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Research Paper

Hepatitis B and C in Acute Lymphoblastic leukemia

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ABSTRACT:

BACKGROUND:

The risk of acquiring both hepatitis B virus (HBV) and hepatitis C virus (HCV) infections in patients with cancer has been documented. Risk of parenteral transmission of viral hepatitis has been well recognized, especially due to blood product transfusions.

PATIENTS AND METHODS:

The duration of the data collection and analysis of the study was from August 2018 till October 2019. A retrospective study included 92 children with Acute Lymphoblastic Leukemia diagnosed consecutively in a 2-year period; 2015-2016 at Oncology Unit in Children Welfare Teaching Hospital. Demographic information, treatment details, vaccination history and baseline hepatitis screen were documented. Follow up data during ALL therapy regarding the mass of blood products received by the patients,

RESULTS:

At the time of diagnosis, all patients were serologically negative from HBV and HCV. During the follow up period, there were 19 (20.6%) patients infected with hepatitis by serological method; 18 with hepatitis C and one with hepatitis B. there was no significant correlation between seroconversion with hepatitis and liver dysfunction, blood product transfusions more than 10 times, chemotherapy delay due to liver dysfunction and risk group. The mean duration from date of diagnosis till date of last follow up was 43.7 months (range 28.6-56.2 months), while the duration from date of diagnosis till seroconversion with hepatitis was 44.2 months (range 6.9-56.4 months).

CONCLUSION:

Low incidence of HBV and high incidence of HCV noticed in this group of patients, there is no direct significant correlation to blood product transfusions.

KEYWORDS: ALL acute lymphoplastic leukemia, hepatitis b and c

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Iraqi Postgraduate Medical Journal, 2024; Vol. 23(2): 191-196
DOI: 10.52573/ipmj.2024.182889 *Received: April 18, 2022,* *Accepted: May 30, 2022*

INTRODUCTION:

Acute lymphoblastic leukemia (ALL) is the most common malignancy in childhood, representing about one third of pediatric malignancies. The annual incidence of childhood ALL is about 3.2 per 100,000 children, with peak incidence between 2 and 5 years of age. Recent improvements in the diagnosis and treatment of ALL have led to cure rates now exceeding about 80% [1].

Hepatitis B virus

Hepatitis B virus (HBV) infection is a serious public health problem worldwide, with about ~400 million chronic HBV surface antigen (HBsAg) carriers [2].

Diagnosis of HBV in leukemia

In early reports, the diagnosis of HBV reactivation based on HBsAg and hepatitis B surface antibody (antiHBs) antibody titers.

There are 2 separate clinical scenarios during immunosuppressive therapy: (1) HBsAg-positive patients experiencing an increase in serum HBsAg titer and (2) HBsAg-negative/anti-HBs–positive patients is show anti- HBs decline associated with the reappearance of HBsAg (seroreversion) [3].

Hepatitis C virus

Hepatitis C virus (HCV) is a RNA virus of the Flaviviridae family and its infection is considered a major cause of chronic liver diseases, with regarding for neoplastic degeneration. The estimated prevalence of HCV infection worldwide is about 3% (> 170 million people). Hepatitis C is not uncommon in patients with various hematological malignancies, and these patients frequently require blood transfusions during the course of their treatment.

The prevalence of hepatitis C virus (HCV) hepatitis in pediatric patients with acute leukemia shows wide variation among different studies in ranging from 1 to 43% [4].

Management and prevention of HCV in leukemia

HCV infection should not contraindicate cancer therapy, and patients with chronic HCV infection and hematologic malignancies should not be excluded from clinical trials of chemotherapy or antiviral therapies. However, hepatologists and infectious disease specialists with experience in treating HCV should participate in the diagnostic work-up,to monitor and for treatment the infected patients [5].

AIM OF THE STUDY:

1. Retrospectively collecting baseline and follow up data to determine the rate of hepatitis B and C infection in children with ALL
2. Determine the extent of liver toxicity in patients infected with hepatitis B and C compared to those who do not acquire the infections.
3. Recognize any relation between seroconversion and different variables.

PATIENTS AND METHODS:

Retrospective study included children with ALL diagnosed consecutively in a 2-year period; 2015-2016.

Patients included should be in clinical and hematological remission after induction and throughout the study

Information were collected as baseline data (at time of diagnosis):

1. Age, sex and date of diagnosis
2. Hepatitis B immunization history
3. Presenting WBC, risk classification (high or standard risk)
4. Baseline liver enzymes
5. Baseline Hepatitis B testing with Hepatitis surface antigen (while hepatitis surface antibody and hepatitis B core antibody were not available).
6. Baseline Hepatitis C testing with Anti Hepatitis C Ab
7. Hep B or C PCR if Elisa testing is positive

Follow up data during ALL therapy:

1. Document number of RBC, platelet and plasma transfusions during therapy.
2. Every 3 months AST, ALT, Alkaline phosphatase, total bilirubin and direct bilirubin
3. Every 3 months repeat hepatitis B and C testing as above
4. Documentation of any interruption or omission of chemotherapy related to liver dysfunction and Neutropenia

Patients who finished maintenance chemotherapy were selected for the study. Files of these patients were reviewed retrospectively for liver function tests and hepatitis infection before starting modified UKALL 2011 protocol; implemented at the oncology unit in Children's Welfare Teaching Hospital consisting of induction of remission, consolidation, and maintenance phases, for a total duration of 113-114 weeks for girls and 165-172 weeks for boys according to risk group, treatment with the following drugs: vincristine, Doxorubicin, L-asparaginase, prednisolone, cyclophosphamide, cytosine arabinoside, 6-mercaptopurine, methotrexate; prophylaxis of central nervous system involvement is performed with intrathecal Methotrexate.

Serial liver function tests were performed to assess the effect of holding maintenance therapy on the rate of recovery.All children treated at Oncology Unit/Children Welfare Teaching Hosptial were vaccinated with Engerix-B as per schedule implemented in oncology unit for four doses of 40mcg/mL given at months 0, 1, 6 & 18.

RESULTS:

Retrospective study included 163 children with ALL diagnosed consecutively in 2015-2016.

Among 163 children with ALL diagnosed in Oncology Unit/CWTH in this 2-year period, 96 (58.9%) completed chemotherapy treatment in first complete remission but 4 were excluded for insufficient information, the study was limited to 92 patients, 14 of them still receiving maintenance therapy in complete remission.All children were treated with antileukemic drugs for a median period of 35.3 months (range 26-44.9 months). Median follow-up was 43.2 months (range: 28.5-56.2 months) from diagnosis and 9.7 months (range: 0-27.9 months) from treatment withdrawal.

Table 1: Demographic data and risk groups for 92 patients with ALL treated during 2015-2016.

Item	No	%
Age group (92)		
<= one year	4	4.3
> one year to 10 year	80	87.0
> 10 years	8	8.7
Sex (92)		
Male	54	58.7
Female	38	41.3
Risk group (92)		
SR	38	41.3
HR	54	58.7
Vaccination history (89)*		
Completed	76	85.3
Incomplete	13	14.6

**Missed information*

Table 1 shows the demographic data of 92 patients, there were 54 boys and 38 girls, male to female ratio was 1.4:1.

Table 2: Profile of liver function tests at time of diagnosis and during maintenance.

Item	At diagnosis Mean (SD)	At follow up Mean (SD)	P value
TSB mg/dl	0.6 (0.4)	1.5(4)	0.02
SGOT mg/dl	30.7 (30.6)	345(1125)	0.009
SGPT mg/dl	31.1 (50.2)	277(357)	0.001

Table 2 shows the relation between the biochemical study of liver function in form of total serum bilirubin (TSB) and liver enzymes;

Mass of blood and its products given during therapy:

At time of first admission, there were 34 (36.9%) patients already received blood or blood products before referral to Oncology Unit/CWTH, they received at least one unit of packed cell (range 1-4 units). After admission with the diagnosis of ALL in the Oncology Unit, only 2 patients were transfusion free through whole period of therapy, while the others got mean transfusion of 8 units (range 1-37 units).

Blood products more than 10 units were recorded in 26 patients, 5 (19.2%) of them were infected and 21 (80.8%) were not.

Table 3: Mass of blood and its products given to patients.

Blood units	Patients	%
None	2	2.2
1-5	38	41.3
6-10	25	27.2
11-15	12	13
16-20	11	11.9
>20	4	4.3
Total	92	100

Hepatitis infection:

At the time of diagnosis, all patients were serologically negative from hepatitis B and hepatitis C infection, eighty-five percent of patients were fully vaccinated with against hepatitis B by the national program for immunization as shown in table 1.

During the follow up period, there were 19 (20.6%) patients infected with hepatitis by serological method; 18 with hepatitis C and one with hepatitis B as shown in table 4.

Confirmation of diagnosis was done by viral load which was done for those with seroconversion during therapy; it was positive in 13/17 (76.5%), undetected in 4/17(23.5%) and not done in 2 patients during the period of treatment.

Table 4: Demography and lab. Results of 19 patients with Hepatitis.

No	Year	Sex	Age/y	Risk Group	Hepatitis B	Hepatitis C	Jaundice	Sero-conversion	Viral load
1.	2015	M	3	HR	-ve	+ ve	No	57	NA
2.	2015	M	6	SR	- ve	+ ve	Yes	8	+ ve
3.	2015	F	8	HR	- ve	+ ve	Yes	28	+ ve
4.	2015	M	7	SR	- ve	+ ve	Yes	8	- ve
5.	2015	M	3	SR	- ve	+ ve	No	23	- ve
6.	2015	M	3	SR	- ve	+ ve	No	35	+ ve
7.	2015	F	3	SR	- ve	+ ve	No	19	+ ve
8.	2015	M	2	HR	- ve	+ ve	Yes	39	+ ve
9.	2015	F	1	HR	- ve	+ ve	No	37	- ve
10.	2015	M	2	SR	- ve	+ ve	Yes	30	+ ve
11.	2015	M	3	SR	- ve	+ ve	Yes	31	+ ve
12.	2015	F	7	HR	- ve	+ ve	Yes	45	+ ve
13.	2015	F	11	HR	+ ve	- ve	Yes	41	+ ve
14.	2016	M	9	HR	- ve	+ ve	Yes	10	+ ve
15.	2016	F	7	SR	- ve	+ ve	Yes	17	NA
16.	2016	F	7	SR	- ve	+ ve	Yes	41	+ ve
17.	2016	F	1	SR	- ve	+ ve	No	37	+ ve
18.	2016	F	2	SR	- ve	+ ve	No	27	- ve
19.	2016	F	8	HR	- ve	+ ve	Yes	29	+ ve

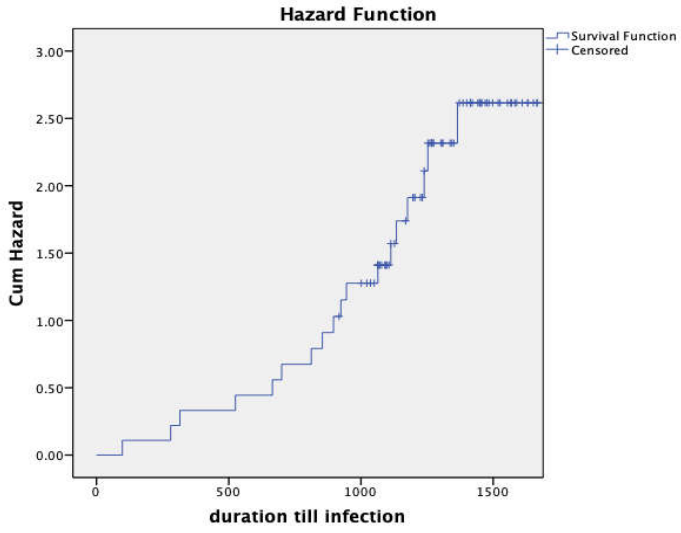

Figure 2: Hazard ratio of the patients to get hepatitis infection according to time of follow up.

DISCUSSION:

Iraq is a developing country where HBV and HCV infections are still prevalent with carrier rate of HBV reaching 2%–5%. Iraq includes HBV vaccination in its Expanded Programme of Immunization, with coverage rate approximating 80%. [6]

In this 2-year study; the prevalence of hepatitis infection (HBV and/or HCV) among children with ALL was found to be high (19/92-20,6%).

The prevalence of hepatitis B in this study was none at the time of diagnosis, same results of the previous study done at the same hospital in 2007-2008 [7] but different from Mostafa A et al [8] study done in Egypt in 2000-2001 which shows seroprevalence of 3.6% at diagnosis for 111 children with malignancy using HBcIgM in addition. In CWTH, although viral test with HBsAg marker only, it might highlight the effectiveness of the national vaccination program of hepatitis B.

During the follow up of this study, the seroprevalence of HBV in this study was 1.1%; a quite different from the previous study done at the same hospital which showed a high prevalence (27.3%) although the patients were not consecutively taken in the previous study. [7]

Hepatitis B seroprevalence in Egypt study of in a group of 111 patients after 6 months of treatment was 18.2% rising to 34.2% after cessation of therapy in another group of the same number in the same study. [8]

There are limited recent studies related to HCV infection might be due to low prevalence of this type of infection in developed counties, and/or limited publication related to this infection in developing countries.

HCV was detected in 18 (19.6%) patients during this study, higher than the prevalence of HBV but within the range of HCV infection mentioned in other studies in children with cancer which ranged from 1.5% to 53.3% like in Japan, Slovenia, Italy, Egypt and Nicaragua. [9, 8]

There was no relation between the number of blood or blood product transfusion and incidence of hepatitis C which might be a denominator of the presence of risk factors other than improper blood bank screening, it might be due to some malpractice of medical staff in the oncology unit during bone marrow aspiration procedures, reconstitution of medication, blood and its product transfusion, cannula insertion, during aspiration of blood for investigation and lacking of proper isolation of infected children from others during routine oncology practice.

Myelosuppression was behind modification of treatment in all children during this study, this also might be related to the liver disease due to use of antimetabolites during maintenance.

As the laboratory results in Iraq might be of questionable standards due to lack of national and international quality control including viral load studies; a correlation between the clinical judgment of hepatic toxicity with impaired liver function tests at time of diagnosis and at different follow up period might highlight to question the negative results of 4 patients with negative viral load shown in table 4. The same suggestion might be applied to those patients with impaired liver function and negative serology.

This study showed a significant correlation between duration after starting treatment and the incidence of Hepatitis C represented by Hazar ratio starting after 2 years which might indirectly be related to unsafe handling of disposals by the health care staffs and the need for better infection control policy.

CONCLUSION:

1. Low incidence of hepatitis B compared to the previous study
2. High incidence of hepatitis C in relation to other studies
3. Conflicting results between serology and viral load

Recommendation:

Primary and secondary prevention from infection as a WHO recommendation and Continue regular screening for HCV for several years after discontinuation of chemotherapy to detect dormant infection

1. Primary prevention from infection: Safe and appropriate use of health care injections; safe handling and disposal of sharps and waste; provision of comprehensive harm-reduction services to people who inject drugs including sterile injecting equipment and effective treatment of dependence.
2. Quality assurance testing of donated blood for HBV and HCV (as well as HIV and syphilis);
3. Training of health personnel; hand hygiene, including surgical hand preparation, hand washing and use of gloves;
4. Secondary prevention for people infected with the hepatitis C virus as per WHO recommendation of education and counseling on options for care and treatment; and regular monitoring for early diagnosis of chronic liver disease.

5. Continue regular screening for HCV for several years after discontinuation of chemotherapy to detect dormant infection.

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