The Long Term Outcome of Thirty Eight Post-Transfusion Hepatitis C

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Abstract

Thirty-eight cases of post-transfustion HCV hepatitis have been followed for 5-24 years. Cirrhosis and hepatocellular carcinoma were found in 44.7 per cent and 13.1 per cent respectively. Cirrhosis was recognised by pathological evidence as early as one and a half years after transfusion and the clinical evidences of decompensated cirrhosis were noted in the fifth year post-transfusion onward. Hepatocellular carcinoma was first recognised in year ten and thereafter. Nine patients died of liver failure or hepatocellular carcinoma during years 8-16 of the follow-up. Therefore, it is of utmost importance to screen out the HCV infected blood donors and to treat the HCV patients as early and as effectively as possible.

Key word : Post-transfusion Hepatitis C, Cirrhosis, Hepatoma

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J Med Assoc Thai 2001; 84: 12-18

Hepatitis C virus (HCV) is the most common etiologic agent for post-transfusion hepatitis everywhere[1,2]. In our previous study on post-transfusion hepatitis[3] non A non B hepatitis virus was responsible for 64 per cent of cases. All of these NANB cases were subsequently confirmed to be HCV. It has been reported that the diseases in post-transfusion hepatitis are more severe than other forms of HCV infection[4]. In Thailand, we recently reported a long term study of 63 HCV patients and hepatocellular carcinoma developed in 15.9 per cent[5].

MATERIAL AND METHOD

At the end of 1997 the authors concluded a long term follow-up study of 38 patients who had

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post-transfusion HCV hepatitis. Most of the patients received blood or blood products transfusion at other hospitals from 1970 to 1993 for various reasons other than for liver ailment. Transfusions for bleeding from gynaecologic problems were the reason in 13 cases, followed by gastrointestinal bleeding in 9 cases, from accidents in 7 cases, operative bleeding in 5 cases and dengue hemorrhagic fever in 4 cases. They came to this clinic for the treatment of acute or chronic hepatitis. The hospital is a private general hospital with the recent capacity of 200 beds. Most of the patients are in the medium to higher income group. Liver biopsy is not always possible. Only major clinical features such as overt signs of decompensated liver cirrhosis, occurrence of hepatocellular carcinoma (HCC) and death were analysed. All cases were followed for a minimum of 5 years at the Liver Clinic until they died or dropped out because of personal reasons. All were positive for HCV antibody using the third generation antigen by microparticles enzyme immunoassays. Liver biopsy and recently available PCR for HCV were done in some cases which will not be included in this study. Associated HBV infections were noted in 2 cases but PCR for HBV and HBeAg were negative. HIV antibody was detected in another case in the 15th year of follow-up.

RESULTS

Of 38 cases, 15 were male and 23 were female. All except one Chinese-Malaysian were Thai citizens with an age range at the begining of the study between 23-72 years old (average 46.4 years of age). The transfusion of blood or blood products were given from 1970 through 1993 (Table 1). The exact amount of blood given was not known in 15 cases and described as "many" in another 4 cases. The known amount of transfusion was 1-28 units (Table 2). Out of 38 patients, clinical and biochemical features of acute hepatitis were observed in only 14 cases. The rest experienced chronic asymptomatic hepatitis detected only by abnormal liver enzymes.

Overt clinical features of liver cirrhosis as presented with symptoms and signs of liver decompensation namely spidor angiomata, icteric sclera, ascites, esophageal varices, hepatic encephalopathy plus laboratory findings of hypersplenism, hypoproteinemia and abnormal coagu-

Table 1. Calender year of receiving blood transfusion in 38 recipients.

	Year 1970-1993																			
	'70	'73	'77	'78	'79	'80	'81	'82	'83	'84	'85	'86	'87	'88	'90	'92	'93	Total
M	-	1	1	1	-	1	1	1	-	1	3	1	-	2	-	-	2	15
F	1	-	2	-	1	1	1	1	1	2	4	1	1	2	2	1	2	23
Both	1	1	3	1	1	2	2	2	1	3	7	2	1	4	2	1	4	38

Table 2. The amount of blood and blood products given to 38 HCV post-transfusion hepatitis cases.

one unit	1	case
two units	8	cases
three units	1	case
four units	1	case
6-10 units	4	cases
more than 10*	4	cases
many	4	cases
not exactly known	15	cases
Total	38	cases

(* highest 28 units)

lation were recorded. The first detected cirrhotic case, a 68 year old male who received 20 units of blood transfusion experienced decompensated cirrhosis in the fifth year. The liver enzymes had always been higher than 4 times the upper limit of normal value which is an indication of chronic aggressive hepatitis. He died on the eighth year post-transfusions from liver failure. In another two cases, surgical liver biopsies which were done one and a half and two years post-transfusion already revealed pathological findings of cirrhosis. However, only one of them showed clinical features of overt cirrhosis in year 15. At the 8th year of the follow-up, three more cases of overt cirrhosis were diagnosed and 2 died of liver failure, one of whom was the first cirrhotic case. (Table 3, Fig. 2) In the tenth year, two more cirrhotic patients were diagnosed and the first HCC case was detected. (Table 3, Fig. 2) Three of them died of liver diseases. From 38 original cases, 26 still attended the clinic in the tenth year and 5 patients have died. From year 11 through 17 more cirrhotic patients as well as HCC were diagnosed. In the 24th year only one patient was still healthy under our care.

At the end of this long term study of 38 cases, at least 12 cases developed full blown liver cirrhosis and another 5 cases experienced HCC associated with cirrhosis. Thus, decompensated cirrhosis has developed in at least 17 cases (44.7%) and HCC in 5 cases (13.1%). Nine deaths (23.6%); 5 from HCC and 4 from cirrhosis occurred during year 8-12. The progression and time correlation are presented in Fig. 1 and 2. Coinfection with HBV was found in 2 patients but HBV PCR and HBeAg were negative. Both of them died of cirrhosis in year 8 and 10 post transfusion. More units of blood and the older patient's age at the time of transfusion seems to relate to a poorer prognosis. The adjusted survival for cirrhosis, HCC and death, using Kaplan GL and Meier P calculation[6] are presented in Table 3 and Graph 1. The significance levels for all 3 test statistics (Log Rank 0.73, Breslow 0.56 and Tarone-Ware 0.65) are larger than 0.05 so the survival distributions for all groups are not significantly different.

DISCUSSION

This study was started at a time when there was no HCV screening test for blood

Table 3. Occurrence of cirrhosis, hepatocellular carcinoma and death during the 24 years after transfusion.

Years after transfusion	Number of patients	Cirrhosis No.	Cirrhosis with Hepatoma No.	Died of Liver Disease No.
5	38	1	0	0
8	32	3	0	2
10	26	2	1	3
11	21	2	2	2
12	16	1	1	1
15	8	1	0	0
16	7	1	1	1
17	6	1	0	0
20	3	0	0	0
23	2	0	0	0
24	1	0	0	0
1-24	All	12	5	9

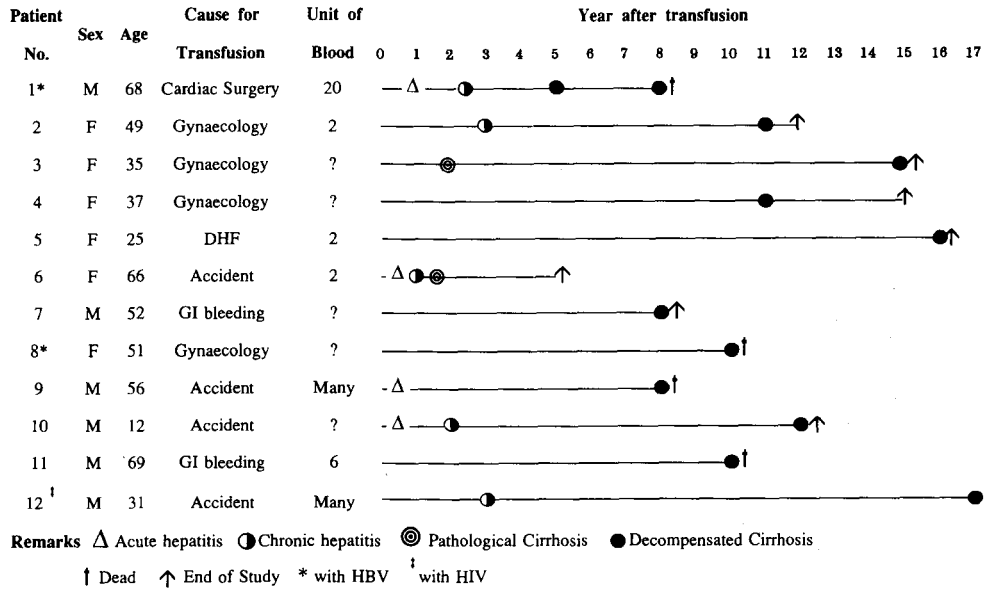


Fig. 1. Progress of HCV hepatitis to clinical decompensated cirrhosis and death.

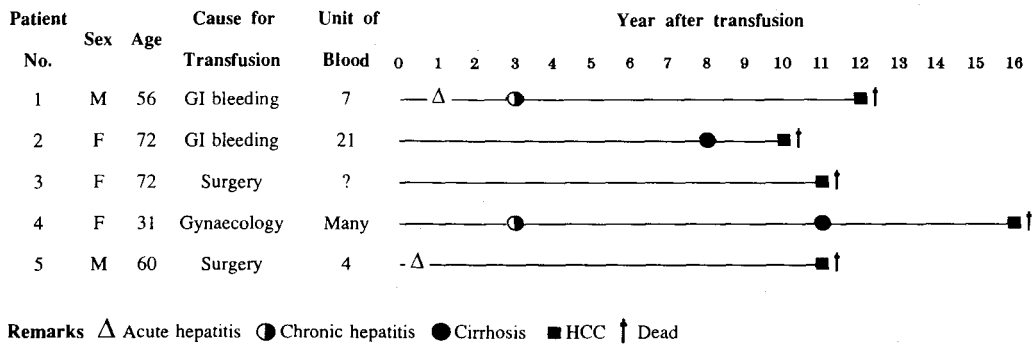
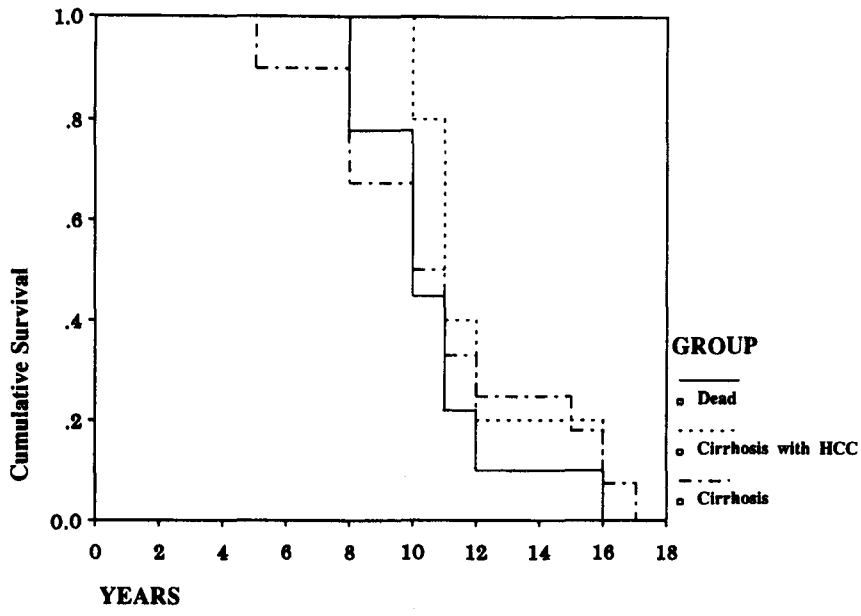


Fig. 2. Progress of HCV hepatitis to hepatocellular carcinoma in 5 cases.

donors. In Thailand all blood donors are healthy volunteers. The Thai National Blood Bank started using the first generation screening test for HCV in July 1990 and switched to the third generation test in 1997. Our last post-transfusion hepatitis patients were diagnosed in early 1993.

The prevalence of HCV antibodies among blood donors who reside in the Bangkok metropolitan area is 0.6-2 per cent[7,8]. However, in a survey of volunteer blood donors from the northeastern region of the country in 1997 Songsivilai S, et al,[9] found the prevalence to be much higher (5.2%) and males are more prevalent than females (6.5% to 0.9%). In our study females are more prevalent than males (1.5 to 1) which may reflect a higher chance for women to receive blood transfusion for treatment of obstetric-gynaecologic conditions.

Considering the low prevalence of HCV positive among volunteer blood donors the chances of getting infected from 1-2 units of blood seems to be quite remote yet in this study of 38 cases, 9 patients received only 1-2 units of blood. It has been reported that in Thailand



*** (Kaplan GL. Meier P. Nonparametic estimation from incomplete observations. J.Am.Stat.Ass. 1958;3:457-481).**

Graph 1. Cumulative survival of 38 chronic HCV hepatitis during 24 years of follow-up for cirrhosis, hepatocellular carcinoma and death from liver diseases.*

HCV RNA was detected in 80.4 per cent of anti HCV positive cases thereby it indicates a high potentiality for transmission[10]. In this study, the majority of cases received more than 6 units of blood and as high as 28 units in one case. The larger infected doses of HCV may possibly induce more severe progressive liver disease. Full blown clinical features of liver cirrhosis were recognised as early as year 5, however, in two patients who underwent abdominal surgery in the one and a half and two years post-transfusion and surgical liver biopsies already revealed pathological evidence of cirrhosis. One of them showed clinical evidence of decompensated cirrhosis at year 15 and another one was lost to follow-up after year 5. (Fig. 1) Coinfection of HCV and HBV was found in 2 cases (case No 1 and 8) and both died of cirrhosis in year 8 and 10. (Fig. 1) This may reflect the severity of coinfection of HBV and HCV.

In five cases HCC developed during the tenth to twelfth year after transfusion (Fig. 2) and the overt clinical features of decompensated cirrhosis were detected in only 2 patients. Four out of five HCC cases received more than 4 units of blood.

Tong MJ et al[11] studied 131 post-transfusion hepatitis for 1-15 years (average 3.9 years) cirrhosis was found in 51 per cent and HCC in 5 per cent. In a long term study of 384 compensated cirrhosis type C (Fattovich G, et al, [12]) reported the 5 year risk of HCC was 7 per cent. Our study of longer duration revealed full blown clinical cirrhosis in 44.7 per cent and HCC in 13.1 per cent. In our other study of 63 HCV patients from various modes of infection including post-transfution for 5-15 years, cirrhosis and HCC were detected in 16 cases (25.4%) and 10 cases (15.9%), respectively[3]. In a study of 247 HCC cases from Chiang Mai, northern Thailand[13] HBV, HBV plus HCV and HCV were found in 69, 13.63 and 18.32 per cent, respectively. In another study of 80 HCC, HCV antibodies were detected in 11.3 per cent[14].

The authors have done a comparable long term study on 148 HBV hepatitis and HCC was detected in only one case and cirrhosis in 9 cases. Based on these studies we consider HCV infection as a strong potential for inducing serious consequences of cirrhosis and HCC as early as year 5 onward. It is generally known that the severity of HCV infection relates to certain genotypes. In Thailand, genotype 1 and genotype 3 are the two most common genotypes in about 70 per cent and 30 per cent, respectively(10) and genotype 3a is found in 62.5 per cent of HCC(13). Both genotypes 1 and 3 are universally considered as a potential for inducing severe liver disease.

(Received for publication on April 20, 1999)

REFERENCES

1. Aach RD, Kalm RA. Post transfusion hepatitis. Current Prospective. Ann Int Med 1980; 2: 539-46.
2. Seeff LB, Wright EC, Zimmerman HJ, et al. VA Co-operative study of post transfusion hepatitis and responsible risk factors. Am J Med Sci. 1975; 270: 355-62.
3. Punyagupta S. Post transfusion hepatitis: Role of Non A Non B Hepatitis Virus. J Inf Dis Antimicrob 1987; 4: 86-91.
4. Lee SD, Tsai YT, Hwang SJ, et al. A prospective study of post-transfusion non-A, non-B (type C) hepatitis following cardiovascular surgery in Taiwan. J Med Virol 1991; 33: 188-92.
5. Punyagupta S, Jitpugdeebodin S. Siwadune T. Hepatitis C Infection and hepatocellular carcinoma in Thailand. A long term study of 63 patients. J Inf Dis Antimicrob 1999; 16: 1-5.
6. Kaplan GL, Meier P. Nonparametic estimation from incomplete observations. J Am Stat Ass 1958; 3: 457-81.
7. Nuchprayoon C. Safety of the blood supply in Thailand. (Editorial) JAMA SEA 1996; 12: 5-6.
8. Suwanagool S, Tieangrim S, Ratanasuwan N, et al. Seroprevalence of anti HCV among HIV infected persons and general population. J Med Ass Thai 1995; 78:611-7.
9. Songsivilai S, Jirathongthai S, Wongsena W, Tiangpitayakorn C, Dharakul T. High prevalence of hepatitis C infection among blood donors in northeastern Thailand. Am J Trop Med Hyg 1997; 57: 66-9.
10. Songsivilai S, Kanistanon D, Panyavinin N, Neelamek M, Dharakul T. Improved Ampification system for detection of hepatitis C virus genome that simultaneously differentiates viral genotypes. Southeast Asian J Trop Med Public Health 1990; 27: 237-43.
11. Tong MJ, El-Farra NS, Reikes AR, Co RL. Clinical outcomes after transfusion associated hepatitis C. N Engl J Med 1995; 332: 1463-6.
12. Fattovich G, Ginstina G, Degos F, et al. Morbidity and Mortality in compensated cirrhosis Type C ; A retrospective follow-up study of 384 patients. Gastroenterology 1997; 112: 463-72.
13. Phornphutkul K, Peerakome S, Yousukon A, Toriyama K, Shimotohno K. Hepatitis C Infection in Northern Thailand. Division of Gastroenterology, Faculty of Medicine Chiang Mai University. Presented at the Annual Scientific Meeting of the Gastroenterological Association of Thailand, Chiang Rai, Thailand, on Jan 31-Feb 2, 1996.
14. Songsivilai S, Dharakul T, Kanistanon D. Hepatitis C virus genotypes in patients with hepatocellular carcinoma and cholangiocarcinoma in Thailand. Trans Roy Soc Trop Med Hyg 1996; 90: 505-7.

การศึกษาระยะยาวของผู้ป่วย 38 รายที่เป็นโรคตับอักเสบจากไวรัส ซี จากการได้รับเลือด

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ผู้ป่วยโรคตับอักเสบจากไวรัส ซี ที่เกิดจากการให้เลือดจำนวน 38 ราย ได้รับการศึกษาติดตามเป็นเวลา 5-24 ปี พบว่าเกิดโรคตับแข็ง 44.7% และมะเร็งตับ 13.1% โรคตับแข็ง วินิจฉัยได้จากพยาธิสภาพของตับภายในเวลา 1 1/2 ปี หลังได้รับเลือด แต่อาการทางคลินิกของโรคตับแข็งตรวจพบตั้งแต่ปีที่ 5 เป็นต้นไป ส่วนมะเร็งตับเริ่มพบในปีที่ 10 ผู้ป่วย 9 รายถึงแก่กรรมจากภาวะตับวาย หรือมะเร็งตับ ในระหว่างปีที่ 8-16 แสดงให้เห็นถึงความสำคัญที่จะต้องคัดแยกเลือดที่ มีเชื้อไวรัสตับอักเสบ ซี และรักษาโรคตับอักเสบไวรัส ซีให้เด็มที่และเร็วที่สุดที่จะทำได้

คำสำคัญ : ตับอักเสบหลังให้เลือด, ไวรัสตับอักเสบ ซี, ตับแข็ง, มะเร็งตับ

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