DCP Snap Shot

Sites Participating: All sites and all patients in the HALT-C Trial

Principal Investigator: Anna S.F. Lok, MD (University of Michigan)

Co-Investigator: Leonard Seeff, MD

Study Name: Measurement of Serum Des-γ-Carboxy Prothrombin (DCP) for Early Detection of Hepatocellular Carcinoma (HCC) in Patients with Chronic Hepatitis C Virus (HCV) Infection

Separate Consent Form: No

Withdrawal Form: No

Eligible Patients: Randomized patients (Lead-in, Express, and Breakthrough/Relapser)

Visit Schedule (additional data/specimen and forms for AS)

Note: "**X**" means all participating sites take part. No additional specimens are collected for this study. Tests are performed on specimens collected for the Steatosis Ancillary Study (seq.#121) or on the specimens stored for the main trial (seq.#110, seq.#111 or seq.#123). DCP results are maintained in a separate data file and are not included in the main HALT-C database.

Lead-In Phase (For Randomized Patients)

Visit Number →	S00	W00	W02	W04	W08	W12	W16	W20	W24
Steatosis sample (#121)		X							
Stored sample (#110, #111 or #123)								X	

Randomized Phase

Visit Number →	R00	M12	M18	M24	M30	M36	M42	M48	M54
Steatosis sample (#121)				X					
Stored sample (#110, #111 or #123)	X	X				X		X	

Measurement of Serum Des-γ-Carboxy Prothrombin (DCP) for Early Detection of Hepatocellular Carcinoma (HCC) in Patients with Chronic Hepatitis C Virus (HCV) Infection

Principal Investigator: Anna S.F. Lok, MD

Co-Investigator: Leonard Seeff

Introduction:

Hepatocellular carcinoma (HCC) is the fourth most common cancer in the world. A major etiology for the development of HCC is chronic infection with the viruses of hepatitis B and hepatitis C. In some parts of the world, Japan in particular, HCV is the leading cause of HCC; HCV is also a leading contributor to HCC among U.S.-born Americans.

The prognosis after development of HCC is extremely poor, particularly in its symptomatic phase. Accordingly, early detection and treatment of small tumors is imperative if there is to be hope of cure. It is therefore common to monitor persons with chronic HCV infection, particularly those with cirrhosis, with the hope of ensuring early detection and appropriate treatment.

The most commonly used screening tests at present are serum alpha-fetoprotein (AFP) and ultrasonography. Screening of high risk populations reveals a sensitivity of 39%-64%, a specificity of 76%-91%, and a positive predictive value of 9%-32% with levels of AFP >20ng/ml. However, raised AFP is not specific for HCC since it can be increased when there is active hepatitis, in the presence of certain tumors, and in pregnancy. Higher levels are helpful, but normal levels can also occur even when HCC exists. Therefore, it would be helpful to have an additional supportive assay to increase the chances of early detection. Des-γ-carboxy prothrombin (DCP), a prothrombin precursor, might possibly play that role. It is a Protein Induced by Vitamin K Absence or Antagonist II and hence is also referred to as PIVKA II.

Several studies have identified it as a tumor marker that is complementary to AFP for the diagnosis of HCC. The assay, recently improved, has a sensitivity of 62%, a specificity of 95%, and a positive predictive value of 74%. A lack of correlation between DCP and serum AFP has been noted and a positive reaction is observed even in cases of low AFP values. However, DCP significantly enhances the rate of detecting tumors $\leq$ 3 cm in conjunction with AFP. DCP may also be used as a marker for the prediction of intrahepatic spread and for the prognosis of HCC.

The HALT-C Trial affords the unique opportunity to evaluate the value of DCP as an early indicator of HCC development and to compare it to other indicators of HCC.

Hypothesis:

It is proposed that serum measurement of DCP will enhance the yield of detection of HCC in conjunction with AFP and ultrasonography during the HALT-C trial. However, this test will not affect decision-making for the diagnosis of HCC.

Aims:

1. Evaluate the usefulness of serum des-γ-carboxy prothrombin (DCP) as a tumor marker for detecting HCC in persons with chronic hepatitis C.

2. Analyze the data of patients who develop HCC during the study period to model the relationship between DCP, AFP, and tumor growth.

Methods:

DCP will be measured on serum samples from all of the approximately 900 randomized patients in the HALT-C Trial at baseline, week 20, randomization visit (R00) for Express, Relapse, and Breakthrough patients, and at months 12, 24, 36, and 48. Testing will be done in conjunction with AFP measurements performed at these same time points. It is anticipated, therefore, that there will be a total of six or seven measurements of DCP for each patient who completes the study, but these same patients will have had more frequent testing for AFP, the sole serologic test used as a marker for incipient HCC, as described in the HALT-C protocol.

Patients who are identified to have developed HCC during the course of the study will have all their stored sera tested for DCP. This will include sera that were tested for AFP but not DCP, thus permitting comparison of the two tests as sensitive markers for HCC. At the same time, DCP testing will be done on similar stored sera of carefully matched study subjects who have not developed HCC.

Tests will be performed at the University of Michigan using kits provided by Eisai Co., Ltd. of Japan. A Cooperative Research and Development Agreement (CRADA) has been signed between Eisai and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Eisai is providing test kits and some funds (via NIDDK) for personnel at the University of Michigan and at the DCC.

Data analysis:

At the end of study year 4, analysis will be performed on all patients who have had more than three samples tested to determine stability of the values as expressed as mean $\pm$ standard deviation. These analyses should confirm that the test results are consistently low in HCV-positive patients without HCC. The Ancillary Studies Committee will review these results, and if the results are widely scattered, the committee may recommend that there be no further testing.

Final analyses will look at changes in DCP among randomized patients and the ability of DCP to predict the development of HCC.

The HALT-C Data Safety and Monitoring Board (DSMB) is responsible for interim review of HALT-C trial, including data on the development of HCC. At this time no patients have developed HCC during the randomized trial. If HCC develops in a sufficient number of patients, then a report on the relationship between DCP and the development of HCC will be prepared for review by the DSMB. If appropriate, the DSMB will make a recommendation that DCP be used as an additional screening measure.

References

1. Nakari T, Watanabe K, Shimazuru Y, et al. Development and evaluation of the EIA kit for detection of PIVKA-II using double antibody sandwich system: Monoclonal antibody to PIVKA-II and polyclonal antibody to prothrombin. Clin Immuno 1986;18:479-92.
2. Fujiyama S, Izuno K, Gohshi K, Shibata J, Sato T. Clinical usefulness of des-gamma-carboxy prothrombin assay in early diagnosis of hepatocellular carcinoma. Dig Dis Sci 1991;36:1787-92.
3. Chan CY, Lee SD, Wu JC, Lin HC, Huang YS, Lo GH, Lee FY, Tsai YT, Lo KJ. The diagnostic value of the assay of des-gamma-carboxy prothrombin in the detection of small hepatocellular carcinoma. J Hepatol 1991;13:21-4.

4. Suehiro T, Sugimachi K, Matsumata T, Itasaka H, Taketomi A, Maeda T. Protein induced by vitamin K absence or Antagonist II as a prognostic marker in hepatocellular carcinoma. Cancer 1994; 73:2464-71.
5. Aoyagi Y, Oguro M, Yanagi M, Mita Y, Suda T, Suzuki Y, Hata K, Ichii K, Asakura H. Clinical significance of simultaneous determinations of alpha-fetoprotein and des-gamma-carboxy prothrombin in monitoring recurrences in patients with hepatocellular carcinoma. Cancer 1996; 77:1781-6.
6. Kuromatsu R, Tanaka M, Shimauchi Y, Shimada M, Tanikawa K, Watanabe K, Yokoo T. Usefulness of ED936 kit for measuring serum PIVKA-II levels in small hepatocellular carcinoma. J Gastroenterol 1997; 32:507-12.
7. Grazi GL, Mazziotti A, Legnani C, Jovine E, Miniero R, Gallucci A, Palareti G, Gozzetti G.The role of tumor markers in the diagnosis of hepatocellular carcinoma, with special reference to the des-gamma-carboxy prothrombin. Liver Transpl Surg 1995;1:249-55.
8. Okuda H, Nakanishi T, Takatsu K, Saito A, Hayashi N, Watanabe K, Magario N, Yokoo T, Naraki. Measurement of serum levels of des-gamma-carboxy prothrombin in patients with hepatocellular carcinoma by a revised enzyme immunoassay kit with increased sensitivity. Cancer 1999;85:812-8.
9. Nomura F, Ishijima M, Kuwa K, Tanaka N, Nakai T, Ohnishi K. Serum des-gamma-carboxy prothrombin levels determined by a new generation of sensitive immunoassays in patients with small-sized hepatocellular carcinoma. Am J Gastroenterol 1999;94:650-4 .
10. Nomura F, Ishijima M, Horikoshi A, Nakai T, Ohnishi K. Determination of serum des-gamma-carboxy prothrombin levels in patients with small-sized hepatocellular carcinoma: comparison of the conventional enzyme immunoassay and two modified methods. Am J Gastroenterol 1996;91:1380-3.
11. Toshima M, Shibasaki K, Aoyagi Y. Serum des-gamma-carboxyprothrombin level by a modified enzyme immunoassay method in hepatocellular carcinoma: clinical significance in small hepatocellular carcinoma. Hepatogastroenterology 1998;45:1737-41.