学 位 論 文 の 要 旨

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学　位　論　文　名　　Clinical Significance of the Highly Sensitive Fucosylated Fraction of α-Fetoprotein in Patients With Chronic Liver Disease

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論 文 内 容 の 要 旨

INTRODUCTION

Hepatocellular carcinoma (HCC) is a type of malignancy that is increasing in various countries throughout the world, with the number of related deaths now surpassing 1 million. More than 80% of HCC cases are associated with chronic hepatitis or cirrhosis. Early detection is essential for curative treatment, and simple and sensitive methods that can be widely applied are urgently needed in current clinical practice. Alfa-fetoprotein (AFP) has been employed as a tumor marker of HCC for a long period of time. However, its sensitivity and specificity is limited, because elevated AFP is often observed in more advanced stages of HCC, as well as in patients with hepatitis or cirrhosis, but without HCC.

To solve this problem, measurement of the fucosylated fraction of AFP (AFP-L3) has been developed and found to be useful, not only for clinical and histological diagnoses, but also for predicting future development of HCC. However, determination of AFP-L3 is difficult when the total serum concentration of AFP is under 10 ng/ml. In the present study, a recently developed novel measurement method for use in patients with lower serum AFP concentrations was utilized to determine AFP-L3 level as a marker for the prevalence and incidence of HCC.

MATERIALS AND METHODS

Two hundred forty-one patients with serum AFP levels below 10 ng/ml being treated for chronic liver disease at the outpatient clinic or hospital of Shimane University School of

Medicine were enrolled. Peripheral blood samples were collected and stored from June to September 2009. We measured the concentrations of AFP-L3 in those samples using a μTAS-Wako i30 (Wako Pure Chemical Industries, Ltd., Osaka, Japan) device, which provides highly sensitive measurements of the AFP-L3 fraction in samples with low (3-10 ng/ml) AFP levels. Imaging studies, including conventional and contrast-enhanced ultrasonography, dynamic triple phase CT, contrast-enhanced MRI using gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA), and abdominal angio CT, were performed to detect HCC within 1 month before and after blood sampling. Based on our results, we set an optimal cut-off value for the AFP-L3 fraction for diagnosis of HCC in these patients and examined its utility as a tumor marker of HCC. Furthermore, we investigated the possible influence of various factors, such as patient and tumor factors, on the obtained value. In addition to its use as a possible marker of prevalent HCC, we also examined the utility of the present highly sensitive AFP-L3 assay for detecting HCC during follow-up examinations of the enrolled patients. The study protocol was approved by the Ethical Committee of Shimane University.

RESULTS AND DISCUSSION

AFP-L3 was above the detectable limit in 60 patients (24.9%), of whom 20 (33.3%) were found to be HCC prevalent, while HCC was found in only 16 patients (8.8%) with undetectable hs-AFP-L3 levels. From those results, we determined the cut-off value of %AFP-L3 to be 5.75%. Thus, as a tumor marker of HCC, sensitivity was 52.8%, specificity was 86.8%, positive predictive value was 41.3%, and negative predictive value was 91.3%. During the follow-up period, HCC was newly detected in 6 patients (22.2%) in the %AFP-L3 elevated group and in 10 (5.6%) in the non-elevated group. Analysis using the Kaplan-Meier method showed that the HCC-free rate of the %AFP-L3 elevated group was significantly lower than that of the non-elevated group (p=0.0038). Independent predicting variants were female gender (p=0.0024) and %AFP-L3 elevation (p=0.0036).

Treatment strategies for patients with HCC as well as their prognosis strongly depend on tumor stage when first discovered. For successful radical treatment, early detection is vital and various diagnostic imaging methods have been developed. In addition, several tumor markers have also been investigated, with the fucosylated fraction of alpha-fetoprotein, AFP-L3, reported to be effective for early diagnosis, recurrence rate, biological malignancy, and prognosis in HCC patients with chronic liver disease. In the present study, AFP-L3 was measurable in

patients with chronic liver disease, even when the serum AFP value was lower than 10 ng/ml, using the present novel automated immunoassay. On the other hand, a previous report noted that most patients with HCC had an AFP level under 15 ng/ml and measurement of AFP-L3 was not possible in those cases. In the present study, we determined the optimal cut-off value for the AFP-L3 fraction following production of a receiver operator characteristic curve and showed its utility for predicting future detection of HCC. Repeated imaging examinations, such as computed tomography or ultrasonography, are recommended at 3-month intervals for patients at high risk for HCC, because the mean doubling time of HCC is known to be about 3 months. However, some investigators have expressed doubt regarding the value of such surveillance from the viewpoint of cost effectiveness. In our study, the detection rate of HCC during follow-up examinations in patients with a %AFP-L3 value of 5.75% or more in serum was significantly greater than that of those with a value lower than 5.75%. Our findings indicate that it is important to develop an improved surveillance protocol for high risk patients based on this highly sensitive %AFP-L3 data.

CONCLUSION

We examined the utility of %AFP-L3 as a tumor marker for HCC in patients with chronic liver disease and low AFP concentration (3-10 ng/dl). Our results suggest that this novel AFP-L3 assay is useful to detect HCC in patients at high risk for tumor development.