Maintenance Peginterferon Therapy and Other Factors Associated With Hepatocellular Carcinoma in Patients With Advanced Hepatitis C

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This article has an accompanying continuing medical education activity on page e12. Learning Objective: Upon completion of this exercise, successful learners will be able to identify patients with chronic HCV infection who are at greater risk for HCC and the efficacy of antiviral therapy in preventing HCV-related HCC.

See related article, Iacobellis A et al, on page 249 in *CGH*.

BACKGROUND & AIMS: Interferon reportedly decreases the incidence of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C. The Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial showed that 4 years of maintenance therapy with pegylated interferon (peginterferon) does not reduce liver disease progression. We investigated whether peginterferon decreases the incidence of HCC in the HALT-C cohort over a longer posttreatment follow-up period. **METHODS:** The study included 1048 patients with chronic hepatitis C (Ishak fibrosis scores ≥3) who did not have a sustained virologic response (SVR) to therapy. They were randomly assigned to groups given a half-dose of peginterferon or no treatment (controls) for 3.5 years and followed up for a median of 6.1 (maximum, 8.7) years. **RESULTS:** Eighty-eight patients developed HCC (68 definite, 20 presumed): 37 of 515 who were given peginterferon (7.2%) and 51 of 533 controls (9.6%; $P = .24$). There was a significantly lower incidence of HCC among patients given peginterferon therapy who had cirrhosis, but not fibrosis, based on analysis of baseline biopsy samples. After 7 years, the cumulative incidences of HCC in treated and control patients with cirrhosis were 7.8% and 24.2%, respectively (hazard ratio [HR], 0.45; 95% confidence interval [CI], 0.24–0.83); in treated and control patients with fibrosis, incidences were 8.3% and 6.8%, respectively (HR, 1.44; 95% CI, 0.77–2.69). Treated patients with a ≥2-point decrease in the histologic activity index, based on a follow-up biopsy, had a lower incidence of HCC than those with unchanged or increased scores (2.9% vs 9.4%; $P = .03$). **CONCLUSIONS: Extended analysis of the HALT-C cohort showed that long-term peginterferon therapy does not reduce the incidence of HCC among patients with advanced hepatitis C who did not achieve SVRs. Patients with cirrhosis who received peginterferon treatment had a lower risk of HCC than controls.**

Keywords: Interferon Therapy; Hepatitis C Clinical Trial; Interferon Nonresponders; Liver Cancer.

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third most common cause of cancer death in the world.[1] In the United States, hepatitis C has been the greatest contributor to both the occurrence of HCC and its observed increased incidence over the past 20 years. Among persons with chronic hepatitis C, risk factors for the development of HCC are incompletely understood. HCC has been found primarily, but not exclusively, in patients with cirrhosis. In addition to the degree of liver fibrosis, biochemical markers of advanced liver disease (eg, low platelet count, low

Abbreviations used in this paper: AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, albumin, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; HAI, histologic activity index; HALT-C Trial, Hepatitis C Antiviral Long-term Treatment against Cirrhosis Trial; HR, hazard ratio; peginterferon, pegylated interferon; SVR, sustained virologic response.

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albumin level), presence of esophageal varices, diabetes, obesity, use of tobacco, and excessive alcohol intake have been associated with an increased risk of HCC. The risk of HCC is decreased in patients with chronic hepatitis C who achieve a sustained virologic response (SVR) to interferon/ribavirin treatment[2,3]; however, the effectiveness of interferon therapy in reducing the incidence of HCC among patients with hepatitis C virus (HCV)-related cirrhosis who do not achieve an SVR is unclear.

The Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial was a randomized multicenter trial to determine whether 3.5 years of half-dose pegylated interferon (peginterferon) treatment reduced liver disease progression among patients with hepatitis C and advanced fibrosis who were nonresponders to peginterferon and ribavirin. Analysis of the HALT-C Trial results after 3.5 years of treatment revealed that peginterferon did not reduce the overall risk of liver disease progression.[4] A subsequent report focusing on development of HCC also showed no difference between the treated and control groups during and immediately after the period of maintenance peginterferon therapy.[5] We continued to follow up the HALT-C Trial cohort off therapy for up to 8.7 years to monitor for the development of decompensated liver disease and HCC. During the extended follow-up period, the number of patients with HCC increased progressively. The aims of the current analysis were to (1) determine the incidence of HCC among the HALT-C Trial cohort after a longer duration of follow-up, (2) identify factors associated with the development of HCC in the HALT-C Trial cohort, and (3) ascertain whether maintenance peginterferon therapy had any delayed posttreatment effect in preventing HCC.

Patients and Methods

The design of the HALT-C Trial has been described previously.[4,6] Briefly, patients with chronic hepatitis C had to meet the following criteria for enrollment: failure to achieve an SVR after previous interferon treatment with or without ribavirin, the presence of advanced hepatic fibrosis on liver biopsy (Ishak fibrosis score $\geq$3), no history of hepatic decompensation or HCC, and the absence of defined exclusion criteria.

All patients had been previously treated with one or more courses of interferon, with the most recent course being a combination of full-dose peginterferon and ribavirin. Patients who remained viremic during treatment and those who experienced breakthrough or relapse after initial response were randomized to maintenance therapy (peginterferon alfa-2a 90 μg weekly) or no further treatment for the next 3.5 years. Following completion of the 3.5 years of the randomized trial, all patients were invited to continue follow-up without treatment until October 2009.

At entry, all patients were required to have hepatic ultrasonography, computed tomography, or magnetic resonance imaging with no evidence of hepatic mass lesions suspicious for HCC and to have a serum α-fetoprotein (AFP) level $<$200 ng/mL.

All patients had a liver biopsy performed before enrollment. Liver biopsies were repeated 1.5 and 3.5 years after randomization and reviewed by a panel of hepatic pathologists blinded to randomization group. The Ishak scoring system was used to grade inflammation (histologic activity index [HAI] 0–18) and to stage fibrosis (0–6).[7] Liver biopsies performed for the diagnosis of HCC and liver explants from patients who underwent transplantation for HCC were also reviewed centrally. Patients were stratified at the time of randomization into 2 groups: those with cirrhosis (Ishak fibrosis stage 5 or 6) and those with noncirrhotic fibrosis (Ishak fibrosis stage 3 or 4).

All patients underwent upper gastrointestinal endoscopy at the time of randomization and 3.5 years after randomization for assessment of the presence and size of esophageal varices. For the current analysis, patients were categorized as not having varices (absent) or as having varices, regardless of their size.

HCC Surveillance and Diagnostic Criteria

Patients were scheduled to be seen every 3 months during the 3.5 years of the randomized trial and every 6 months thereafter. A complete blood cell count, a liver panel (albumin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, and bilirubin), international normalized ratio of prothrombin time, and AFP level were obtained at the local clinical center at each visit. Ultrasonography was repeated at the time of randomization, 6 months after randomization, and every 6 to 12 months thereafter. Patients with an elevated or rising AFP level and those with new lesions on ultrasonography were evaluated further with computed tomography or magnetic resonance imaging. Diagnostic liver biopsy and treatment of HCC were performed at the discretion of the investigators at each of the clinical sites.

Two definitions of HCC were adopted.[5] Definite HCC was defined by histologic confirmation or a new mass lesion on imaging with AFP levels increasing to $\geq$1000 ng/mL. Presumed HCC was defined as a new mass lesion on ultrasonography in the absence of histology and AFP level $<$1000 ng/mL in conjunction with one of the following characteristics: (1) 2 liver imaging studies showing a mass lesion with characteristics of HCC (vascular enhancement with or without washout), (2) a progressively enlarging lesion on ultrasonography leading to death of the patient, or (3) an additional imaging study showing a mass lesion with characteristics of HCC that either increased in size over time or was accompanied by increasing AFP levels. All cases of HCC (presumed and definite) were reviewed by an outcomes review panel composed of rotating panels of 3 trial investigators. An earlier report included all patients with definite or presumed HCC as judged by the outcomes review panel before October 15,