Seroprevalance of Hepatitis B&C In Pediatric Malignancies

Nada Ali Ahmed AL-Ali*, Thalfaa Nathim Al-Kayatt**

ABSTRACT:

BACKGROUND:

Children with cancer who are on intensive chemotherapy require multiple blood and its products transfusion which increases the risk of blood transmissible infection

OBJECTIVE:

To know the prevalence of HBV and HCV infection in pediatric malignancy after starting anti cancer therapy and To identify the risk factor, that increased the possibility of infection

Design a Prospective interventional study

Participants The present study was conducted on 85 children with malignancies who were attending the department of pediatric oncology in Mosul,(Ibn-Alather hospital) the age of the patients were between 1-15 years with male: female ratio of 1.5: 1

Main outcome measure. All our patients were tested for HBsAg and HCV antibodies at diagnosis of malignancy and before starting chemotherapy then after six and twelve months

RESULTS:

Two patients (2.3%) had HBV infection, and no patient had HCV infection initially, while after 6 month of receiving chemotherapy we have 8/70 (11.4) had HBV and also no patient with HCV, and after 12 months of receiving chemotherapy the percentage of patients with HBV and HCV were increase to 13/63 (20.6%) and 2/63 (3.2%) respectively .

CONCLUSION:

Its important to ensure on accurate screening of blood and its products before transfusion to these patients, and also ensure on the receiving HB vaccine before starting chemotherapy. Before this study, the prevalence of HBV and HCV infection in pediatric malignancy in Mosul city were unknown, the present study was designed to fill this gap.

KEY WORDS: hepatitis B&C, Pediatric malignancy**.**

INTRODUCTION:

Viral hepatitis is a major health problem in developing and developed countries [(1)]. Both hepatitis B virus (HBV) and hepatitis C virus (HCV) infection causes major problems in management of cancer patients. Many of these patients received multiple transfusions of different blood components, and this could be appositional risk factor for acquiring such infection [(2,3)]

***Hepatitis* B** Although direct cytotoxic liver injury can occur when the viral load is very high ,the predominant mechanism involve the cytotoxic T-cell mediated lyses of infected hepatocyte . This event presumably explain why patient with fulminant hepatitis have no evidence of HBV replication and why patients who have cleared HBV have more vigorous immune responses compared with chronic HBV carrier [(4,5)] .

There are many routes that contribute to increase the chance of getting HBV infection. These are :[(6,7,8)]

- Blood and blood product transfusion as platelets, fresh frozen plasma, cryoprecipitate.
- Percutaneous or per mucosal exposure to infectious body fluid as saliva, serum, or through needle stick accidents, shared tooth brusher.
- Intravenous drug users as in addicts or in patient with chronic disease who received frequent intra venous drugs for long period as in patients with malignancy.
- During surgical procedures when contaminated equipments is used.
- Sexual transmission of virus also can occur .
- Vertical transmission from infected mother to her neonate.

*College of Medicine /Mosul University.
**Ibn-Al-Ather Teaching Hospital.

Hepatitis C Virus

Many routes play role in the getting of HCV infection , these are :

- HCV transmitted most reliably through transfusion of infected blood or blood product[9], before routine blood screening for anti-HCV antibodies , 17% of new infections was attributed to transfused blood products while after blood screening was implemented the risk decrease to 4% [10,11] .
- The parenteral drug use is the strongest predictor of HCV infection [12] .
- Nosocomial transmission of HCV has ranged from 0-10% [13] .
- The infection can also occur by vertical transmission [14] .
- More than 40% of hepatitis C cases in United States today are acquired by some other (unknown) route [15] . Infection in infancy and early childhood is asymptomatic in majority of patients . In children , jaundice may be in apparent, or it can be severe and may persist for many weeks [16,17] ..

Studies indicate that a combination of interferon – Alfa with antiviral ribavirin produce better result than have been obtained with interferon Alfa alone. Lamivudine (2-3 dideoxycyosine) is a cytosine analog , that effectively inhibit HBV replication and clear HBV-DNA in 23% of positive children with chronic hepatitis [18]

HB vaccine and HB immunoglobulin (HBIG) are the most effective strategy to prevent HBV infection [6] . HB vaccine is given intramuscularly into anterolateral thigh for infants, while in older children the vaccine is injected in the deltoid muscle [19, 20]. Children with malignancy who received anticancer therapy are causes susceptible to infection by bacteria, fungi, virus, and protozoa. HBV infection is one of such infection which is common in children on chemotherapy. Control of this disease can be achieved through effective vaccination; however the immunogenic response may be impaired due to prolonged immunosuppressive therapy [21, 22]

PATIENT AND METHODS:

A cohort study were done upon eighty five patients who proved to have different types of malignancies and who were attending the department of pediatric oncology in mosul , during the period from 1st July 2006 to 30th of December 2006 and follow up was done on this group of patients for 1 year .

Their ages were between 1-15 years of age, 52 patients were male and 33 were females. A questionnaire form was designed to collect specific information about all the patients included in the study.

The following information were taken, age, sex, type of malignancies, history of surgery, history of invasive procedure (bone marrow aspiration, fine needle aspiration and bone biopsy) and history of blood and its product transfusion . Our patients were evaluated initially before starting anticancer therapy by aspirating 3ml of blood sample from each patient enrolled in the study for the following tests :

1. HBsAg: was detected by third generation ELISA for determination of HBsAg subtype in human serum.
2. HCV antibodies were detected by third generation ELISA which is intended as screening test to detect antibody to HCV in human serum .These tests also were repeated for each patient after 6 month and after 12 month of starting anticancer therapy. During our study we lost 22 patients, 18 were died from infection, bleeding, or other causes other than hepatitis. The remaining 4 patients were lost to follow up.

The data were analyzed statistically to identify the potential risk factors, chi-square test (x^2) used to test for the significance between the groups , P-value is not significant if its > 0.05 , significant if its < 0.05 , and highly significant if < 0.001

RESULTS:

Table No. 1: Sex Distribution.

Sex	No.	%
Male	52	61.2
Female	33	38.8
Total	85	100%

Of the 85 patients with malignancy, 52(61.2%) were male and 33(38.8%) were female, giving male: female ratio of 1.5:1

Table No. 2:Types Of Malignancy.

Type of malignancy	No.	%
Acute lymphoblastic leukemia (ALL)	44	51.8
AML	2	2.4
NHL	11	12.9
HD	7	8.2
Neuroblastoma	8	9.4
Wilms tumor	7	8.2
Retinoblastoma	1	1.2
Osteosarcoma	2	2.3
Others	3	3.6
Total	85	100 %

ALL form the most common type of malignancies in this group, followed by lymphoma (NHL, HD) neuroblastoma, Wilms tumor and then other types of malignancies.

Table No. 3: Prevalence Of HBV Infection .

State of HBV screening	No. of patients with HBV infection	%	p-value	
At diagnosis	2/85	2.3%	0.02	<0.001
After6month of treatment	8/70(85-15=70)	11.4%		
After12month of treatment	13/63	20.6%		

- After 6months we lost 15 patients (died or missed) so the remaining patients (85-15=70 patient).
- After 12 months we lost 22 patients (died or missed) so the remaining patients (85-22=63 patients) .
- It's found that the prevalence of HBV infection increased significantly from 2(2.3%) to 8(11.4%) after 6months of treatment and to 13(20.6%) patients after 12months.

Table No. 4: Prevalence Of HCV Infection.

State of HCV screening	No. of patients with HCV infection	%	p-value
At diagnosis	Zero/85	0%	
After6month of treatment	Zero/70	0%	
After12month of treatment	2/63	3.2%	0.18

- Total No. of remaining patients after 12month 63 patients.
- Its found that the prevalence of HCV infection at initial diagnosis and after 6months of treatment is zero, but after 12months of treatment there is insignificant increase in the patients 2(3.2%) .

Table No. 5: Correlation between hepatitis markers and blood and its products transfusion after 12months of treatment .

Hepatitis marker	Mean no. of blood and its products transfusion	p. value
HBsAg - ve + ve	 3.8 8	< 0.001
HCV-Ab - ve + ve	 4.2 11	0.001

Total No. of blood and its products received by negative patients for HBsAg divided by total no. of patients , the total no. of blood and its products received by patients with positive HBsAg divided by their total no. , this applied also for HCV . There is a significant correlation between the no. of blood units transfused and the incidence of HBV and HCV infection .

Table No. 6: Correlation between HBV infection and others risk factors.

Risk factors	No. of HBV+ve		No. of HBV-ve		p. value
Invasive procedure (BM asp,bone bx,fine needle asp)	No.	%	No.	%	0.36
	13	100%	47	94%	
Surgery	6	46.1%	17	34%	0.2
Chemotherapy	13	100%	50	100%	1.0

This table shows all these factors have insignificant effects on the incidence of HBV.

Table No. 7:Correlation between HCV infection and others risk factors.

Risk factor	No. of HCV+ve		No. of HCV-ve		p. value
	No.	%	No.	%	
Invasive procedure (BM.asp.bone bx,fine needle asp.)	2	100%	52	85.2%	0.2
Surgery	Zero	0%	23	37.7%	0.14
Chemotherapy	2	100%	61	100%	1.0

This table show all these factors have insignificant value on the incidence of HCV .

DISCUSSION:

Children with cancer who are on intensive chemotherapy require multiple blood and its products transfusion which increases the risk of blood transmissible infection such as HBV and HCV infection, also the need for frequent blood counts, invasive diagnostic procedures (bone marrow aspiration, bone biopsy, fine needle aspiration), intravenous therapy, surgery, in addition to immunosuppressed status of these patients, all of these will further increase the risk of HBV and HCV [23].

We found that male: female ratio of 1.5:1, this difference is because of the increased risk of ALL, lymphoma, and medulloblastoma among the young boys [8]. These results go with that obtained by Ali Mostafa etal. Where they obtained male: female ratio of 1.7:1 [23] . Of the 85 patients, 44(51.8%) suffered from ALL, 2(2.4%) had AML, 11(12.9%) had NHL, 7(8.2%) had HD, 8(9.4%) of cases had neuroblastoma,7(8.2%)had wilms tumor, 1(1.2%) had retionoblastoma, 2(2.3%) osteosarcoma, and other 3(3.6%) had PNET and rabdomyosarcoma . these results reveal that the acute lenkemia is the most commen type of malignancies in children, which goes with results in united state where the acute leukemia account 41% of all malignancies

In our study we had significant increase in HBV this was comparable to a study done by Ali Mostafa etal [31], in Egypt a group of pediatric malignancy, where they found the prevalence of HBV and HCV before start treatment, 3.6%, 0.9% respectively, and after 6 months of anticancer therapy, they also have significant increase in prevalence of HBV (18.2%) . While in contrast to our result, where we have insignificant increase in HCV, Ali Mostafa [23] study has significant increase in HCV. Also another study was done by S.A.AL-Hadad in Baghdad on group of pediatric malignancy where they found that there is significant increase in HBV 27.3% while the HCV had insignificant result, so these study go with our study [25]. This difference in the prevalence of HCV between our study and the results of above studies may be related to the fact of low prevalence of HCV in our country [26].

If we compare the seropsitivities for HBV in our work it's much higher than that obtained by a study done by Monteleone P.M. In USA where they have no seroconversion of their malignant patients after receving anticancer therapy for several months [27] . This difference in the prevalence of HBV is due to that in USA since

1980 all blood and its products have been routinely tested for HBsAg in addition to highly public health education, improved sanitation, infection control policies in hospital and clincs, and most importantly the availability of the safe and effective vaccine have led to adramatic decline in HBV infection. All of these factors are lacking or at least inadequent in developing countries (like our country) which explain the high seroprevalnce of hepatitis [27]. While for prevalence of HCV infection they have higher than our results.

Correlating between the number of blood and its products units transfused and the seroprevalnce 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 increase in HBV and HCV seropositivties after 12 months of treatment (p value = < 0.001) for HBV infection which is in agreement with study by Ali Mostafa etal [23] , and for HCV (p value = 0.001) which is in contrast to study done by Ali Mostafa [23] , in which there is no significant correlation between number of blood units and increase in HCV.This difference may be related to many routes of transmission of HCV other than blood transfusion.

In contrast to our results, a study done in Turkey by Kebudi etal [28] where there is no significant correlation between the number of blood units transfused and the risk of acquiring HBV or HCV , this difference may be related to that of the transmission of HBV and HCV infection may not only depend on blood transfused, but also on other routes of transmission in addition to the immunosuppressive state of patients .

In agreement with our results for the prevalence of HCV , study done by Fink F. etal [29] where they found that the anti-HCV positive children had received significanty more blood transfusion compared to seronegative patients . Its found that the children with oncologic disease are at significant risk of acquiring HCV mainly by multiple blood transfusion because the blood screening for antibloodies to HCV could not completely eliminate the risk of HCV transmission by blood because these antibodies usually appear within 2-3 weaks after acquiring the infection [24] .

We found that the risk of invasive procedures (bone marrow aspirate, bone biopsy, fine needle aspiration) on the prevalence of HB infection and HC infection was statistically insignificant (p-value = 0.36 , 0.2 respectively) these results were the same as the results of Ali Mostafa where they also have insignificant difference between positive and negative patients [23] .

About the risk of major surgery we were not able to demonstrate any significant difference between negative and positive cases for HB and HC patients, (p-value = 0.2 , 0.1 , respectively). This will go with a study of Ali Mustafa etal[23], and another study of Kristen Visona etal[3,30]. Where they found the surgical procedures have no rote on the prevalence of hepatitis.

Because all our patients who were seronegative and seropositive for both HBV and HCV infection (100%) received chemotherapy, so we can not get an informative p-value that reflect the actual effects of chemotherapy on the prevalence of HBV and HCB infection .

Its clear that the chemotherapy play an important role in increasing prevalence of HBV and HCV infection by its immunosuppressive effects which lead to decrease the antibodies titer which is previously acquired, also impaire the immunogenic response to HB vaccine [22], which is given to all seronegative patients in schedule of (0,1,6 month) at diagnosis of cancer, inspite of that fact all our patients receive 3 doses of hepatitis B vaccine according to national Iraqi vaccination schedule, and its showed that after 3 doses of the vaccine 67% of patients receiving anticancer therapy had protective anti-HBs antibody titer compared with 97% of those not receiving chemotherapy

Recommendation

All seronegative patients should receive HB vaccine Accurate screening of blood and blood products for HBV and HCV. Health education of paramedical personnel, patients , and patients family. Use of disposable equipment. Use of GM-CSF as adjuvant given with HB vaccine.

REFERENCE:

1. Nada Yazigi,William F, Balistreri Viral hepatitis,Nina S.Kadan-Lottick cancer &Benign Tumors.In: Behrman R.E,Kliegm R.M,Jenson H.B.and Stanton B.F(eds) Nelson textbook of pediatric . 18th ed. , Philadelphia , W.B.Sannders company , 2007:1680-1687 , 2097-116 .
2. Alter M.J., Mast E : The epidemiology of viral hepatitis in the United States , Gastroenerol Clin North Am 1994;23: 437-55 .
3. Kirsten Viesona, Fulgnecio B.,etal: Impact of Hepatitis B and C virus infection in Hematology-oncology unit at childrens hospital in Nicaragua. Clinical and diagnostic laboratory immunology 2002 ;9:622-26 .

4. D.Ganem , A.M.Prince : Hepatitis B virus infection-natural history and consequence . N Engl J Med 2004 ; 350:1118-29
5. B.Rehermann , D.Lan , etal : Cytotoxic T Lymehocyte Responsivenss after resolution of chronic hepatitis B virus infection . J Clin Invest 1996 ; 97:1655-65.
6. Kenneth B.Reberts : Manual of clinical problems in pediatric . 5th ed , Lippincott WW , Philadelphia , 2001;287-90
7. Melnick J. Dreesman G : Approaching the control of viral hepatitis B. J Infect Dis 1976 ; 133-210 .
8. Araham Rudolph,Hepatitis C ,Colin D Rudolph etal:Rudolph pediatric.21ed,Mcgraw-Hill company,2003:1498-99.
9. G.M. Lauer , B.D.Walker : Hepatitis C virus infection . N Engl J Med 2001 ; 345:41-51
10. Center for Disease control and prevention : Public health service interagency guide lines for screening blood , plasma for evidence of hepatitis B and C . MMWR 1991; 40:1-17.
11. G.B. Schreiber , M.P.Busch , etal : The risk of transfusion – transmitted viral infection . N Engl J Med 1996 ; 334:1685-90.
12. M.Giuliani , F.Caprilli , etal : Incidence and determinants of hepatitis C virus infection among individual at risk of sexually transmitted disease , Sex Transm Dis 1997 ; 24 : 533-37.
13. T.Mitsui, K.Iwano , etal : Hepatitis C virus infection in medical personal after needle stick accident . Hepatology 1992 ; 16:1109-14.
14. E.A.Reberts , L.Yeung : Maternal – infant transmission of hepatitis C virus infection . Hepatology 2002 ; 36:5106-5113 .
15. Ronald Kleinman,Hepatitis C ,Laurence F.,Ronald E.:Saunders manual of pediatric practice.2ed,W.B.Saunders company,2002:401-3.
16. 24. Anne A.Gerston,Viral hepatitis,Samuel L.K. ,Anne A.G.,Peter J.H. :Krugmans infectious disease of children. 10ed ,Mosby,Inc., 1998: 163-167 .
17. Mary F.H : Nursing care of the critically ill child , 2nd ed , Mosby – year book , 1992 : 783-74 .
18. M.M.Jonas , J.Mizerki , etal : Clinical trail of lamivudine in children with chronic hepatitis B. N Engl J Med 2002 ; 346:1706-13 .
19. Jim B.,Hepatitis B ,Jim B., Rebert C :Practical Pediatric Problems. 1 ed , Hodder Arnold ,London ,2005:153.
20. Hadi J.S. : Epidimiologyical study of viral hepatitis b in Najaf government . A thesis submitted to university of Al.Nahrain , Iraq , 2004 .
21. Paul R. , Chellam K., etal : Immunogenicity of hepatitis – B vaccine in children with malignancy . Pediatric Oncall 2005 .
22. M.Ramesh , R.K. Marwaha , etal : Seroconversion after hepatitis B vaccination in children receiving cancer chemotherapy . Indian pediatrics . 2000 ; 37: 882-86 .
23. Ali Mostafa , Emad Ebeid , etal : Seroprevalence of hepatitis B and C in pediatric malignancy . Journal Of Egyptian Nat . Cancer Inst . 2003;15:33-42 .
24. David G.Poplak,Epidimiology of childhood cancer,Philip A.Pizzo, David G.Poplack:Principles and Practice of pediatric oncology. 4ed ,Lippincoot Wiliam and Wilkins,2002: 13-20.
25. . S.A.AL-Hadad ,M.F.AL-Jadiry,etal:High incidence of HB infection after treatment for pediatric cancer at teaching hospital in Baghdad.EMHJ.2013;19:130-134.
26. Jassim M.Chadhban : Prevalence of serological markers of hepatitis B virus and hepatitis C virus among blood donors , A thesis submitted to the scientific council of medical specialization 1997 .
27. Monteleone P.M. , Andrzejewski C. , etal : Prevalence of antibodies to hepatitis C virus in transfused children with cancer . Am J . Pediatric . Hematol / oncol . , 1994 ;16:309 .
28. Kebudi R., Ayai , etal : Seroprevalence of hepatitis B,C and HIV virus infection with cancer at diagnosis and following therapy in Turkey . Med . Pediatric . oncol. , 2000;34 : 102-5 .
29. Fink F.M. , Hocker – Schulz S. , etal : Association of hepatitis C virus infection with chronic liver disease in pediatric cancer patients . Eur.J. Pediatric 1993 ; 152-490
30. Sukran Kose,Ali Olmezoglu,etal:Seroprevalance of hepatitis B andC among oncology patiente in Turkey. J Health Nutr.2011;29:652-55.