

CLINICAL OUTCOMES AFTER TRANSFUSION-ASSOCIATED HEPATITIS C

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Abstract *Background.* The extent of serious complications in people who have acquired chronic hepatitis C after a blood transfusion is unclear.

Methods. We studied 131 patients with chronic post-transfusion hepatitis C who were referred to our center between February 1980 and June 1994. Eighty-two other patients were excluded because they had multiple transfusions, hemophilia, intravenous drug use, human immunodeficiency virus infection, hepatitis B infection, hemochromatosis, or alcoholic liver disease. Liver biopsies were performed in 101 patients; biopsies were not performed in the other 30 patients, all with signs of cirrhosis, because the results of coagulation tests were abnormal.

Results. The mean age of the patients was 57 years (range, 21 to 81) at the time of our initial evaluation. The mean age at the time of the blood transfusion was 35 years (range, 1 to 76). The mean duration of follow-up af-

ter presentation to us was 3.9 years (range, 1 to 15). Eighty-eight of the patients (67.2 percent) initially had fatigue, and 89 (67.9 percent) had hepatomegaly. Twenty-seven patients (20.6 percent) initially had chronic hepatitis, 30 (22.9 percent) had chronic active hepatitis, 67 (51.1 percent) had cirrhosis, and 7 (5.3 percent) had hepatocellular carcinoma. Hepatocellular carcinoma developed in an additional seven patients an average of 36 months (range, 7 to 121) after the initial visit. During follow-up, 20 patients (15.3 percent) died: 8 from complications of cirrhosis (1 after a liver transplantation); 11 from hepatocellular carcinoma; and 1, with chronic active hepatitis, from pneumonia.

Conclusions. In a group of patients seen at a referral center, chronic post-transfusion hepatitis C was a progressive disease and, in some patients, led to death from either liver failure or hepatocellular carcinoma. (N Engl J Med 1995;332:1463-6.)

SEROLOGIC testing for antibodies to hepatitis C virus (HCV) has shown that over 90 percent of cases of post-transfusion non-A, non-B hepatitis in the United States are caused by HCV. Acute HCV infection is usually not detected clinically. Less than one third of infected patients have jaundice after receiving a transfusion.^{1,2} Sustained elevations of serum aminotransferase concentrations for six months or longer have been noted in up to 60 percent of people with post-transfusion non-A, non-B hepatitis. These people have been considered to have chronic hepatitis.^{2,3} In a recent study, the detection of HCV RNA in serum from patients with HCV antibodies and concomitant elevations of aminotransferase concentrations after a transfusion confirmed HCV as the principal cause of chronic hepatitis.⁴

The natural history of chronic HCV infection acquired through a blood transfusion is unclear. One report suggested that there is a sequential but slow progression from acute HCV infection to chronic infection, cirrhosis, and eventually, hepatocellular carcinoma.⁵ In one study, clinical evidence of cirrhosis was present in 20 percent of patients with chronic HCV infection 16 years after the initial blood transfusion.⁶ In another study, very few patients had complications of chronic infection after an average follow-up of 18 years.⁷ Thus, the progression of HCV infection acquired from a blood transfusion remains unclear. To elucidate the clinical course of post-transfusion HCV infection, we studied a group of patients referred to a tertiary care center.

METHODS

Patients

Between February 1980 and June 1994, 213 patients with chronic hepatitis C and a history of a blood transfusion were evaluated at the Liver Center at Huntington Memorial Hospital. All the patients had

positive tests for antibodies to HCV, according to the methods described below. Eighty-two patients were excluded from the study because they had received multiple blood transfusions or had hemophilia, coexisting intravenous drug abuse, coinfection with the human immunodeficiency virus, or coexisting chronic liver disease (hepatitis B, hemochromatosis, or alcoholic liver disease). The remaining 131 patients with chronic post-transfusion HCV infection were enrolled in the study.

The year of the blood transfusion was documented according to the patient's recollection. During interviews, all patients recalled the year of either surgery or a medical illness leading to a blood transfusion. Six of the patients (4.6 percent) were self-referred because of an abnormal alanine aminotransferase concentration or a positive test for antibodies to HCV after a blood donation; the other 125 patients (95.4 percent) had been referred by their private physicians. Of the 131 patients, 118 (90.1 percent) had been referred because of abnormal results of liver-function tests or positive tests for antibodies to HCV, 8 (6.1 percent) because of chronic liver disease, and 5 (3.8 percent) because of a liver mass.

Liver biopsies were performed in 101 patients. Biopsies were not performed in the other 30 patients, all of whom had signs of cirrhosis, because the results of coagulation tests were abnormal. Liver-biopsy specimens were evaluated according to established histologic criteria for four categories of liver disease: chronic hepatitis, chronic active hepatitis, cirrhosis, and hepatocellular carcinoma.⁸ Chronic hepatitis, previously referred to as chronic persistent hepatitis, was diagnosed if the histologic features included portal lymphoid hyperplasia, focal hepatocytolysis, and preservation of the limiting plate.⁹ Chronic active hepatitis was characterized by piecemeal necrosis and parenchymal inflammation with or without bridging necrosis. Cirrhosis was diagnosed when nodular formation was present in addition to the above changes. Hepatocellular carcinoma was diagnosed on the basis of histologic findings or elevated alpha-fetoprotein levels and ultrasonographic or radiographic changes consistent with hepatocellular carcinoma.¹⁰ During follow-up, all patients were screened for hepatocellular carcinoma by means of alpha-fetoprotein tests performed at six-month intervals and yearly ultrasound examination of the liver.

Laboratory Tests

Serum samples from the 131 patients were tested for HCV antibodies with assays from Chiron (Emeryville, Calif.).¹¹ The antigens used were the C25 fusion protein; C22, C100-3, and C33c in a second-generation assay; and the individual HCV recombinant proteins C22, E1, E2, NS3, C100-3, and NS5. The liver tests, which included determinations of serum albumin, bilirubin, aspartate aminotransferase, and alanine aminotransferase, were performed with the Hitachi 747 analyzer (Boehringer-Mannheim, Indianapolis). Alpha-fetoprotein levels

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were measured by radioimmunoassay at the Nichols Institute (San Juan Capistrano, Calif.); the upper limit of normal was 18 ng per milliliter. All data are reported as means \pm SD.

RESULTS

At the time of the initial evaluation at our hospital, the average age of the 131 patients was 57 years (range, 21 to 81). The mean age at the time of the blood transfusion was 35 years (range, 1 to 76). There were 81 women and 50 men; 101 of the patients were white, 22 were Asian, and 8 were African American (Table 1). Nineteen patients recalled a period of jaundice after the blood transfusion. The mean duration of follow-up after the initial visit to our hospital was 3.9 years (range, 1 to 15).

The presenting symptoms and signs are shown according to disease category in Table 2. Fatigue was the most common symptom (occurring in 67.2 percent of the patients), followed by abdominal pain (in 19.8 percent), anorexia (in 14.5 percent), and weight loss (in 6.1 percent). Jaundice was noted in only 2 of the 67 patients with cirrhosis. Hepatomegaly and splenomegaly were detected in 67.9 and 21.4 percent of the 131 patients, respectively. The initial mean laboratory values were as follows: albumin, 4 g per deciliter (range, 2.4 to 5.4); bilirubin, 0.96 mg per deciliter (16.4 μ mol per liter) (range, 0.2 to 6.0 mg per deciliter [3.4 to 103 μ mol per liter]); aspartate aminotransferase, 105 U per liter (range, 20 to 550); and alanine aminotransferase, 132 U per liter (range, 13 to 670).

All 131 patients had antibodies to the chimeric protein C25. The most frequent antibodies to individual recombinant HCV proteins were antibodies to NS3 (in 97.0 percent of the patients), C22 (in 95.4 percent), NS5 (in 71.8 percent), and C100-3 (in 65.7 percent). Antibodies to E1 and E2 were detected in 51.2 and 35.9 percent of the patients, respectively.

Twenty-seven patients (20.6 percent) had chronic hepatitis, 30 (22.9 percent) had chronic active hepatitis, 67 (51.1 percent) had cirrhosis, and 7 (5.3 percent) had hepatocellular carcinoma (Table 2). Fatigue was present in more than 50 percent of the patients with chronic or chronic active hepatitis, in 75 percent of

those with cirrhosis, and in all the patients with hepatocellular carcinoma (Table 2). One patient with a histologic diagnosis of chronic hepatitis also had lymphoma. Splenomegaly in this patient may have been due to the lymphoma. Of the 67 patients with cirrhosis, 54 (80.6 percent) had thrombocytopenia (mean platelet count, 80,900 per cubic millimeter; range, 27,000 to 107,000) with splenomegaly, 28 (41.8 percent) had ascites, 12 (17.9 percent) had esophageal varices, and 12 (17.9 percent) had hepatic encephalopathy. Only 12 patients (17.9 percent) had none of the clinical signs that we studied. The incidence of cirrhosis and hepatocellular carcinoma, according to ethnic or racial background, is shown in Table 1.

Five of the 14 patients with hepatocellular carcinoma were initially referred to our unit for evaluation of a liver mass. Two other patients had elevated serum alpha-fetoprotein levels and radiologic findings consistent with hepatocellular carcinoma within a month after the first visit. Hepatocellular carcinoma developed in an additional seven patients an average of 36 months (range, 7 to 121) after the initial visit. These seven patients are included in the group with hepatocellular carcinoma in Table 1. All the patients with hepatocellular carcinoma also had clinical or histologic evidence of cirrhosis. The mean serum alpha-fetoprotein level in the patients with hepatocellular carcinoma was 22,730 ng per milliliter (range, 7.4 to 183,915). The mean alpha-fetoprotein level in the patients without hepatocellular carcinoma was 7.7 ng per milliliter (range, 1.6 to 58). Serum alpha-fetoprotein levels were normal on repeated determinations in all patients with chronic or chronic active hepatitis and above the normal range in six of the patients who had cirrhosis without hepatocellular carcinoma.

The mean interval between the time of the blood transfusion and the diagnosis of chronic hepatitis, chronic active hepatitis, cirrhosis, or hepatocellular carcinoma is shown in Figure 1. The mean interval was 13.7 years (range, 1 to 42) for chronic hepatitis, 18.4 years (range, 1 to 37) for chronic active hepatitis, 20.6 years (range, 3 to 42) for cirrhosis, and 28.3 years (range, 8 to 42) for hepatocellular carcinoma.

A total of 103 patients received a transfusion before the age of 50 years (average age, 29.2 years), and 28 patients received a transfusion when they were 50 or older (average age, 58.5 years). These two groups had similar or identical percentages of patients with chronic hepatitis (20 and 21 percent, respectively), chronic active hepatitis (23 and 21 percent, respectively), cirrhosis (46 percent in both groups), and hepatocellular carcinoma (11 percent in both). Among the patients who were 50 or older at the time of the transfusion, the average time from the transfusion to the development of chronic

Table 1. Types of Liver Disease According to Race and Ethnic Group among 131 Patients with Transfusion-Associated Hepatitis C.

RACE	NO. OF PATIENTS	CHRONIC HEPATITIS	CHRONIC ACTIVE HEPATITIS	CIRRHOSIS	HEPATOCELLULAR CARCINOMA*
White	101 (77.1)	25 (92.6)	22 (73.3)	45 (75.0)	9 (64.3)
North American	82	22	22	32	6
Armenian	2	0	0	2	0
Italian	3	2	0	1	0
Cuban	1	0	0	1	0
Hispanic	13	1	0	9	3
Asian	22 (16.8)	1 (3.7)	4 (13.3)	12 (20.0)	5 (35.7)
Chinese	8	0	1	4	2
Japanese	6	1	1	4	0
Vietnamese	4	0	1	2	2
Korean	3	0	1	1	1
Mongolian	1	0	0	1	0
African American	8 (6.1)	1 (3.7)	4 (13.3)	3 (5.0)	0
Total	131	27	30	60	14

*Includes seven patients with cirrhosis in whom hepatocellular carcinoma developed after the initial evaluation.

Table 2. Presenting Symptoms and Signs in 131 Patients with Transfusion-Associated Hepatitis C.

SYMPTOM OR SIGN	NO. OF PATIENTS (N = 131)	CHRONIC HEPATITIS (N = 27)	CHRONIC ACTIVE HEPATITIS (N = 30)	CIRRHOSIS (N = 67)	HEPATOCELLULAR CARCINOMA (N = 7)*	<i>no. of patients (%)</i>				
Symptom										
Fatigue	88 (67.2)	14 (51.9)	17 (56.7)	50 (74.6)	7 (100)					
Abdominal pain	26 (19.8)	4 (14.8)	3 (10.0)	16 (23.9)	3 (42.9)					
Anorexia	19 (14.5)	3 (11.1)	4 (13.3)	9 (13.4)	3 (42.9)					
Weight loss	8 (6.1)	1 (3.7)	0	4 (6.0)	3 (42.9)					
Jaundice	2 (1.5)	0	0	2 (3.0)	0					
Sign										
Hepatomegaly	89 (67.9)	15 (55.6)	18 (60)	50 (74.6)	6 (85.7)					
Splenomegaly	28 (21.4)	1 (3.7)	0	25 (37.3)	2 (28.6)					

*All the patients with hepatocellular carcinoma had either clinical or histologic evidence of cirrhosis.

hepatitis, chronic active hepatitis, cirrhosis, and hepatocellular carcinoma was 6.3, 10.7, 9.8, and 14.7 years, respectively. Among the younger patients, the average time to the development of these diseases was 15.9, 20.4, 23.6, and 31.5 years, respectively.

During follow-up, 20 patients died, including 8 from complications of cirrhosis (1 of whom underwent a liver transplantation) and 11 from hepatocellular carcinoma. One patient with chronic active hepatitis died from pneumonia. Three patients with cirrhosis underwent orthotopic liver transplantation and were alive as of April 1, 1995.

DISCUSSION

The 213 patients considered for this study represented approximately one third of the patients with HCV antibodies referred for evaluation during the study period. We have no information on the pool of patients receiving transfusions (i.e., the denominator) from which these 213 patients were drawn. Before the identification of HCV, from 5 to 12 percent of patients in the United States may have contracted acute non-A, non-B hepatitis after receiving a transfusion, and 91 percent of these infections may have been caused by HCV.¹ The Centers for Disease Control and Prevention have estimated that 20 percent of acute HCV infections progress to chronic active hepatitis or cirrhosis.⁴

In our study, 104 patients had chronic active hepatitis, cirrhosis, or hepatocellular carcinoma. Using these estimates and assuming that we saw all the patients with serious liver disease related to post-transfusion HCV in the population of patients referred to our center, we calculated that the pool from which our patients were drawn included approximately 4700 to 11,400 people with a history of a transfusion. Since our institution is a tertiary care center, many of the patients may have been referred after they had already been evaluated elsewhere and had become seriously ill. Therefore, we may have seen a larger proportion of chronically ill patients with HCV infection and liver disease than might be seen in other settings.

A majority of the patients with HCV infection had symptoms and signs of chronic liver disease when they were evaluated initially. Both fatigue and hepatomegaly were frequent findings, especially in the patients with

cirrhosis and hepatocellular carcinoma (Table 2). Other investigators have reported that most patients with chronic infection from post-transfusion non-A, non-B hepatitis or hepatitis C had few clinical symptoms and signs of liver disease.^{6,7} Only about one sixth of the patients we studied recalled being jaundiced after the transfusion. This proportion is consistent with the range in other studies (15 to 41 percent).^{6,12} At the time of presentation, the mean serum bilirubin level among the 131 patients in our study was 0.96 mg per deciliter (16.4 μ mol per liter). Only

two patients with cirrhosis had clinical jaundice. In contrast, patients with chronic active hepatitis B are often jaundiced during periods of clinical exacerbation.¹³

The mean time between the transfusion and our initial evaluation was 22 years. The mean time from the transfusion to the diagnosis of liver disease was 20.6 years for the patients with cirrhosis and 28.3 years for those with hepatocellular carcinoma. We have reported elsewhere the development of hepatocellular carcinoma in both Asian and white patients with anti-HCV antibodies, regardless of the route of transmission.¹⁰ In other reports in which few patients with HCV infection after a transfusion had complications, the mean follow-up times were 16 and 18 years for the two diagnoses, respectively.^{6,7} The incidence of serious liver disease may be higher over a longer period. In our study, the mean times to the progression of liver disease were similar to those in a previous report from Japan.⁵ In that study of 89 patients, the mean times from the transfusion to the development of chronic hepatitis, cirrhosis, and hepatocellular carcinoma were 10.0, 21.2, and 29.0 years, respectively.

Twenty of the 131 patients referred to us died, all but 1 from complications of cirrhosis or hepatocellular carcinoma. In a previous report of post-transfusion non-A,

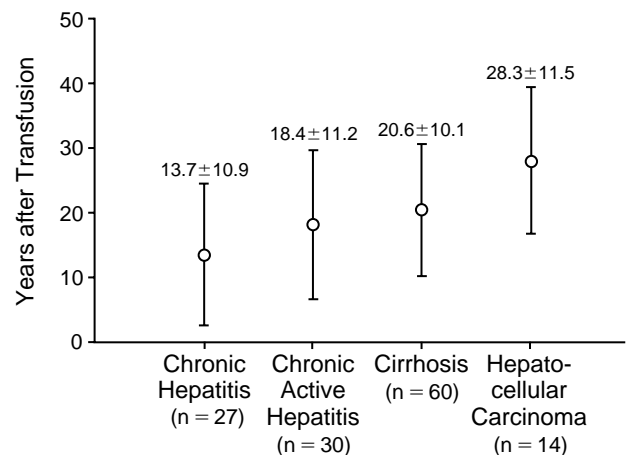


Figure 1. Mean (\pm SD) Interval from Blood Transfusion to the Diagnosis of Diseases Associated with Hepatitis C in 131 Patients.

non-B hepatitis, only 3.3 percent of the deaths were considered to be related to the underlying liver disease.⁷ In that study, 78 percent of the patients who died also had a history of alcoholic liver disease. We excluded patients with a history of excessive alcohol intake.

In summary, in a group of patients referred to a tertiary care center, we found that HCV infection was a progressive disease and, in some patients, led to death from either liver failure or hepatocellular carcinoma. Screening of blood products for hepatitis C before transfusion will substantially reduce the incidence of post-transfusion HCV infection. For people who are already infected with HCV, our findings support the use of antiviral therapy to eradicate the virus and halt the progression of chronic liver disease.

We are indebted to Drs. George Kuo and David Chien of the Chiron Corporation for performing the assays of anti-HCV antibodies, and to Ms. Tina Jordan for assistance in the preparation of the manuscript.

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