatric patients undergoing chemotherapy for hematological malignancies and whether if it has an effect on viral load of infected patient.

2- To evaluate ribavirin safety and impact on duration of stoppage of chemotherapy compared to an HCV-infected control group under chemotherapy.

3- To show hepatotoxic effect of chemotherapy on pediatric patients with hematological malignancies represented by ALT level at different phases of chemotherapy, moreover the effect of HDMTX on ALT level in HCV infected cancer patients during 2 years of follow up.

# Chapter 1

# HEPATITIS IN PEDIATRIC CANCER PATIENTS

## Viral Hepatitis:

Advances in supportive care over the past two decades have decreased the morbidity and mortality attributed to opportunistic infections in immunocompromised patients, including those with hematologic malignancies, hematopoietic stem cell transplantation (HSCT), and aplastic anemia. Despite advances in antiviral therapy, opportunistic viral infections still cause significant morbidity and mortality in patients with compromised host defenses ***(Jancel and Penzak, 2009).*** In immunocompetent patients, primary infection by herpes simplex virus (HSV), varicella-zoster virus (VZV), cytomegalovirus (CMV), human herpesvirus 6, and Epstein-Barr virus (EBV) generally produces mild, self-limited hepatitis ***(Cisneros-Herreros and Herrero-Romero, 2006).***

## Herpes Simplex Virus

Infections caused by HSV are the most common viral infections in patients with lymphoma and acute leukemia. These infections occur predominantly in patients with preexistent antibodies to HSV, indicating that most represent reactivation of endogenous latent infection. More

than 80% of bone marrow transplant recipients will have reactivation of latent HSV residing in the neuronal ganglia .Dissemination of HSV infection is uncommon and occurs most often in patients with Hodgkin disease. The liver, spleen, adrenal glands, kidneys, pancreas, lungs, brain, and gastrointestinal tract may be involved in disseminated infection ***(Perry and Faulds, 1996)***. Herpes virus hepatitis (HSV) represents a form of acute necrotizing hepatitis, which most frequently develops in immunocompromised patients ***(Longerich et al., 2005).*** Hepatitis is a rare complication of herpes simplex virus (HSV), often leading to acute liver failure (ALF), liver transplantation (LT), and/or death. Patients who are male, older, immuno-compromised, and/or presenting with significant liver dysfunction are more likely to progress to death ***(Norvell et al., 2008*)**. The diagnosis is frequently obscured by the absence of mucocutaneous involvement. Elevated transaminases with leucopenia and a relatively low bilirubin level may provide clues to the diagnosis ***(Chatni et al.,2008*)** .Therapeutic options include high-dose intravenous acyclovir and liver transplantation ***(Longerich et al., 2005).***

## Varicella Zoster virus

VZV is a double-stranded, linear DNA virus. Primary infection with VZV causes chicken pox in susceptible hosts ***(Heininger and Seward, 2006)***. Varicella hepatitis in immunocompetent hosts is usually self-limiting and asymptomatic, with subclinical elevation in serum transaminase levels ***(Pitel et al., 1980)***. However, severe