REVIEW ARTICLE

간세포암종 감시 검사에서 종양 표지자의 역할

임영석

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Role of Tumor Biomarkers in the Surveillance of Hepatocellular Carcinoma

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Biomarkers are key components of the clinical management of cancer patients because they have contributed to significant survival improvements in these patients. They allow the classification of patients based on common features and facilitate risk stratification, early detection, diagnosis, and prediction of the prognosis or treatment response. In hepatocellular carcinoma (HCC), there are few biomarkers incorporated in clinical practice. Despite this, this has been an extensive area of research in recent years, with increasing efforts to identify the biomarkers across the cancer care continuum from risk stratification to early detection to prognostication and treatment response. The heterogeneous nature of HCCs has restricted the performance of biomarkers. HCC biomarkers have limited roles in risk stratification, diagnosis, and treatment response. Currently, the main role of biomarkers is in the surveillance of HCC to detect it at an earlier stage and reduce mortality, which is the focus of this review. (*Korean J Gastroenterol* 2021;78:284-288)

Key Words: Biomarkers; Carcinoma, hepatocellular; Surveillance

INTRODUCTION

Biomarkers are key components of the clinical management of cancer patients because they have contributed significantly to survival improvements in these patients.¹ They allow the classification of patients based on common features and facilitate risk stratification, early detection, diagnosis, and prediction of prognosis or treatment response. Few biomarkers for hepatocellular carcinoma (HCC) have been incorporated into clinical practice despite this being an extensive area of research in recent years. Nevertheless, there

have been increasing efforts to identify biomarkers across the cancer care continuum from risk stratification to early detection to prognostication and the treatment response.

The performance of biomarkers is limited by the heterogeneous nature of HCCs. HCC biomarkers have limited roles in risk stratification, diagnosis, and treatment response. Currently, the main role of biomarkers is in the surveillance of HCC to detect the disease at an early stage and reduce mortality.

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THE NECESSITY OF HCC BIOMARKERS IN THE SURVEILLANCE

HCC is a major cause of cancer death worldwide.^{2,3} The incidence and mortality rates of HCC have remained relatively unchanged, reflecting a dismal prognosis.^{4,5} The prognosis of patients with HCC depends largely on the tumor stage, and curative treatments are available only for patients diagnosed at an early stage.^{6,7} Even for patients with early-stage HCC, the success of local ablation, the most cost-effective treatment for HCC,⁸ is often limited to a very early stage (a single lesion <2 cm),⁹⁻¹¹ highlighting the importance of surveillance to detect HCCs at a very early stage.

The current guidelines recommend regular ultrasonography (US) with or without serum AFP for the early detection of HCC in at-risk populations, based on the effectiveness of surveillance on decreasing mortality from HCC.^{12,13} Nevertheless, there is currently an unsatisfactory compilation of surveillance tools. In a meta-analysis, the sensitivity of US for the detection of early-stage HCC was only 47% in cirrhotic patients.¹⁴ The addition of AFP to US increased the sensitivity of detecting early-stage HCC significantly from 45% to 63%, which remains suboptimal. Further, the sensitivity of US to detect very early-stage HCC is only 18-28% in patients with cirrhosis.¹⁵⁻¹⁸ Accordingly, there is an anticipation of new biomarkers with higher performance and accuracy. Although strong consensus has not been reached, lectin-reactive AFP (AFP-L3) and des- γ -carboxy prothrombin (DCP, or prothrombin induced by vitamin K absence II [PIVKA II]) have been suggested to increase the surveillance performance of AFP.¹⁹⁻²¹

PHASES OF TUMOR BIOMARKER DEVELOPMENT

According to the National Cancer Institute's Early Detection Research Network (EDRN) guidelines, studies evaluating cancer biomarkers should be classified into five phases, similar to those used in drug discovery studies.^{22,23} Based on the EDRN definition, most studies reporting the performance of serologic biomarkers in HCC were phase 2 studies, i.e., case-control studies in patients with established HCC diagnoses.^{20,21} As a next step, a phase 3 study is needed to determine the ability of these biomarkers to detect pre-clinical disease using prospectively collected longitudinal

specimens from cohorts of at-risk patients. A biomarker phase 3 study helped eliminate potential biases, mainly inclusion and verification biases.^{23,24} On the other hand, few phase 3 studies have been conducted thus far because of the difficulty in maintaining a large cohort longitudinally; the only biomarker phase 3 study conducted for HCC was comprised only of HCV-infected patients.¹⁹

EDRN-defined biomarker phase 3 study analyzes biomarkers using longitudinally collected serum samples from prospective studies.²³ By adopting this study design, biases prevalent in case-control studies can theoretically be minimized because the samples had been prospectively collected according to the pre-defined protocol of each study rather than by the physicians' request. The prospective collection of specimens and data in a phase 3 study will eliminate potential biases because the HCC status will be unknown at the time of specimen and data collection.

Very few EDRN phase 3 biomarker studies for HCC surveillance have been conducted to date. A previous study included only patients with HCV-related cirrhosis and analyzed only two biomarkers (AFP and DCP) using samples collected prospectively from a hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) trial.¹⁹ Two other phase 3/4 biomarker studies are ongoing in cirrhotic patients, mainly with a HCV infection. According to their interim analysis, the use of serum biomarkers resulted in considerable improvement in sensitivity for HCC detection at an early stage, despite the increasing the false positive rate.^{25,26}

CHANGES IN THE OPTIMAL CUTOFF VALUE OF BIOMARKERS BY ANTIVIRAL TREATMENTS

The majority of the patients with chronic HBV or HCV infection who have a risk of HCC development are under antiviral treatments. Therefore, most have normal ALT levels, which minimizes the false elevation of the biomarkers due to active hepatitis or cirrhosis.^{27,28} Hence, changes in biomarkers may be reflected mainly by the presence of a tumor. For these reasons, in the era of potent antiviral treatment for HBV and HCV, a lower AFP threshold may be justified for HCC surveillance. Profound suppression of viral replication induces the normalization of the ALT levels in most patients and reduces the possibility of false elevation of tumor bio-

markers,^{29,30} which may justify lowering the optimal cutoffs of the biomarkers to ensure high sensitivity in the setting of a HCC surveillance program, particularly to detect very early-stage HCC.

These points may be related to the lower optimal cutoff value of AFP than previously suggested by Asia-Pacific guidelines of HCC (200 ng/mL)³¹ or Practice Guidance by the American Association for the Study of Liver Diseases (20 ng/mL).³² A previous study suggested 6 ng/mL as the optimal cutoff value of AFP in virally-suppressed CHB patients in Hong Kong.³³ A recent study also suggested 5 ng/mL as the optimal cutoff value for AFP in the surveillance of HCC.³⁴ On the other hand, applying the lower cutoff value of AFP has not been well studied in patients with cirrhosis of non-viral hepatitis, such as alcoholic or non-alcoholic steatohepatitis. Moreover, lowering the cutoff value of AFP may inevitably increase the false-positive rate. Hence, its cost-effectiveness should be further clarified.

RATE OF AFP CHANGE

In clinical practice, clinicians are more concerned about consistently up-trending AFP than one isolated elevation of AFP. Previous studies reported that incorporating the rate of AFP changes (delta AFP) over time during surveillance might predict HCC more accurately than using a single threshold of AFP.³⁵⁻³⁷ The authors' study also confirmed that the standard deviation and rate of increase in AFP were independently associated with identifying HCC cases from the controls.³⁴ Therefore, incorporating the rate of AFP changes (delta AFP) over time or using different cutoff values of AFP according to the liver disease etiology during HCC surveillance may lower the false positivity.

COMBINED ROLE OF AFP, AFP-L3, AND PIVKA-II IN HCC SURVEILLANCE

Despite criticism, AFP was reported to have additional value to US, significantly increasing the sensitivity of detecting early-stage HCC from 47% to 63% by a recent meta-analysis.¹⁴ Furthermore, no better biomarker than AFP has been identified for HCC surveillance to date.

In the present phase 3 biomarker study,³⁴ including predominantly patients who had HBV-related cirrhosis with sup-

pressed viral loads and normal ALT levels, most cases (74%) had very-early stage HCC (single lesion <2 cm) at diagnosis. AFP exhibits the best performance as a single biomarker in differentiating HCC from the controls, with an AUC of 0.77 at the diagnosis of HCC. In addition, AFP and AFP-L3 began to increase from six months before HCC diagnosis, while they remained unchanged in the controls. New novel cutoff values for AFP (5 ng/mL), AFP-L3 (4%), and DCP (20 mAU/mL) were suggested to discriminate HCC cases from controls. AFP had the best performance in discriminating HCC cases from controls, and the combination of AFP and AFP-L3 showed better performance than AFP alone. By contrast, DCP had limited additional value in improving the surveillance performance. These data suggest that AFP-L3 may serve as a supplementary test for AFP to improve the effectiveness of surveillance for HCC. Similar to the meta-analysis,¹⁴ the sensitivity of US in the present study was 48.6%, which was increased considerably to 88.6% by the addition of AFP and 94.3% by addition of AFP+AFP-L3, without decreasing specificity significantly (from 96.4% to 82.7%) when using a cutoff of 5 ng/mL for AFP and 4% for AFP-L3. When combined with AFP, AFP-L3 increased the detection sensitivity significantly from 62% (AFP alone) to 79% (AFP and AFP-L3) without sacrificing the specificity.

A previous study reported that DCP has lower performance in small HCC. DCP had a better performance in intermediate and advanced HCC, which is the goal of HCC surveillance, compared to that of AFP.³⁸ In the present study, the triple combination of biomarkers including AFP, AFP-L3, and DCP showed slightly better performance than a dual combination of AFP and AFP-L3 (AUROC at month 0, 0.86 vs. 0.83). On the other hand, DCP has been investigated in many studies for the detection of early-stage HCC^{19,20,39} and is being used widely. Moreover, the combined testing of AFP, AFP-L3, and DCP are being recommended by clinical practice guidelines in Japan and China.⁴⁰⁻⁴² Therefore, other EDRN phase 3 studies will be needed to provide evidence for the utility of DCP in detecting very early-stage HCC in a surveillance program.

CONCLUSIONS

The prognosis of patients with HCC largely depends on the tumor stage, and curative treatments are available only for patients diagnosed when the cancer is at a very early stage

(a single lesion <2 cm). Therefore, the goal of HCC surveillance is to detect HCCs at a very early stage.

In the surveillance for HCC, sensitivity may have a higher priority than specificity because a late diagnosis of HCC may render it incurable. Therefore, although sensitivity offsets specificity, efforts to enhance sensitivity should be considered in the surveillance of HCC. Profound suppression of viral replication normalizes the ALT levels in most patients at risk of HCC with chronic HBV or HCV infections and reduces the possibility of a false elevation of tumor biomarkers. These points may justify lowering the optimal cutoffs of the biomarkers to ensure high sensitivity in a HCC surveillance program setting, particularly to detect very early-stage HCC.

The combination of AFP (cutoff 5 ng/mL), AFP-L3 (cutoff 4%), and DCP (cutoff 20 mAU/mL) showed better performance for the detection of HCC at a very early stage than single biomarkers. Until new biomarkers with higher performance in detecting HCC can be found, AFP may still have a role in the surveillance of HCC, and AFP-L3 and DCP could be used as supplementary tests to AFP in conjunction with imaging tests.

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