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Incidence Proportion of Hepatitis C Virus infection among Leukemia patients at a Tertiary Cancer Centre

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Abstract

Background: Hepatitis C Virus (HCV) infection is a transfusion transmitted disease.The leukaemia patients are multitransfused and are at risk of acquiring HCV. There is scarcity of data regarding epidemiology of HCV in leukaemia patients in India.

Methods: The donor blood was tested with Anti-HCV till 2012 and with Ag-AB Monolisa Ultra V2from 2012 onwards.The patients blood was tested with Anti HCV. The patient samples that were reactive with Anti-HCV and confirmed with RT-PCR during the period 2009-2015 are included in this study. The incidence with respect to number of transfusions, demographic profile, time gap between detection of leukaemia and HCV seroconversion, genotype, viral load, Liver function tests and coinfection was analysed.

Results: During the period 2009-2015, a total of 1788 leukemia patients enrolled for treatment at Cancer Institute were included in the study. Among them, a total of 79 cases were detected anti-HCV and HCV –RNA positive. ALL accounted for 94%, AML accounted for 5%, CLL accounted for 1%. Mean age of presentation was 13.60 +/-11.09 years.64.1 %.were males and 36%were females. Most patients (65 %) belonged to low income group. The average number of total transfusions received by these patients before seroconversion was 7.35+/-3.77 units and mean time gap between diagnosis of leukaemia to HCV seroconversion was found to be 13.42+/_18.50 months All the cases were HCV genotype 1.The mean HCV viral load detected in these patients was 76699.55+/-80099.65 IU/ml. 5% of the HCV infected individuals tested positive for HBV.45.56 % of these patients reported abnormal liver function parameters (serum AST,ALT and alkaline phosphatase levels). Of these patients with abnormal liver function tests 27.78% had reversal of AST/ALT ratio(AST/ALT >1). The incidence proportion of HCV dropped from 62.5 cases per 1000 population (2009) to 7.17 cases per 1000 population in 2015.

Conclusions: To encourage repeat voluntary blood donation .To adopt sensitive serology screening assays as Chemiluminescence along with molecular techniques (NAT) for testing donor blood. To mandate pathogen inactivation techniques.To conduct systematic studies for epidemiology of HCV in order to enable participation in complete eradication.

Introduction

Hepatitis C Virus (HCV) is a hepatotropic RNA virus transmitted predominantly via blood transfusion apart from injection drug use and unsafe injection practices(1).Despite advances in screening assays of donated blood by volunteers ,patients undergoing transfusion therapy are at greater risk of acquiring HCV infection. The probable risk for transmission of HCV is 0.10 to 2.33 per million units transfused(2). Hepatitis C is the major cause of chronic blood borne infection and 90%

of cases previously known as post –transfusion non-A,non-B Hepatitis (3,4).

Hepatitis C is a major global health problem.The mean frequency of HCV infection in the world is about 3% and 3-4million people are affected every year.150 million people are chronically infected(5).Approximately 15-25% of HCV infected individuals develop only an acute infection with a range of clinical manifestation from asymptomatic to severe illness (6) and 75-85% of the affected individuals may become Hepatitis C carriers and develop chronic infection(7).HCV is a known etiologic agent for chronic liver disease and can lead to liver cirrhosis and hepatocellular carcinoma(8). HCV infection is known to play a key role in etiology of liver disease in leukaemia patient undergoing treatment or in remission(9). Hepatitis B Virus (HBV) and HCV infection accounted for 96% of viral hepatitis related mortality in 2003. Chronic HCV infection is one among the leading causes of death globally. Approximately 3,99,000 people die every year due to Hepatitis C related diseases as cirrhosis and hepatocellular carcinoma(10).

The probability of being affected with Transfusion Transmissible Infections (TTI) is related to the prevalence among the blood donors. The global prevalence of HCV among blood donors varies from 0.4-19.2 %(2).The prevalence of HCV in blood donors in India is 0.4-1.09%(11,12,13,14). The prevalence is known to vary in different regions of the country.

Blood transfusion support plays an important role in care of leukaemia patients (15)and substantial amount of blood may be required per patient. The patients are transfused leukodepleted and irradiated cellular components(RBC and platelets) apart from Fresh Frozen Plasma (FFP) .The American association for the study of liver disease recommends screening of HCV in recipients of blood and blood components.

The reported HCV prevalence in various population groups as injection drug users, hemodialysis patients , health care workers, pregnant women, thalassemia patients, differs with region and country . Pediatric acute leukaemia patients have shown a wide variation of HCV prevalence ranging from 1-43% documented by different studies (16).

There is a necessity to understand HCV prevalence and incidence rates in different countries of the world to help prevent transmission via blood transfusions (17).A survey of HCV infection is important for prevention and treatment of the disease.HCV is a major health and economic burden for the population in both developed and developing nations .No vaccine is available against HCV.

Methodology

A retrospective single centre study was carried out during the period 2009-2015 at Department of Transfusion Medicine, of a tertiary care hospital on leukaemia patients diagnosed with Hepatitis C with respect to disease, number of transfusions, demographic factors, socioeconomic status ,type of leukaemia, the time gap between detection of leukaemia and seroconversion, Liver function tests, viral load, genotype, co infection, transfusion therapy with donor blood screened by anti-HCV (upto2012) and Antigen-Antibody Assay(2012 onwards) with help of electronic health records.

The donor blood was screened by fully automated Elisa Biorad Anti-HCV (third generation) until 2012 and Biorad HCV Ag-AB monolisa Ultra V2 since 2012 according to manufacturer’s instructions. The Biorad Ag-AB monolisa Ultra V2 detects HCV antibodies (to NS3, NS4 region) and /or Hepatitis C capsid antigen.

The first generation assay incorporated the NS 4 region(recombinant c 100-3 epitope).The second generation assay additionally incorporated HCV core (c22-3) and NS3 (c33)regions .The third generation assays contained reconfigured core ,NS3 antigens and an antigen of NS5 region. The fourth generation tests detect HCV capsid antigen and also antibodies to core, NS3, NS4,and NS5 regions of the virus. The window period detection decreased from 16 weeks to 10 weeks and finally to 8 weeks since introduction of first generation , second and third generation assay respectively. The fourth generation assay may further reduce the window period detection by 17 days.

The leukaemia patients were tested for anti-HCV antibody before commencement of treatment and subsequently on developing symptoms suggestive of hepatitis. The repeat reactive patient samples were tested for HCV RNA with RT-PCR as per national recommendations. This study involves RT-PCR confirmed HCV patients.

Data analysis was carried out using statistical package (SPSS version 16).

Results

The summary of the distribution profile of the sample population is shown in Table 1.During the period 2009-2015, a total of 1788 leukemia patients enrolled for treatment at Cancer Institute were included in the study. Among them, a total of 79 cases were detected anti-HCV and HCV –RNA positive. ALL accounted for 94%,AML accounted for 5%,CLL accounted for 1%. Mean age of presentation was 13.60 +/-11.09 years. Most patients (65 %) belonged to low income group. All the cases were HCV genotype 1.The mean HCV viral load detected in these patients was 76699.55+/-80099.65 IU/ml.45.56 % of these patients reported abnormal liver function parameters (serum AST,ALT and alkaline phosphatase levels). Of these patients with abnormal liver function tests 27.78% had reversal of AST/ALT ratio(AST/ALT >1).

Pearson Correlations (sig 2 tailed) between the variables was studied (Table 2). Highly significant ($P<0.010$) correlation between the time gap for HCV seroconversion and the number of RDP units transfused was established. There is a significant ($p<0.050$) correlation between HCV viral load and the number of FFP transfusions given to the leukemia patient. Likewise the liver enzymes levels showed significant correlations within themselves. Also age was found to be weakly correlated with the serum alkaline phosphatase level.

Table1: Profile of sample population

Variable		Number of cases in the year						
		2009	2010	2011	2012	2013	2014	2015
TOTAL No. OF LEUKEMIA PATIENTS attending Cancer Institute		256	248	261	237	246	261	279
NUMBER OF NEW HCV SEROPOSITIVE CONVERSIONS among leukemia patients attending cancer Institute		16	10	16	15	10	10	2
Age Distribution of Patients								
	0 to 10 years	8	4	9	8	4	2	1
	10 to 20 years	5	6	4	5	3	4	1
	20 to 30 years	3	0	2	0	3	2	0
	30 to 40 years	0	0	1	1	0	0	0
	40 to 50 years	0	0	0	0	0	1	0
	50 to 60 years	0	0	0	1	0	0	0
	above 60 years	0	0	0	0	0	1	0
Gender of Patients								
	male	11	3	11	11	7	8	1
	female	5	7	5	4	3	2	1
Demography Distribution of Patients								
	rural	13	8	12	10	6	7	1
	urban	3	2	4	5	4	3	1
Socio economic Status of Patients								
	Gr1 < Rs 450	8	7	5	3	3	4	0
	Gr2 Rs 451 to Rs 2000	7	3	8	7	6	3	1
	Gr3 Rs 2001 - Rs 4000	1	1	2	3	1	3	1
	Gr4 Rs 4001	0	0	1	1	0	0	0
Leukemia Type -								
	ALL	16	10	13	14	10	10	1
	AML	0	0	2	1	0	0	1
	CLL	0	0	1	0	0	0	0
	CML	0	0	0	0	0	0	0
Raised Liver Function Tests								
	Serum Bilirubin total	0	0	0	0	0	0	0
	SGOT	2	0	4	3	2	1	0
	SGPT	6	2	4	6	3	5	2
	Alkaline phosphatase	4	0	0	0	3	2	0
Genotype		1	1	1	1	1	1	1
Co Infection								
	Hepatitis B	0	1	0	2	0	1	0
	Hepatitis A	0	0	0	0	0	0	0
	HIV	0	0	0	0	0	0	0
	Other Infections	0	0	0	0	0	0	0

Table 2: Significant Correlations between study variables [Pearson correlation sig 2 tailed]

Correlation between study Parameters	"r"	"p"	Correlation Interpretation
HCV seroconversion Time & RDP Transfusion	0.444	0.000	Highly Significant moderately positive correlation
HCV Viral Load & FFP Transfusion	0.287	0.011	Significant weak positive correlation
SGPT & Serum Total Bilirubin	0.385	0.000	Highly Significant moderately positive correlation
SGPT & SGOT	0.763	0.000	Highly Significant strong positive correlation
SGPT & Serum Alkaline Phosphatase	0.325	0.004	Highly Significant weak positive correlation
Serum Alkaline Phosphatase & Age	0.231	0.042	Significant weak positive correlation

A multivariate linear regression model was studied where in HCV viral load was proposed to be a dependent variable on independent variables – age, gender, HCV seroconversion time, Number of PRC, FFP, RDP, SDP Transfusion units, Serum Total Bilirubin Level, SGOT level, SGPT level and Serum Alkaline Phosphatase Level. The model showed a significant positive influence of number of FFP units Transfused on HCV Viral load, whereas all the other study variables were found to be insignificantly influencing the HCV viral load. Though the model showed that the number of FFP units transfused to the leukemia patients was a significant predictor of the HCV viral load, the model has a weak explanatory power(r^2=0.082), thus inferring that variations in independent variable correlated with variations in dependent variable to an estimated precision of only 8.2%.(Table 3). Small Sample size and limited number of independent variables chosen in this study is the reason for the weak explanatory power of the proposed model.

Table 3: Multivariate analysis – linear regression (n=78)

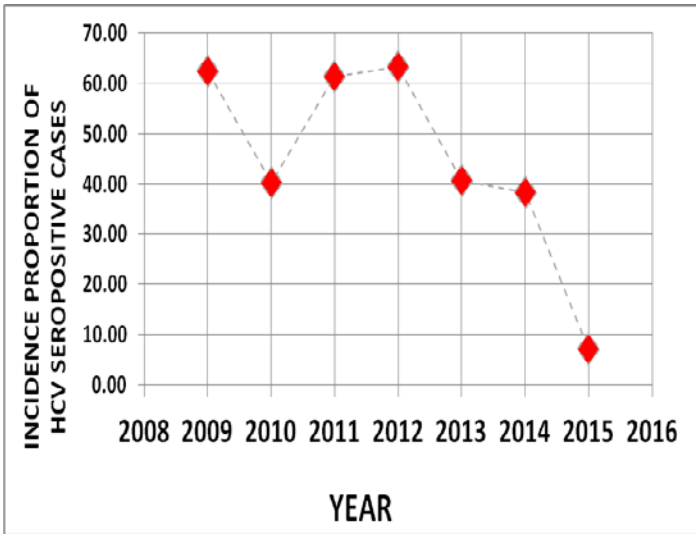
Independent Variables	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	57904.850	11324.268		5.113	**0.000**
FFP Transfusions	16109.744	6167.080	0.287	2.612	**0.011**

R^2=0.082, F = 6.824, Sig. 0.011 [p< 0.050 is significant]

Dependent Variable : HCV Viral Load; Predictors : (Constant),FFP Transfusions.

The incidence of seropositive HCV cases decreased during the period 2013 to 2015 (Donor blood screening was done using Ag-AB Monolisa Ultra V2) when compared with the period 2009 to 2011 (Donor blood screening was done using Anti HCV assay). The Incidence proportion of HCV seroconversion among Leukemia patients attending the Institute was calculated using the Denominator as the size of population at risk and numerator as the number of new cases among that population The incidence proportion of HCV seropositive cases decreased significantly from 62.5 cases per 1000 population (2009) to 7.17 cases per 1000 population (2015) (Figure 1).

Figure1: Incidence Proportion of HCV seropositive patients among Leukemia patients attending Cancer Institute



Discussion

HCV infection is common in persons with leukaemia who receive frequent blood transfusions(18).The average number of blood and component transfusions received by these patients to seroconvert was 7.35+/-3.77 units. The possibility of acquiring Transfusion Transmitted Infections is related to the number of units transfused was demonstrated in multitransfused patients as thalassemia (19) and haemodialysis(20). Each blood transfusion received by the patient was responsible for increase in Anti-HCV prevalence (21).

Nearly 90% of post transfusion non A non B Hepatitis cases occur within 5-12 weeks after transfusion and incubation period maximum of 6 months has been reported (22).An impaired immune response might explain the prolonged period of 13.42+/-18.50 months for seroconversion in this study. Anti-HCV appears delayed in viremic children who have been infected early during the course of antileukamic chemotherapy. HCV RNA identification is required for diagnosis in patients with a prolonged time gap for development of antibodies and also patients on immunosuppressive treatment as Chemotherapy (23). Certain assay as elecsys anti- HCV II assay may be preferred for detection of acute HCV infection. This assay detects HCV infection 3.5 days after a positive HCV-RNA nucleic acid test and earlier than the comparator assays. The electrochemiluminescence assay is recommended for screening and early detection of HCV infection (24).Anti-HCV is still the test of choice for HCV screening as recommended by Centres for Disease Control.

Nearly 25% of the infected individuals clear the infection spontaneously in the first 6 months (25).The natural history of HCV Infection is affected by many factors. Progression of chronic liver disease in patients with HCV Infection is closely related to age at infection, sex and HCV associated comorbidities, including HBV and HIV co-infections, alcohol intake, cancer, immunosuppression, insulin resistance ,obesity etc (1,26).It may not be possible to determine which factor impacts the most. Nearly 90% of persons with HCV infection may have identifiable risk factors. Source of infection may not be identified in the remaining 10% though most persons in this category are associated with low socioeconomic status (26).

.The earlier immune-compromised status of the leukaemia survivors probably promoted more rapid viral replication or impaired host viral clearance. 64.1% were males and 36% were females. (Table 1)Studies have implied greater prevalence in men(27,28). Females had higher rates of spontaneous viral clearance. The gene IL 28B is an independent predictor of spontaneous HCV clearance according to studies conducted on liver diseases. Female sex, immune response ,neutralising antibodies and genetics are also factors affecting viral clearance according to previous prospective studies. Certain studies have not implicated any gender difference and also

reported higher prevalence in females (29) and controversy about sex differences in HCV clearance rates persists.

HCV prevalence was higher among rural residents . This study indicates 72% were from rural background and 28% were from urban area. HCV infection was more common in less educated patients receiving blood transfusion. Living in crowded areas with poor sanitary conditions was also a risk factor(21,30).

Most reported studies in India suggest predominance of genotype 3 in North India and genotype 1 in Southern India (31).Genotype 4 is found in states of Andhra Pradesh and Tamil Nadu(32).

The study shows 5% of the HCV infected individuals tested positive for HBV.1.89 % HBV/HCV co-infection prevalence was seen in India (33). The prevalence rate was found to be higher in Chronic Liver Disease group patients. A high prevalence of HBV and HCV co-infection in hematologic malignancies is noted and attributed to transfusion therapy and parenteral interventions (34).

Pearson correlations between age and ALP,AST and AST and ALT,ALT and ALP,ALT and Serum Total bilirubin among the study group were found to be significantly positive with r values (0.231,0.763,0.325,0.385) respectively. Similar results were reported in the study on assessment of liver enzymes among Sudanese patients with myeloid leukaemia (35)and also in another study on relationship between ALP and atherogenic indices in apparently healthy Nigerian men (36).

Our study revealed 27.78% of the study group with elevated liver enzymes (AST,ALT and ALP) to have reversal of AST/ALT ratio.AST/ALT parameter is very significant in terms of the usefulness and diagnostic ability in identifying manifestations of chronic liver disease(37).

Conclusion

The present study shows a drastic decrease in the incidence proportion of HCV infection among the study group especially with the use of ELISA test kits(Monolisa Ag-AB ULTRA V2) which detect HCV capsid antigen as well as antibodies to NS3, NS4 regions of the virus. The incidence of HCV infection in the sample population was higher among young male individuals suffering from ALL, belonging to low socio economic and rural background.

Repeat voluntary blood donation is the cornerstone of safe blood transfusion. Screening of donated blood for HCV may be performed with more sensitive serology (chemiluminesence) and molecular (NAT) techniques .The pathogen inactivation techniques may be mandated for blood safety.

The epidemiology of hepatitis C needs to be studied systematically in order to achieve the WHO goal aimed at eradiaction of HCV by 2030.

Limitations

Sample size (n=79) could be a limitation in generalising the findings of the presented study.

Apart from Transfusion transmitted HCV infection, Immunosupression in these individuals due to chemotherapy and the frequent use of parenteral interventions in them could also be the cause of HCV infection in the study group.

The age of the study data could be a limitation in making current assumptions about incidence proportions.

Ethics approval : Not applicable as this is a retrospective study.

Competing interests: The authors declare that they have no competing interests.

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