Excess Mortality in Patients with Advanced Chronic Hepatitis C Treated with Long-Term Peginterferon

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Chronic hepatitis C virus infection can cause chronic liver disease, cirrhosis and liver cancer. The Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial was a prospective, randomized controlled study of long-term, low-dose peginterferon therapy in patients with advanced chronic hepatitis C who failed to respond to a previous course of optimal antiviral therapy. The aim of this follow-up analysis is to describe the frequency and causes of death among this cohort of patients. Deaths occurring during and after the HALT-C Trial were reviewed by a committee of investigators to determine the cause of death and to categorize each death as liver- or nonliver-related and as related or not to complications of peginterferon. Rates of liver transplantation were also assessed. Over a median of 5.7 years, 122 deaths occurred among 1,050 randomized patients (12%), of which 76 were considered liver-related (62%) and 46 nonliver-related (38%); 74 patients (7%) underwent liver transplantation. At 7 years the cumulative mortality rate was higher in the treatment compared to the control group (20% versus 15%, $P = 0.049$); the primary difference in mortality was in patients in the fibrosis compared to the cirrhosis stratum (14% versus 7%, $P = 0.01$); comparable differences were observed when liver transplantation was included. Excess mortality, emerging after 3 years of treatment, was related largely to nonliver-related death; liver-related mortality was similar in the treatment and control groups. No specific cause of death accounted for the excess mortality and only one death was suspected to be a direct complication of peginterferon. *Conclusion:* Long-term maintenance peginterferon in patients with advanced chronic hepatitis C is associated with an excess overall mortality, which was primarily due to nonliver-related causes among patients with bridging fibrosis. (HEPATOLOGY 2011;53:1100-1108)

Hepatitis C virus (HCV) infection is the most important cause of chronic hepatitis in the United States and is a major cause of morbidity and mortality resulting from cirrhosis and hepatocellular carcinoma (HCC).[1-3] Although successful antiviral therapy with clearance of HCV appears to decrease the rate of progression of disease and death from chronic hepatitis C, no known beneficial therapy

Abbreviations: HALT-C, Hepatitis C Antiviral Long-term Treatment against Cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SSDI, Social Security Death Index.

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is available currently for patients who fail to respond to standard treatment.[4] The Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial was a large, randomized controlled trial to evaluate the effects of a 3.5-year course of low-dose, maintenance therapy with peginterferon compared to no therapy in retarding the progression of liver disease and in preventing endstage liver disease, HCC, and death in patients with advanced chronic hepatitis C who had failed to achieve a sustained response to a previous course of optimal antiviral therapy.[5] The HALT-C Trial was initiated in 2000 and the randomized treatment phase completed in 2007. The results of the randomized phase showed the lack of a beneficial effect of long-term peginterferon on clinical outcomes or death.[6] Moreover, excess mortality occurred in the treatment group among patients with advanced fibrosis but without cirrhosis. To investigate whether this difference in mortality persisted with longer follow-up and to evaluate its possible explanations, the HALT-C Trial cohort was followed for an additional 3 years and analyzed for the causes of deaths.

Patients and Methods

Study Design. The design of the HALT-C Trial has been described.[5,6] Briefly, between August, 2000 and August, 2004, patients meeting the following criteria were enrolled at 10 clinical centers in the United States: (1) failure to achieve a sustained virological response with previous interferon-based therapy; (2) presence of advanced hepatic fibrosis on liver biopsy categorized as either fibrosis without cirrhosis (Ishak Stage 3 or 4, "fibrosis stratum") or cirrhosis (Ishak Stage 5 or 6, "cirrhosis stratum")[7]; (3) a history of compensated liver disease (i.e., absence of a history of hepatic decompensation or HCC); and (4) absence of exclusion criteria (e.g., liver disease other than hepatitis C, uncontrolled medical or psychiatric conditions, or interferon contraindications).

Participants in the HALT-C Trial were treated initially with peginterferon alfa-2a (180 μg subcutaneously weekly) and ribavirin (1,000-1,200 mg daily) in a 24-week lead-in phase, and those who failed to clear HCV RNA by week 20 were categorized as nonresponders and were eligible for randomization to treatment with half-dose, maintenance peginterferon alfa-2a (90 μg weekly) or to an untreated control group for 3.5 years. Patients in whom HCV RNA was undetectable at week 20 were categorized as responders and continued full-dose combination therapy for up to 48 weeks. Initial responders were eligible for randomization into the trial if virologic breakthrough occurred during extended therapy or relapse followed 48 weeks of therapy. In addition, patients who were treated with peginterferon and ribavirin outside the lead-in phase of the HALT-C Trial were also eligible for randomization ("express" group) if they met criteria for nonresponse, breakthrough, or relapse. This approach to enrollment ensured that all patients had received optimal therapy with peginterferon and ribavirin[8,9] before they were enrolled into this long-term trial, during which they might not be treated.[5]

After randomization, patients in both groups were seen at 3-month intervals for 3.5 years, at which point peginterferon was discontinued in the treatment group. Nine patients assigned to the control group were treated "off-protocol" by nonstudy physicians, but they were included as controls in our intention-to-treat analysis. Thereafter, all patients remained untreated and were seen at 6-month intervals. At each visit the occurrence of clinical outcomes (which had been established prospectively) was noted, including clinical events and laboratory markers of hepatic decompensation, HCC, or death. Although not a primary clinical outcome in the HALT-C Trial, liver transplantation was included in this mortality analysis because these patients were likely to have died in the absence of liver transplantation. Most deaths were identified by study

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Table 1. Death According to Baseline Stratum and Liver-Relatedness

Stratum	Outcome	Death*
Cirrhosis (n = 428)	Liver-related	
	Endstage liver disease	34 (4)
	HCC	12 (3)
	Other	6
	Nonliver-related	28 (1)
	Total	80 (8)
Fibrosis (n = 622)	Liver-related	
	Endstage liver disease	13 (1)
	HCC	9
	Other	2 (1)
	Nonliver-related	18
	Total	42 (2)

*Numbers in parentheses represent the patients who died after liver transplantation.

coordinators interacting with family members by way of telephone. In addition, periodic on-line searches were performed of the U.S. Social Security Death Index (SSDI) (http://ssdi.rootsweb.com/), which is generated from the U.S. Social Security Administration's Death Master File. The SSDI was queried for any participant with whom the study site had no contact for at least 6 months. The last search of the SSDI was conducted in October, 2009. To account for the potential lag between date of death and report to the SSDI, we included in our analysis deaths occurring on or before December 31, 2008.

All deaths were reviewed by a seven-person, central review committee consisting of HALT-C Trial investigators blinded to the identity of the subject, study site, fibrosis versus cirrhosis stratum, but not randomization allocation (treatment or control), this information being required to assess treatment relatedness. The committee classified the primary cause of death into one of 15 categories (Supporting Table 1). Furthermore, the likelihood that hepatitis C-related liver disease ("liver-related") or that peginterferon were contributing causes of death ("treatment-related") was assessed as "unlikely" (<25% likelihood), "possible" (25%-49% likelihood), "probable" (50%-75% likelihood) or "highly likely" (>75% likelihood). Differences of opinion were resolved by discussion among the group to achieve consensus or by majority vote. For purposes of this analysis, when the role of hepatitis C or treatment was judged to be unlikely or only possible (i.e., <50% likelihood), the death was categorized as nonrelated (to hepatitis C and/or treatment), whereas the role of hepatitis C or treatment in any death considered probable or highly likely (≥50% likelihood) was classified as related.

Data Analysis and Statistics. Statistical analyses were performed at the Data Coordinating Center with SAS release 9.1 (SAS Institute, Cary, NC). Time-to-event analytic methods were used to compare survival distributions in the groups defined by randomization group and cirrhosis stratum at baseline. Significance was tested with the log-rank test of equality of survival distributions. Time-to-event was defined as the time between randomization and date of death if before December 31, 2008 or the date the participant was last known to be alive. Participants not known to have died were censored at the date of last study contact or December 31, 2008, whichever occurred first. Last study contact included the latest of the following: last study visit, last telephone contact, last biopsy, liver transplantation, study outcome (excluding death), or date of randomization. Participants who died after December 31, 2008 were censored at that date.

We report the *P*-value for the test of the overall hypothesis of equality of survival distributions and the 7-year cumulative death rates as a measure of the size of the difference at the end of the observation period.

Results

Patient Characteristics. Extensive details on the composition of the HALT-C Trial cohort have been provided in previous publications.[5,6] The 1,050 randomized patients all had chronic hepatitis C, active viremia, and a liver biopsy showing advanced fibrosis (n = 622) or cirrhosis (n = 428). Participants were predominantly male (n = 745, 71%), and half were older than 49 years (range, 19-80, median 49 years). Most patients were non-Hispanic white (n = 812, 77%), 108 (10%) were non-Hispanic black, 107 (10%) Hispanic, and 23 (2%) were of other or mixed ethnicity. The sample included 306 (29%) people who reported being current smokers and 221 (21%) who were diabetic. The overall design, numbers of patients, and flow of patients in the treatment and control arms at the different timepoints are shown in Fig. 1.

Mortality Rates, Overall and by Cirrhosis Status. A total of 122 deaths occurred among 1,050 randomized patients (12%) over a median period of 5.7 years (range, 0-8 years). In addition, 74 patients (7%) underwent liver transplantation, 10 of whom subsequently died and were included in the total number of deaths (Table 1). 53 deaths (43%) occurred during the randomized phase of the trial, defined as 3.8 years (3.5 years plus a 3-month window around the final study milestone) after randomization when patients were being treated actively with peginterferon

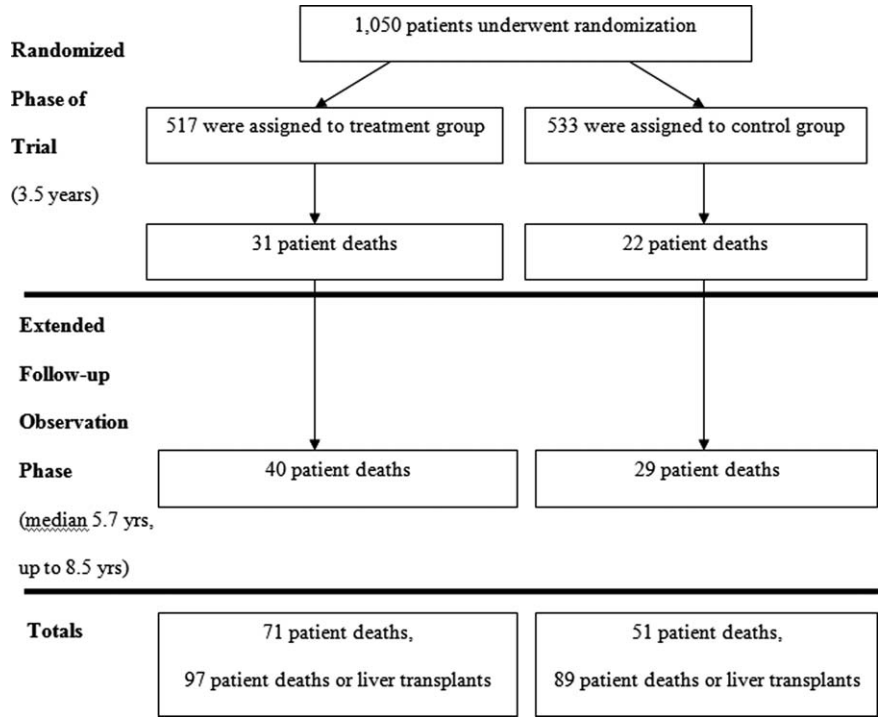

Fig. 1. Overview of the HALT-C Trial, showing flow of the patient cohort from time of randomization, through the 3.5 years of the randomized trial phase, and during the extended follow-up phase showing numbers of deaths.

or followed on no therapy. The remaining 69 deaths (57%) occurred after the conclusion of the randomized phase when all patients were being followed but no study treatment was offered.

More deaths occurred in patients in the cirrhosis stratum (n = 80) than the fibrosis stratum (n = 42), and the survival distributions differed significantly ($P < 0.0001$, Fig. 2). Seven-year cumulative mortality rates were more than two times higher in patients in the cirrhosis stratum than the fibrosis stratum (27% versus 11%), which is equivalent to average annual death rates of 3.9% in the cirrhosis and 1.5% in the fibrosis stratum. Similarly, the distributions of the combined outcome of death or liver transplantation differed significantly in the two strata ($P < 0.0001$), resulting in a 7-year cumulative rate of 36% (n = 120) in the cirrhosis stratum compared to 16% (n = 66) in the fibrosis stratum.

Of the 122 deaths, 76 were categorized as liver-related (62%) and 46 as nonliver-related (38%) (Table 1). The majority of liver-related deaths were attributable directly to complications of endstage chronic hepatitis C or HCC; however, eight deaths (11%) were attributed to liver disease even though other potentially fatal medical conditions were present (e.g., cancer other than HCC, septicemia, influenza and pneumonia, or accident). The proportion of liver-related deaths was slightly higher among patients in the cirrhosis stratum compared to those in the fibrosis stratum, but this difference was not statistically significant (65% versus 57%, $P = 0.39$).

Mortality Rates by Treatment Group and Fibrosis Stratum. Overall, as well as within each stratum, the death rate was higher in patients in the treatment group compared to patients in the control group ($P =$

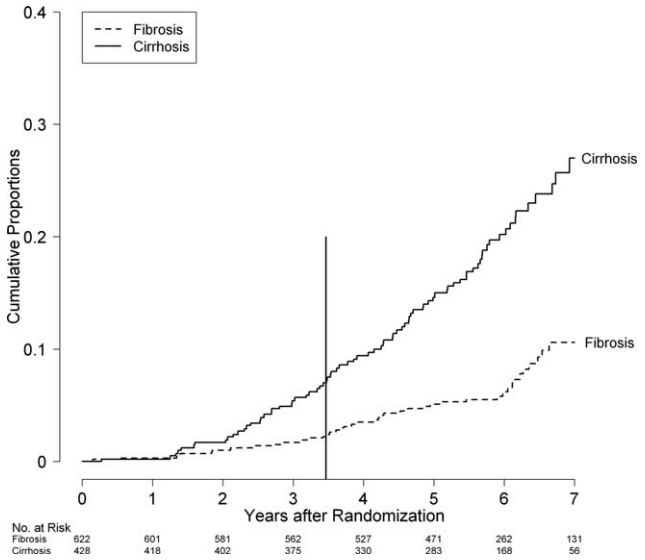

Fig. 2. Cumulative rates of death by fibrosis/cirrhosis stratum in the HALT-C Trial cohort: Kaplan-Meier analysis of 622 patients in the fibrosis stratum (fibrosis: dotted line) versus 428 patients in the cirrhosis stratum (cirrhosis: solid line). The vertical line at 3.5 years marks the end of the randomized trial phase. Test of equality of distributions, $P < 0.0001$.

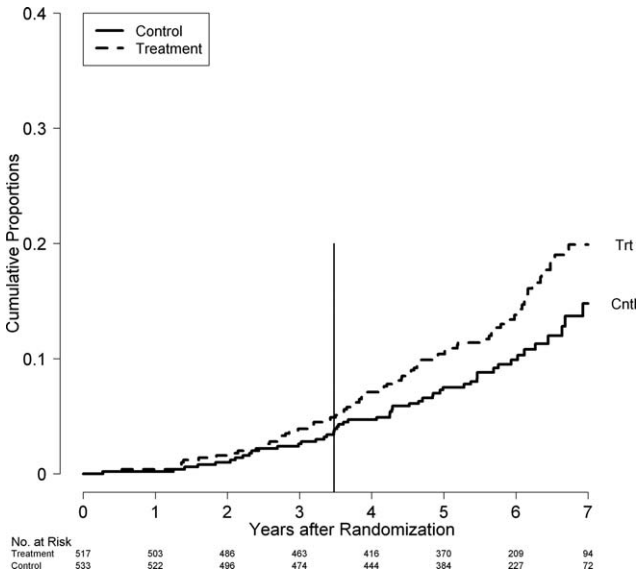

Fig. 3. Cumulative rates of death by randomization group in the HALT-C Trial cohort: Kaplan-Meier analysis of deaths in 517 patients randomized to the treatment group (Trt: dotted line) versus 533 patients randomized to the control group (Cntl: solid line). The vertical line at 3.5 years marks the end of the randomized trial phase. Test of equality of distributions: Fibrosis treatment versus control $P = 0.21$; Cirrhosis treatment versus control $P = 0.85$.

0.049, Fig. 3). The cumulative 7-year death rate was 20% in treated and 15% in control patients. The mortality rates began to separate after 3 years of therapy and continued to separate during the 2 to 3 years of follow-up observation after treatment.

The difference in mortality rates between patients in the treatment and control groups was statistically significant in the fibrosis stratum ($P = 0.01$) but was not significant in the cirrhosis stratum ($P = 0.49$) (Fig. 4A). In the fibrosis stratum, at the end of the randomized phase (3.8 years) the cumulative mortality rate was 5.0% in patients in the treatment group compared to 1.9% in patients in the control group ($P = 0.04$).[6] By 7 years these rates increased to 14% and 7%, respectively. In the cirrhosis stratum the mortality rates in patients in the treatment and control groups were 9.1% and 8.4% at the end of the randomized phase[6] and, during follow-up observation, increased to 28% and 26%. In the fibrosis stratum, as in the group overall, the major separation of mortality rates occurred after 3 years of treatment.

Death and Liver Transplantation as an Endpoint. The results were similar when liver transplantation and death were combined as outcomes. Among the 1,050 patients enrolled, 186 patients (18%) either died or underwent liver transplantation. The rates of death or transplantation were minimally higher in the treated than control patients and the difference was not statistically significant ($P = 0.45$), with 7-year cumulative rates of 25% and 24%, respectively. When separated by fibrosis stratum, however, the differences were statistically significant (Supporting Fig. 1). In the fibrosis stratum the rates of death or transplantation were significantly higher in treated compared to control patients ($P = 0.02$), with 7-year cumulative rates of 19% and 12%, respectively, whereas in the cirrhosis stratum rates of death or transplantation were similar in the two groups ($P = 0.46$), with 7-year cumulative rates of 34% and 39%, respectively.

Specific Causes of Death and Liver Relatedness. When causes of death were categorized by liver-relatedness, the excess mortality in the treatment group fibrosis stratum was primarily from nonliver causes. Thus, rates of liver-related deaths were similar in the treatment and the control groups ($P = 0.42$), with 7-year cumulative liver-related death rates of 12% and 11%, respectively. The rates of liver-related deaths in treatment and control groups were similar in both the fibrosis stratum ($P = 0.21$) and the cirrhosis stratum ($P = 0.85$), although the 7-year death rates did begin to show some separation in the fibrosis stratum (8% versus 5%) but not in the cirrhosis stratum (19% versus 20%, Fig. 4B). On the other hand, nonliver-related deaths were significantly more frequent among patients in the treatment group compared to the control group ($P = 0.03$), with 7-year cumulative mortality rates of 8% and 4%, respectively. These differences were more marked in the fibrosis stratum ($P = 0.03$) than in the cirrhosis stratum ($P = 0.36$, Fig. 4C). The cumulative 7-year mortality rates were 6% and 2% in the treatment and control groups, respectively, in the fibrosis stratum and 12% and 8%, respectively, in the cirrhosis stratum.

Causes of Nonliver-Related Deaths. Examination of the specific causes of nonliver-related deaths failed to identify an excess frequency of any single diagnosis or category of diseases as a cause of death. The nonliver-related deaths reflected a spectrum of expected conditions, including non-HCC cancer as well as cardiac and cerebrovascular disease (Table 2). The distribution of these categories of illness appeared to be similar between those in the fibrosis and cirrhosis strata and in treated versus untreated patients. Cases of death resulting from malignant neoplasms other than HCC were assessed further in an attempt to identify a pattern (Table 3). The distribution of cancers appeared to mirror their relative frequencies in the general population—among the 11 patients whose deaths were attributed to cancer, four died of lung and two of colon cancer. Among the five deaths resulting from septicemia (two liver-related and three not liver-related: Table 2), three occurred in

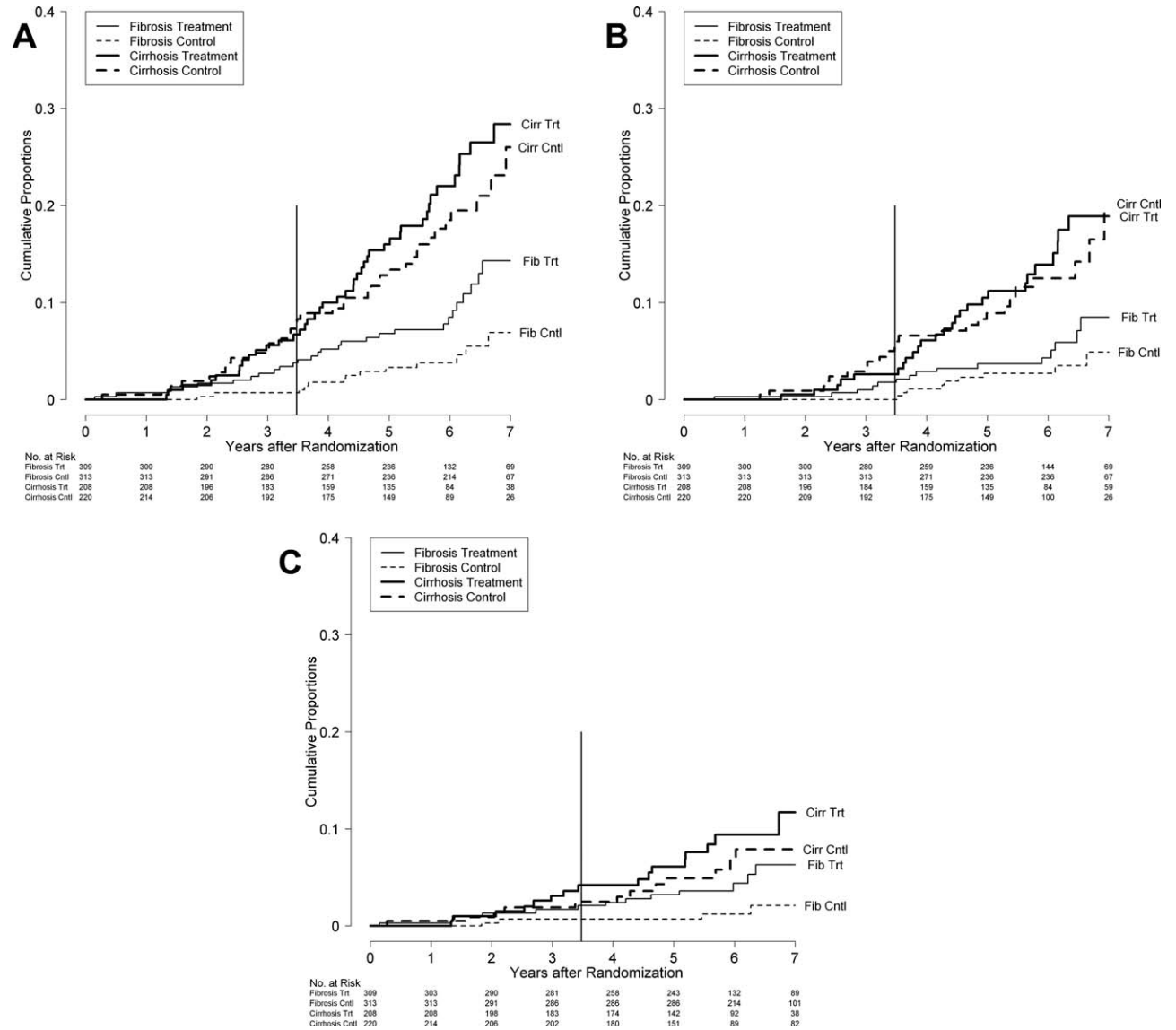

Fig. 4. Cumulative rates of death by fibrosis/cirrhosis stratum and randomization group in the HALT-C Trial cohort: all deaths (A), liver-related deaths only (B), and nonliver-related deaths only (C). Kaplan-Meier analysis of deaths in 309 patients in the fibrosis stratum and treatment group (Fib Trt), 313 patients in the fibrosis stratum and control group (Fib Cntl), 208 patients in the cirrhosis stratum and treatment group (Cirr Trt), and 220 patients in the cirrhosis stratum and control group (Cirr Cntl). The vertical line at 3.5 years marks the end of the randomized trial phase. Test of equality of distributions: (A) Fibrosis treatment versus control $P = 0.01$; Cirrhosis treatment versus control $P = 0.50$. (B) Fibrosis treatment versus control $P = 0.21$; Cirrhosis treatment versus control $P = 0.85$. (C) Fibrosis treatment versus control $P = 0.03$; Cirrhosis treatment versus control $P = 0.36$.

association with underlying cardiac or pulmonary disease, one in association with acute pancreatitis, and one ≈2 years after liver transplantation. Deaths in nine patients were categorized as "other" and included trauma (3), intoxication or overdose (2), pneumonia and respiratory failure (2), ischemic colitis (1), and status epilepticus (1).

Role of Peginterferon Side Effects in Excess Mortality. Special attention was given to whether peginterferon therapy was a direct contributing factor or cause of death in the treatment group. Most deaths in the treated group occurred well after peginterferon was stopped, with only eight patients dying within 2 months of receiving peginterferon (11% of deaths in the treatment group). Independent assessment identified only one death as probably peginterferon-related. A 52-year-old man with chronic hepatitis C and advanced fibrosis had an episode of severe *Staphylococcus aureus* septicemia followed by multiorgan failure and death within a week of a last injection of peginterferon and after almost 2 years of maintenance therapy.

Table 2. Causes of Death by Fibrosis Stratum, Treatment Group, and Liver-Relatedness

Cause of Death	Fibrosis		Cirrhosis		
	Treatment	Control	Treatment	Control	Totals
	n = 309	n = 313	n = 208	n = 220	n = 1,050
Liver-related deaths					
Chronic liver disease	8	5	20	14	47
HCC	6	3	3	9	21
Malignant neoplasm (not HCC)*	0	1	0	1	2
Septicemia*	1	0	1	0	2
Accidental*	0	0	0	1	1
Influenza and pneumonia*	0	0	0	1	1
Unknown*	0	0	2	0	2
Totals	15	9	26	26	76
Nonliver-related deaths					
Malignant neoplasm (not HCC)	5	0	2	2	9
Other	1	0	5	3	9
Accidental	2	1	1	2	6
Heart disease	2	0	2	2	6
Septicemia	3	0	0	0	3
Cerebrovascular disease	0	0	2	0	2
Influenza and pneumonia	0	1	0	0	1
Unknown	1	2	4	3	10
Totals	14	4	16	12	46

*These eight deaths were attributed to liver disease even though other potentially fatal medical conditions were present.

Discussion

The overall death rate in this cohort of patients with advanced chronic hepatitis C was remarkably high. Of the 1,050 patients, 18% died or underwent liver transplantation during a median follow-up time of 5.7 years, and approximately two-thirds of deaths (62%) could be attributed to endstage liver disease or HCC. Among patients with cirrhosis at baseline, the rate of death or liver transplantation was particularly high (7-year cumulative rate 36%, annualized rate 5.2%). Among those with fibrosis without cirrhosis at baseline, rates of all outcomes were less frequent, and the overall rate of death or liver transplantation was lower (7-year cumulative rate 16%, annualized rate 2.2%).

Several prospective studies have shown that chronic HCV infection is associated with an increased mortality rate,[10-17] but the degree of this increase has been difficult to ascertain.[18] The mortality rates observed in the HALT-C Trial cohort were similar to those reported in similar cohorts from other areas of the world. For example, in a recent systematic analysis of natural history studies, the annual rate of death or transplantation among patients with compensated cirrhosis associated with hepatitis C averaged 4.6%.[19] In comparison, the annual mortality rate among HALT-C Trial patients in the compensated cirrhosis stratum was 3.9%, and the annual rate of death or transplantation in this stratum was 5.2%. Although the HALT-C Trial did not include uninfected control patients for comparison, the high mortality rates observed, particularly in the cirrhosis stratum, confirm the poor outcomes among patients with chronic hepatitis C and advanced hepatic fibrosis.

The unique finding of higher mortality among patients in the peginterferon-treatment group noted in the initial report of the randomized phase of the HALT-C Trial[6] persisted when analyzed with a longer period of follow-up, the focus of the current analysis. An important feature of the current analysis was that all deaths were reviewed by a central committee blinded to the patient's identify. A cause of death was determined by committee consensus based on preselected criteria. Because reviewers were also asked to assess possible causality due to interferon treatment, they could not be blinded to group assignment. During subsequent follow-up, the difference in death rates between patients in the treatment and control groups remained statistically significant and actually increased further. This was particularly true in the noncirrhotic fibrosis stratum, the trial subset in which increased mortality was found to be associated with maintenance therapy during the randomized phase.[6] The difference in mortality in the cirrhosis stratum between patients in the treatment and control groups also increased during extended observation but did not reach statistical significance.

Of note, the excess mortality in the treatment group cohort did not begin to arise until 3 years into treatment and continued for several years after

Table 3. Malignant Neoplasms Other than HCC Causing Death in 11 Patients

Stratum	Randomization Group	Diagnosis
Liver-related*		
Fibrosis	Control	Colon cancer with liver metastases
Cirrhosis	Control	Lymphoma
Nonliver-related		
Fibrosis	Treatment	Nonsmall cell lung cancer
Fibrosis	Treatment	Nonsmall cell lung cancer
Fibrosis	Treatment	Squamous cell lung cancer
Fibrosis	Treatment	Prostate cancer
Fibrosis	Treatment	Colon cancer with liver metastases
Cirrhosis	Treatment	Gallbladder cancer
Cirrhosis	Treatment	Pancreatic cancer with lung metastases
Cirrhosis	Control	Lung cancer
Cirrhosis	Control	Gastric adenocarcinoma

*Death was considered to be liver-related in these patients because, even though they had otherwise potentially fatal nonliver diseases, the circumstances of their deaths were most consistent with advanced liver disease, which may have been exacerbated by treatment of the malignancies.

peginterferon was stopped. Nevertheless, a review of each case failed to identify an immediate or direct relationship between the increased death rate and peginterferon therapy. Interferon therapy has been associated in rare instances with fatal severe adverse events, including suicide, acute myocardial infarction, cerebrovascular accident, precipitation of severe autoimmune disease, and septicemia.[20] These complications, however, did not account for the increased rate of death associated with treatment in the HALT-C Trial cohort. Indeed, of the 71 deaths that occurred in patients in the treatment group, only eight occurred within 2 months of a peginterferon injection, and in only one instance was peginterferon thought to have probably played a contributing role (an episode of septicemia in close temporal proximity to a peginterferon injection).

Importantly, the excess mortality in the treatment group resulted largely from nonliver-related causes. Indeed, rates of death attributable to endstage liver disease and HCC were similar in the treatment and control groups. Careful review of the nonliver-related deaths, however, failed to reveal a specific disease category associated with this excess mortality, although the combination of death by non-HCC malignancy and systemic infection might suggest a potential effect on host immunity. Nevertheless, the excess mortality arising after 3 years of peginterferon treatment remains unexplained and did not result from a specific adverse effect of treatment or single type of fatal condition (such as heart disease, lung disease, or cancer); the link between treatment and mortality was both noncause-specific and delayed. Risk factors for nonliver-related death such as obesity and smoking were included in the analysis but did not obviously account for the excess deaths (data not shown).

Theoretical explanations might be offered to explain excess mortality associated with long-term peginterferon treatment. Interferon-alpha is not a direct-acting antiviral but rather acts on cell-surface receptors to trigger signaling pathways that activate "interferon-stimulated genes," which render the cell resistant to viral infection and less capable of supporting viral replication.[21,22] The basis of the antiviral activity of alpha interferon is complex and involves multiple, often redundant cellular pathways, such as those involved in regeneration; cell turnover; apoptosis; and protein, lipid, and carbohydrate metabolism. Possibly the continuous stimulation of interferon-induced genes by long-term maintenance therapy is detrimental, particularly to cells and tissues without active viral replication. These effects may be diverse and, therefore, not manifested as a single adverse reaction.

An alternative explanation for the difference in mortality between the treatment and control groups in the HALT-C Trial is the presence of an undefined confounding factor, such as baseline difference in the randomization groups, or difference in subsequent management. However, given the size of the trial, the success of randomization,[6] and the uniformity of management in the two groups, these differences are unlikely to have accounted for a statistical difference in mortality rates. Currently, hypotheses to explain excess mortality linked to interferon are not supported by clinical or experimental observations, but warrant further study.

Thus, the HALT-C Trial was not able to show a benefit of long-term peginterferon maintenance on rates of clinical progression, histologic progression to cirrhosis, hepatic decompensation, HCC, or death.[6] In this extended follow-up analysis, as in the analysis of the randomized trial, the mortality rate appeared to be higher among patients in the peginterferon treatment group. In other post-hoc analyses of the HALT-C Trial cohort, long-term peginterferon therapy appeared to be associated with a lower rate of late HCC, diverging from the control group after 4 years of observation, but only in patients with cirrhosis at baseline.[23] As shown in the current analysis, the lower rate of late HCC was not accompanied by a lower rate of death or liver transplantation.

In summary, long-term observation of a large cohort of patients with chronic hepatitis C and advanced hepatic fibrosis revealed a high rate of death, particularly among those with cirrhosis at baseline. Approximately two-thirds of deaths were attributable to liver disease. An increase in mortality occurred in patients in the long-term peginterferon treatment group, but this increase in mortality was attributed to nonliver-related deaths and occurred largely among patients with precirrhotic advanced fibrosis at baseline. No pattern to this excess mortality was discernible; deaths were unrelated to direct effects of peginterferon treatment. These findings suggest that the long-term use of interferon should be evaluated cautiously and that attention to unrelated complications is warranted.

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