

## Seroprevalence of Hepatitis B and C in Pediatric Malignancies

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### ABSTRACT

**Background and Purpose:** Patients treated for pediatric malignancy are at high risk of parentally transmitted viral hepatitis. Blood product transfusions are the major risk factor. The aim of this study is to detect the seroprevalence of hepatitis B and C viral infections in pediatric malignancy patients, before, during and after chemotherapy.

**Material and Methods:** Two hundred and twenty two pediatric malignancy patients, presenting to the National Cancer Institute, Cairo University during the period from June 2000 to March 2001, were enrolled in this study. They were classified into two groups (I & II). Group I included 111 newly diagnosed cases of pediatric malignancy. Patients in this group were evaluated initially before starting chemotherapy and after six months of treatment. Group II included 111 cases of pediatric malignancy who ended chemotherapy and were already put under follow up from the beginning. Patients of both groups were subjected to full clinical evaluation. Sera of these patients were investigated for liver functions and hepatitis markers including HBsAg, HbCIGM, HBV-DNA by PCR (if HBsAg and/or HbCIGM were positive), HCV-Ab (IgG) and HCV-RNA by PCR (if HCV Ab was positive).

**Results:** In-group I, the seropositivities for HBV and HCV were found to be 3.6% and 0.9%, respectively, at diagnosis and increased significantly to 18.2% and 13.1%, respectively, after 6 months of therapy. In-group II, the seropositivities for HBV and HCV after cessation of therapy were found to be as high as 34.2% and 39.6%, respectively. Correlation between hepatitis markers and number of blood transfusions, surgery, sex, type of malignancy and liver function were listed.

**Conclusions:** There is high seroprevalence of hepatitis B and C in pediatric malignancy. Blood product transfusion is the major risk factor. It is possible that the very high rate of HCV seroconversion in these patients may not only depend on clearly documented parenteral exposure, but also on other unrecognized routes of transmission.

**Key Words:** Pediatric malignancy - Hepatitis B - Hepatitis C - HbsAg - HbcIGM - PCR - Blood transfusion.

### INTRODUCTION

Patients treated for pediatric malignancy are at high risk for parenterally transmitted viral hepatitis [1]. Blood product transfusion is the major risk factor. Moreover, when compared with immunocompetent patients, the immunodepression caused by chemotherapy increases the chronicity rate of viral hepatitis [2,3].

During the last 2 decades, screening blood donors for the hepatitis B virus (HBV) has resulted in a remarkable reduction of post-transfusion B virus hepatitis [4]. Thus, non-A non-B hepatitis virus has become the major cause of the parenterally transmitted hepatitis [5,6].

The successful cloning of hepatitis C virus (HCV) genome and the development of serologic markers of HCV infection showed that HCV was responsible for 85-90% of parenterally transmitted non-A non-B hepatitis [7].

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 [8,9]. Furthermore, recent studies have shown that HCV infection is a risk factor for hepatocellular carcinoma [10]. On the other hand, Seeff et al. [11], after an average follow-up of 18 years, reported a low incidence of deaths related to chronic HCV infection acquired from blood transfusion.

The aim of this study is to determine the seroprevalence of hepatitis B and C viral infec-

tions in pediatric malignancy patients, before, during and after chemotherapy.

## PATIENTS AND METHODS

### *Patients:*

Two-hundred and twenty-two (222) patients, who proved to have pediatric malignancies and who were attending the department of pediatric oncology at the National Cancer institute (NCI), Cairo University, Egypt, during the time period from June 2000 to March 2001, were enrolled in this study.

Our patients were classified into 2 groups, I and II.

Group I included 111 newly diagnosed patients with pediatric malignancies. The patients in this group were evaluated initially before starting treatment (subgroup A) and after 6 months of chemotherapy (subgroup B). Subgroup A included all 111 patients, while subgroup B included 99/111 patients. The rest of the patients (12 patients) included 6 who died, 5 lost to follow-up and 1 patient in whom therapy was discontinued due to progressive disease.

Group II included 111 patients with pediatric malignancies who ended chemotherapy and were already put under follow-up. These patients were randomly selected and their follow-up periods varied from 6 months to 5 years.

### *Methods:*

Cases in both groups, whether with hematological or solid tumors, were subjected to full clinical evaluation according to a standard clinical sheet with special emphasis on history of blood transfusion, parenteral therapy, previous surgeries, history of jaundice and history of hepatic dysfunction.

Exposure to blood products was expressed in blood units (one blood unit is defined as one unit of packed red blood cells, platelets, or fresh frozen plasma derived from one donor) [12].

Surgical exposure was classified into major or minor surgery. Major surgery included admission in a hospital, operating theatre and general anesthesia, whereas minor surgical procedures were carried out in an outpatient clinic setting with or without local anesthesia.

In addition to clinical evaluation, hepatitis laboratory workup was carried out for all patients.

This workup included 1- liver function tests, 2- detection of hepatitis B surface antigen (HBsAg), 3- detection of hepatitis B core IgM antibody (HBc- IgM), 4- HBV-DNA by PCR if HBV markers were positive, 5- detection of hepatitis C virus IgG antibody (HCV-Ab) and 6- HCV-RNA by PCR if HCV markers were positive.

## RESULTS

### *Group I:*

The ages of the patients in this group ranged from 1 to 16 years with a mean of  $7.6 \pm 4.2$  years and a male to female ratio of 1.7 : 1. Of the 111 patients, 44 cases (39.6%) suffered from leukemia, 28 (25.3%) had lymphoma, while 39 (35.1%) patients had solid tumors. Leukemia patients included 35 cases (31.5%) of acute lymphoblastic leukemia (ALL) and 9 (8.1%) acute myeloid leukemia (AML). Lymphoma patients included 18 cases (16.2%) of non-Hodgkin's lymphoma (NHL) and 10 Hodgkin's disease (HD) cases (9%). Cases with solid tumors included 7 (6.3%) with neuroblastoma (NB), 12 (10.8%) soft tissue sarcomas [peripheral neuroectodermal tumor (PNET), rhabdomyosarcoma (RMS) and synovial sarcoma], 5 (4.5%) bone tumors [osteosarcoma (OS) and Ewing's sarcoma (ES)], 5 (4.5%) retinoblastoma (RB), 4 (3.6%) brain tumors, 2 (1.8%) Wilm's tumor (WT), 3 (2.7%) germ cell tumors and 1 case (0.9%) of histiocytosis.

### *Group II:*

The mean age of the patients in this group was  $10.4 \pm 3.8$  years (ranging from 2 to 17 yrs), with a male to female ratio of 1.4 : 1. Leukemia cases in this group included 33 patients (29.7%) with ALL and 3 (2.7%) with AML. Lymphoma cases included 34 patients (30.6%) with NHL and 6 cases (5.4%) of HD. Solid tumor cases comprised 3 (2.7%) NB, 3 (2.7%) soft tissue sarcomas (RMS, PNET and synovial sarcoma), 19 (17.1%) bone tumors (E.S, O.S), 5 (4.5%) Wilm's tumor, 3 (2.7%) germ cell tumours (2.7%), 1 (0.9%) RB and 1 case (0.9%) of histiocytosis.

The seropositivities for HBV (HBsAg and/or HBcIgM) and HCV in group I (111 /222, 50%) were 3.6% (4/111) and 0.9% (1/111), respectively, at diagnosis (Table 1). The seropositivities for HBV and HCV infection after six months of chemotherapy increased significantly to 18.2% (18/99,  $p = 0.0001$ ) (Tables 2 & 3) and 13.1%

(13/99;  $p = 0.0001$ ), respectively (Table 4). On the other hand, the seropositivities for HBV and HCV in group II (111 patients) were found to be as high as 34.2% (38/111) and 39.6% (44/111), respectively.

There was a statistically significant increase in the number of blood units transfused with increased HBV seropositivity after 6 months of chemotherapy and after cessation of therapy ( $p$  values of 0.03 and 0.02, respectively) (Tables 5 & 6). However, there was an insignificant increase in the number of blood units transfused with the increased HCV seropositivity after 6 months of chemotherapy and after cessation of therapy ( $p = 0.88$  and 0.66, respectively) (Table 7).

As regards the risk of surgical exposure, no significant difference could be detected between those who were exposed and those who were not exposed either after six months of chemotherapy ( $p = 0.8$  and 0.14) or after cessation of chemotherapy ( $p = 0.21$  and 0.19), respectively.

There was no significant difference among the different types of malignancy. After 6 months of chemotherapy, the seropositivities for hepatitis B and C were 64.7% and 38.5% in hematological malignancies versus 35.3% and 61.5% in solid tumours, with  $p$  values of 0.46 and 0.16, respectively. After the end of chemotherapy, the seropositivities for hepatitis B and C were 63.2% and 63.6% in hematological malignancies versus 36.8% and 36.4% in solid tumours, with  $p$  values

of 0.99 and 0.92, respectively.

There was a significant elevation in liver enzymes in cases seropositive for hepatitis B after six months of chemotherapy or after cessation of therapy with a  $p$  value of  $< 0.001$  in either group (Tables 8 & 9). There was no significant difference in liver functions in cases with hepatitis C seropositivity either after six months of chemotherapy or after cessation of therapy, with  $p$  values of 0.31 and 0.22 in both groups, respectively.

#### *Hepatitis-infulence on clinical management and relapse:*

In group B (after 6 months of therapy), 18 patients developed hepatitis B while 13 patients developed hepatitis C. The total number of patients who developed hepatitis B and C was 31/99 patients (31.3%).

Accordingly, the treatment was changed, modified or delayed due to elevated liver enzymes in 23/31 patients (74.19%). These changes and modifications included cancelling of some hepatotoxic drugs, dose modification according to degree of hepatic injury and delay of chemotherapy protocols.

After one year of follow up, 4/31 (13%) patients had persistant elevation of liver enzymes and bilirubin 6 months after stopping chemotherapy. This was followed by relapse. These cases included 3 ALL patients and 1 patient with osteosarcoma.

Table (1): Results of hepatitis markers in both groups.

Marker	Group I				Group II	
	A		B		No.	%
	No.	%	No.	%		
<i>HBs Ag:</i>						
-ve	107/111	96.4	82/99	82.8	73/111	65.8
+ve	4/111	3.6	17/99	17.2	38/111	34.2
<i>HbcIgM:</i>						
-ve	110/111	99.1	90/99	90.9	106/111	95.5
+ve	1/111	0.9	9/99	9.1	5/111	4.5
<i>HBV DNA:</i>						
-ve	3/4	75	7/18	38.9	26/38	68.4
+ve	1/4	25	11/18	61.1	12/38	31.6
<i>HCV-Ab:</i>						
-ve	110/111	99.1	86/99	86.9	67/111	60.4
+ve	1/111	0.9	13/99	13.1	44/111	39.6
<i>HCV RNA:</i>						
-ve	1/1	100	8/13	61.5	23/44	52.3
+ve	0/1	0	5/13	38.5	21/44	47.7

Table (2): Correlation between HBsAg in group I A &amp; B.

Group I B	Group I A		Total
	-ve	+ve	
-ve	82	-	82
+ve	13	4	17
Total			99
<i>p</i> value 0.0001			

Table (3): Correlation between HBcIg in group I A &amp; B.

Group I B	Group I A		Total
	-ve	+ve	
-ve	89	1	90
+ve	9	-	9
Total			99
<i>p</i> value 0.021			

Table (4): Correlation between HCV-Ab in group I A &amp; B.

Group I B	Group I A		Total
	-ve	+ve	
-ve	86	-	86
+ve	12	1	13
Total			99
<i>p</i> value 0.0001			

Table (5): Correlation between hepatitis markers and blood transfusion in group I A.

Hepatitis marker	Mean number of blood transfusions	SD	<i>p</i> value
<i>HBs Ag:</i>			
-ve	0.4	±1.24	0.88
+ve	0.5	±1	
<i>HBc IgM:</i>			
-ve	0.4	±1.2	
+ve	-	-	
<i>HBV-DNA:</i>			
-ve	0.6667	±1.15	
+ve	-	-	
<i>HCV-Ab:</i>			
-ve	0.4	±1.2	
+ve	-	-	
<i>HCV RNA:</i>			
-ve	-	-	
+ve	-	-	

Table (6): Correlation between hepatitis markers and blood transfusion in group I B.

Hepatitis marker	Mean number of blood transfusions	SD	<i>p</i> value
<i>HBs Ag:</i>			
-ve	5.9	±4.5	0.03
+ve	8.9	±6.7	
<i>HBc IgM:</i>			
-ve	6.2	±5.01	0.14
+ve	8.89	±5.08	
<i>HBV-DNA:</i>			
-ve	9.7	±6.2	0.62
+ve	8.09	±6.99	
<i>HCV-Ab:</i>			
-ve	6.45	±4.9	0.88
+ve	6.69	±5.8	
<i>HCV RNA:</i>			
-ve	7.75	±5.57	0.44
+ve	5	±6.4	

Table (7): Correlation between hepatitis markers and blood transfusion in group II.

Hepatitis marker	Mean number of blood transfusions	SD	<i>p</i> value
<i>HBs Ag:</i>			
-ve	5.5	±4.0	0.02
+ve	8.9	±9.4	
<i>HBc IgM:</i>			
-ve	5.7	±4.2	0.02
+ve	8.9	±6.7	
<i>HBV-DNA:</i>			
-ve	7.5	±8.1	0.41
+ve	10.8	±11.9	
<i>HCV-Ab:</i>			
-ve	7.0	±8.3	0.66
+ve	7.7	±7.4	
<i>HCV RNA:</i>			
-ve	6.4	±6.8	0.419
+ve	9	±7.9	

Table (8): Correlation between hepatitis markers and liver functions in group I B.

	Non elevated L.F.ts		Elevated L.F.ts		<i>p</i> value
	No.	%	No.	%	
<i>HBs Ag:</i>					
-ve	78/82	(95.2)	4/82	(4.8)	< 0.001
+ve	4/17	(23.5)	13/17	(76.5)	
<i>HBc IgM:</i>					
-ve	68/90	(75.5)	22/90	(24.4)	0.003
+ve	2/9	(22.2)	7/9	(77.8)	
<i>HBV-DNA:</i>					
-ve	2/7	(28.6)	5/7	(71.4)	0.39
+ve	5/11	(45.5)	6/11	(54.5)	
<i>HCV-Ab:</i>					
-ve	64/86	(74.4)	22/86	(25.6)	0.31
+ve	8/13	(61.5)	5/13	(38.5)	
<i>HCV RNA:</i>					
-ve	7/8	(87.5)	1/8	(12.5)	0.41
+ve	3/5	(60)	2/5	(40)	

Table (9): Correlation between hepatitis markers and liver functions in group II.

	Non elevated L.F.ts		Elevated L.F.ts		<i>p</i> value
	No.	%	No.	%	
<i>HBs Ag:</i>					
-ve	68/73	(93.2)	5/73	(6.8)	< 0.001
+ve	10/38	(26.3)	28/38	(73.7)	
<i>HBc IgM:</i>					
-ve	78/106	(73.6)	28/106	(26.4)	0.002
+ve	—	—	5/5	(100)	
<i>HBV-DNA:</i>					
-ve	5/26	(19.2)	21/26	(80.8)	0.14
+ve	5/12	(41.7)	7/12	(58.3)	
<i>HCV-Ab:</i>					
-ve	50/67	(74.6)	17/67	(25.4)	0.22
+ve	28/44	(63.6)	16/44	(36.4)	
<i>HCV RNA:</i>					
-ve	16/23	(69.6)	7/23	(30.4)	0.39
+ve	12/21	(57.1)	9/21	(42.9)	

## DISCUSSION

The survival rates of children with cancer have dramatically increased in correlation with advances in therapy, including intensive chemotherapy. Children require multiple transfusions during intensive therapy and are at increased risk of blood transmissible infections, such as HBV and HCV infections. The need for frequent blood counts, invasive diagnostic procedures (e.g. bone marrow aspiration / biopsy), intravenous therapy and surgery in addition to the immunosuppressed status of these patients further increase the risk [1].

Hepatitis C virus (HCV) infection is now the most commonly encountered blood transmissible hepatitis infection among cancer patients. The previously reported risk of acquiring HCV infection in 25% of multiply transfused adults in the United States has dropped to 0.1% after routine screening for anti-HCV antibodies in blood and blood products followed by elimination of high risk donors [3].

Egypt is a developing country where hepatitis B and C infections are still prevalent. The overall prevalence of antibodies to HCV in the general population is around 15-20% [8]. This apparently high prevalence of HCV infection in Egypt is of importance, because of the potential adverse impact of HCV on the public health of Egyptians

[5,13]. The risk factor for HCV transmission that specifically sets Egypt apart from other countries is a personal history of parenteral anti-schistosomal therapy [14]. The mechanism by which schistosomiasis enhances HCV seropositivity is still unknown, but several possibilities exist. First, it is possible that Tartar Emetic therapy could have transmitted HCV via contaminated needles and syringes. Second, schistosomiasis may have enhanced HCV replication in the liver [15,16]. Furthermore, schistosomiasis may enhance hepatitis virus effects by modulating the cytokine system in the liver [5].

In the present study, seropositivities for HBV (HBsAg and/or HBcIgM) and HCV in group I (111/222, 50%) of pediatric malignancy patients were found to be 3.6% (4/111) and 0.9% (1/111), respectively, at diagnosis. The seropositivities for HBV and HCV infection after six months of chemotherapy were found to increase significantly to 18.2% (18/99, *p* value = 0.0001) and 13.1% (13/99; *p* value = 0.0001), respectively. On the other hand, the seropositivities for HBV and HCV in group II (111/222, 50%) of pediatric malignancy patients who ended chemotherapy and were evaluated while under follow-up were found to be as high as 34.2% (38/111) and 39.6% (44/111), respectively. Similar results were obtained in a study carried by Maurizio et al. [12]. This study included 102 children after their completion of ALL-directed chemotherapy. These patients were investigated for evidence of HCV infection by enzyme immunoassays 2 and 3, second-generation recombinant immunoblot assay and reverse transcription-polymerase chain reaction (PCR) for detection of circulating HCV-RNA. The prevalence of HCV infection in those children who completed leukemia-directed treatment was 43% [12].

Our results are in accordance with those of a clinical study carried out on Italian children to detect chronicity of HCV infection after treatment with pediatric malignancy protocols [17]. In this study, sera of 658 patients who had completed treatment with pediatric malignancy protocols were analyzed by a second-generation enzyme-linked immunosorbent assay (ELISA) and recombinant immunoblot assay test to assess the prevalence of hepatitis C virus (HCV) seropositivity. One-hundred and seventeen of the 658 patients (17.8%) were positive for HCV infection. This figure is high considering a 0.36% preva-

lence of HCV infection among Italian children in another study [18].

Our results are in agreement with another clinical study done to detect HCV infection among survivors of childhood cancer in St Jude's Children Research Hospital [10]. St. Jude's study included 1521 survivors who received blood products during treatment of childhood cancer between 1961 and 1992. These patients were screened for HCV and 77 (6.6%) of the surviving patients tested had evidence of HCV infection. Geographic variations in HCV seroprevalence may account for the lower risk for HCV infection among these patients when compared with risks ranging from 17.8% to 57% in other childhood cancer survivor cohorts [19-22].

Our results are similar to those of Kebudi et al. [1] to determine the prevalence of hepatitis B & C infections, as well as HIV infections in children with cancer at diagnosis and following therapy in Turkey. This study included 50 children (24 females and 26 males) with solid tumours who were receiving intensive chemotherapy and multiple transfusions. These children were investigated, by the ELISA technique, for HBsAg, anti-HBs, anti-HBc, anti-HCV and anti-HIV at diagnosis and at the end of therapy. The seropositivities for HBV and HCV infections were 4% (2/50) and 2% (1/50) at diagnosis and it increased significantly to 20% (10/50,  $p = 0.008$ ) and 14% (7/50,  $p = 0.031$ ), respectively after therapy. Improvement of blood screening procedures and the use of disposable equipment for invasive diagnostic procedures has decreased the incidence of HBV infections in children with cancer in Turkey in recent years [1].

Another study was carried out on 45 transfused children with cancer in the United States to determine the prevalence of HCV infection [23]. HBsAg, HBsAb, HBcAb and anti-HCV Ab were assessed. In contrast to our results, no seropositivity for HBsAg, HBsAb, or HBcAb could be detected. However, in agreement with our results, 9.8% (4/45) of the patients were positive for HCV antibodies. The seroprevalence of HCV in healthy children in the United States has been reported to be 0.2-0.4% [23]. Geographic variations in HCV seroprevalence may account for the lower risk of HCV infection among their pediatric malignancy patients. Since the mid-1980s, all blood and blood products have been routinely tested for HBsAg. In addition to public

health education, improved sanitation, infection control policies in hospitals and clinics and most importantly, the availability of safe and effective vaccines have led to a dramatic decline in HBV infection [24]. All the above mentioned factors are lacking, or at least inadequate, in underdeveloped countries, which explains the high seroprevalence of hepatitis in these countries. In an Egyptian study, GM-CSF proved to be a safe adjuvant that can be given with HBV vaccine to pediatric malignancy patients in order to increase the anti-HBs antibody titres [25].

In Saudi Arabia, a study including 53 children (31 males, 22 females, 1-12 years of age) receiving cycled cancer chemotherapy and 168 healthy Saudi children as controls, was carried out [26]. Exposure to HBV in the patients was similar to the controls (6% HBsAg in patients versus 7% in the controls; 19% exposure rate in patients versus 20% in controls). In contrast to the situation with HBV, the prevalence of anti-HCV in patients (11%) was significantly higher than that in the controls (1%) ( $p = 0.003$ ).

Correlating between the number of blood units transfused and the seroprevalence of hepatitis B and C in our study, we were able to find a statistically significant correlation between the number of blood units transfused and the increased HBV seropositivity after 6 months of chemotherapy and after cessation of therapy ( $p = 0.03$  and  $0.02$ , respectively). However, we were not able to find any statistically significant correlation between the number of blood units transfused and the increased HCV seropositivity after 6 months of chemotherapy and after cessation of therapy ( $p = 0.88$  and  $0.66$ , respectively). It is possible that the very high rate of HCV infection in these patients may not only depend on clearly documented parenteral exposure, but also on other unrecognized routes of transmission, possibly favored by associated conditions such as immunosuppressive therapy. Also, the use of non-disposable materials, e.g needles of bone marrow aspiration or biopsy, intra-venous manipulations, repeated blood counts and surgical procedures may have played a major role in HCV prevalence in these patients.

Similar results were obtained in a study of hepatitis C virus infection in children treated for acute lymphoblastic leukemia [12] which included one-hundred and two patients, 56 males and 46 females, with ages ranging from 2.5 to 21.1

years (median age 10.5 years). All the patients, except one, received blood derivatives as part of their antileukemic treatment. Furthermore, all donors were screened for anti-HCV. There was no significant difference in terms of the total number of blood units administered and the seroconversion rate. These results are in agreement with the study done by Monteleone et al. [23] in the United States, who showed that the mean number of donor exposures was insignificantly different between HCV negative versus HCV positive patients.

In the Italian study of chronic hepatitis C virus infection after treatment for pediatric malignancy [17], the researchers reported that 20% of HCV positive patients, particularly patients with solid tumours, did not receive any blood or blood products and were most probably infected by another route.

In the study done in Turkey by Kebudi et al. [1], there was no statistically significant correlation between the number of blood units transfused and the risk of acquiring HBV (in contrast to our results) or HCV infections (in agreement with our results) in seronegative patients at diagnosis, in spite of the fact that the patients acquiring HCV during therapy had received more transfusions.

Screening of blood donors for anti-HCV coupled with the increased awareness of the disease has practically eradicated TAH-C (Transfusion Associated Hepatitis C), so that transfusion of screened blood should no longer be considered a primary risk factor for HCV infection [27]. Since 1994, the estimated risk of transfusion-associated HCV infection ranged from 0.01 to 0.001% per unit transfused [13].

A study was conducted by Fink et al. [21] to detect the association of HCV infection with chronic liver disease in pediatric cancer patients. It included 203 children and showed that anti-HCV positive children had received significantly more blood product transfusions compared to seronegative patients.

Similarly, Donald et al. [10] detected HCV infection among survivors of childhood cancer in St Jude's Children Research Hospital. They reported that there was a strong correlation between the volume of blood infused and the risk of HCV infection, which likely explains the

higher prevalence of HCV infection among their patients before anti-HCV testing was available.

On comparing the seroprevalence of hepatitis B and C in pediatric patients with different types of malignancy (i.e. hematological Vs solid tumours), we were not able to demonstrate a significant difference. These results were found despite the higher frequency of blood transfusions in the hematological malignancy group compared to the solid tumour group, where the seropositivities for hepatitis B and C were 64.7% and 38.5% in hematological malignancies versus 35.3% and 61.5% in solid tumours, respectively ( $p = 0.46$  and  $0.16$ ). After the end of chemotherapy, the seropositivities for hepatitis B and C were 63.2% and 63.6% in hematological malignancies versus 36.8% and 36.4% in solid tumours, respectively ( $p = 0.99$  and  $0.92$ ).

Similar results were obtained in a study by Simone et al. [17], who reported that the prevalence of hepatitis C virus infection did not show any significant change in the distribution between leukemia / lymphoma (17.2%) and solid tumour (18.9%) patients, even if the former group had a higher exposure to risk factors for HCV infection in the form of more frequent blood product transfusions, invasive diagnostic procedures such as bone marrow aspiration or biopsy and frequent blood sampling.

On comparing the seroprevalence of hepatitis B and C with liver functions, we were able to demonstrate a significant elevation in liver enzymes in cases with hepatitis B seropositivity, either after six months of chemotherapy or after cessation of therapy ( $p < 0.001$  in both groups). However, no significant difference in liver functions was found in cases of hepatitis C seropositivity, either after six months of chemotherapy or after cessation of therapy ( $p = 0.31$  and  $0.22$  in both groups, respectively).

Similar results were obtained in the study done by Maurizio et al. [12], who showed that all the viremic patients, except one who lacked anti-HCV, had normal transaminase activity, suggesting mild or absent liver damage. However, this does not exclude the presence of chronic liver disease in these patients since it has been reported that viremic patients with normal transaminase levels may occasionally have chronic liver lesions. Thus, transaminase determination is inadequate to predict HCV infection, as normal

ALT levels did not exclude the presence of HCV infection in more than half of the viraemic patients [12]. These results are in conflict with the study done in the United States by Monteleone et al. [23], who showed that ALT levels during and after cessation of treatment in children with cancer were significantly higher in the HCV-positive group versus the HCV-negative group. This may be due to the immunological response of the host which is variable from one patient to another.

In the current study, the seroprevalence of hepatitis B & C was compared with the risk of surgical exposure. We were not able to demonstrate any significant difference between negative and positive cases either after six months of chemotherapy ( $p$  value of 0.8 and 0.14) or after cessation of chemotherapy ( $p$  value of 0.21 and 0.19). We could not detect any statistical difference even in patients with solid tumours as osteosarcoma who were exposed to a major procedure, like limb sparing surgery with vascularized fibular graft and who required more than 6 units of blood transfusion intraoperatively.

On comparing the seroprevalence of hepatitis B and C with sex, we were not able to demonstrate any significant difference either after six months of chemotherapy ( $p = 0.65$  and  $0.09$ ) or after cessation of chemotherapy ( $p = 0.96$  and  $0.88$ ).

Delay of chemotherapy and its influence on relapse due to hepatitis was observed for one year in our study after the end of sample collection. In this series, the total number who developed hepatitis B or C were 31/99 (31.3%). The treatment in these patients was changed/ modified in 23/31 (74.19%) patients due to deterioration in liver functions. These changes included cancelling some hepatotoxic drugs, dose modification according to degree of hepatic injury and delay of chemotherapy protocols.

After one year of follow-up, 4/31 (13%) patients had continuous elevation of liver enzymes and bilirubin for 6 months after cessation of chemotherapy, followed by disease relapse. This suggests that hepatitis may indirectly contribute to the occurrence of relapse in these patients, due to change, modification or delay of chemotherapy.

In a Spanish study by Lopez-Jimenez et al. [28] on 65 patients with AML, to evaluate the

incidence of hepatitis and its influence on clinical outcome, 35% of the patients developed hepatitis, a rate which is higher than that reported with pediatric ALL [29] and lower than that in adult AML patients (52-81%) [30]. The treatment was changed and/or modified because of hepatitis in 13/65 patients (20%). Only 43% of patients with hepatitis underwent the full course of chemotherapy. Patients who did not complete the scheduled consolidation chemotherapy, because of hepatitis or other causes, had a higher relapse rate than patients who did complete the course of chemotherapy (56.5% vs. 40.4% respectively,  $p = 0.1$ ). This difference suggests a diminished antileukemic effect in patients in whom the treatment was changed [28].

Another study reported a lower relapse rate for ANLL patients with hepatitis [27].

The lower recurrence rates in ANLL patients with hepatitis may be either due to non-specific suppression of the leukemic cells by the hepatitis virus [27], or due to the presence of a more competent immune system in patients with aspartate transaminase elevation [28].

#### Conclusions:

From our study, we can conclude the following:

- There is a high seroprevalence of hepatitis B & C in pediatric malignancy in Egypt.
- Transfusion of blood and/or blood products are the major risk factors in the development of hepatitis B or C.
- The very high rate of HCV infection in these patients may not only depend on clearly documented parenteral exposure, but also on other invasive procedures carried out by paramedical personnel.

#### Recommendations:

- Accurate screening of blood products for HBV & HCV.
- Use of disposable equipment.
- Health education of paramedical personnel.
- All seronegative patients with malignant disease should be routinely vaccinated against HBV at diagnosis.
- Long term follow-up for patients with hepatitis should be done to detect if these patients are less liable to develop a relapse, due to the anticancer effect of hepatitis.

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