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ORIGINAL ARTICLE

Value of MRI apparent diffusion coefficient for assessment of response to sorafenib in hepatocellular carcinoma

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Summary

Purpose: *Efficient and adequate evaluation of therapeutic response in hepatocellular carcinoma (HCC) is an evolving field. We aimed to evaluate apparent diffusion coefficient (ADC) values in the prediction of response to sorafenib and prognosis in patients with advanced HCC.*

Methods: *Baseline magnetic resonance (MR) imaging was performed before treatment. After sorafenib started, clinical and radiological response were evaluated at approximately 3 months later. ADC measurements were performed by a 12-year experienced radiologist who evaluated MR before and after sorafenib therapy.*

Results: *A total of 17 patients (median age 60 years, range 51-66 and M/F ratio=3.25/1) were analyzed. A significant increase in ADC levels in responders was observed 3 months after sorafenib therapy. Baseline and post-sorafenib ADC values were not significantly associated with mortality (hazard ratio/HR baseline ADC=1.003, p=0.98) and after sorafenib (HR 0.480, p=0.48, respectively).*

Conclusion: *Advanced HCC patients with a favorable response to sorafenib had a significant increase in ADC value at the first radiological evaluation. The predictive and prognostic role of ADC for overall survival is still unknown and further research is needed to investigate any possible association.*

Key words: *ADC, HCC, monitoring response, sorafenib*

Introduction

Hepatocellular carcinoma (HCC) is an aggressive and relatively chemotherapy-resistant tumor. Palliative chemotherapy is not been used in patients with advanced stage HCC [1]. The antineoplastic agent sorafenib, which acts as cytostatic rather than cytotoxic via the mechanism of tyrosine kinase and vascular endothelial growth factor (VEGF) inhibition, is the standard treatment for advanced stage HCC. On the other hand, treatment response to systemic therapy is being assessed by radiologic imaging using response criteria such as the modified Response Evaluation Criteria (mRECIST) for HCC [2]. Histological response changes to sorafenib may initially be manifested as an enlarging rather than shrinking lesion(s) [1]. Therefore, reduction in viable tumor burden in sorafenib treatment may be more accurate with dynamic tests and the efficient and adequate evaluation of response in HCC is an evolving field.

Diffusion weighted MR imaging (DW-MRI) has emerged as a non-invasive sequence which works on the microscopic motion of water in tissue. Highly cellular tumors are associated with more restriction of motion of water molecules

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and hence ADC values are considerably lower in malignant lesions [3]. ADC changes in response to treatment may be a valuable predictive marker to assess the treatment efficacy. Faster and more accurate radiological assessment could help the physician to manage the patient on sorafenib treatment.

The present study investigated whether changes in ADC values between baseline and after sorafenib treatment could be a valuable marker to evaluate sorafenib response in patients with HCC.

Methods

Study design

This was a retrospective descriptive study which was approved by our institutional review board. A total of 24 biopsy-proven and treatment-naive HCC patients were evaluated. Among them, 7 patients were excluded because their MR imagings were unsuitable for ADC measurement. Seventeen patients had MR imaging with DWI sequences both before and 3 months after sorafenib therapy. Sorafenib has been used orally 400 mg twice daily and continued until no longer clinically benefiting or until unacceptable toxicity.

Clinical data were obtained from the patient files. In addition, radiological response assessment according to mRECIST was based on the following criteria: Complete response: absence of enhanced areas in all target lesions; Partial response: at least 30% reduction in the sum of viable target lesion(s) from those of baseline; Progressive disease: at least 20% increase in the sum of the diameters of viable target lesions, taking as a reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started; and Stable disease: less than 30% reduction or less than 20% increase from baseline [4].

Accordingly, 11 patients were classified as responders (partial response:2 and stable disease: 9), and 6 patients as non-responders.

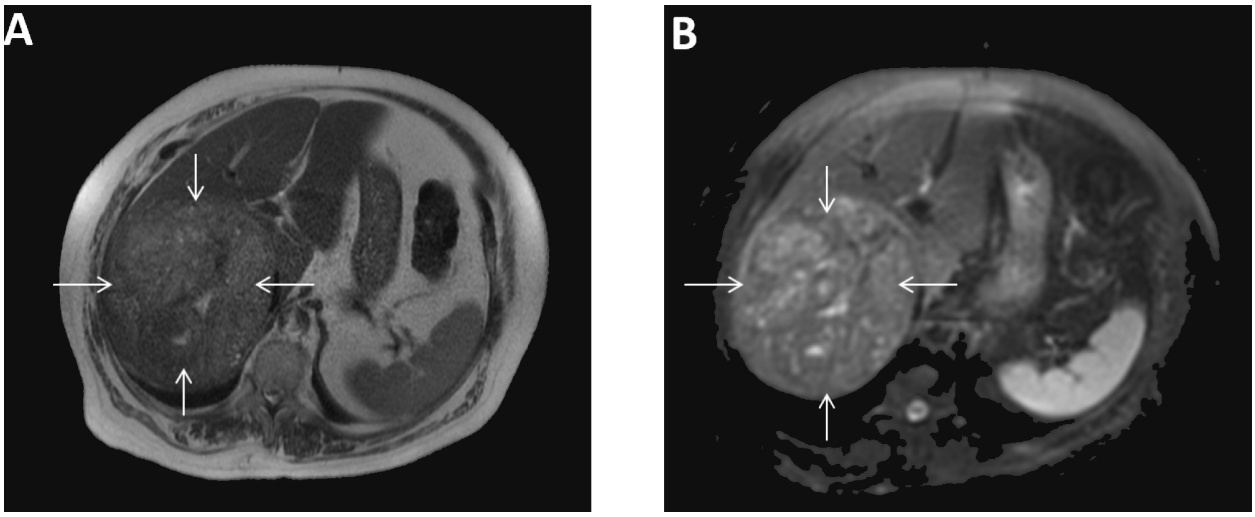

Figure 1. Axial T2 **(A)** and diffusion **(B)** weighted images show that HCC (arrows) is more hyperintense than normal liver parenchyma.

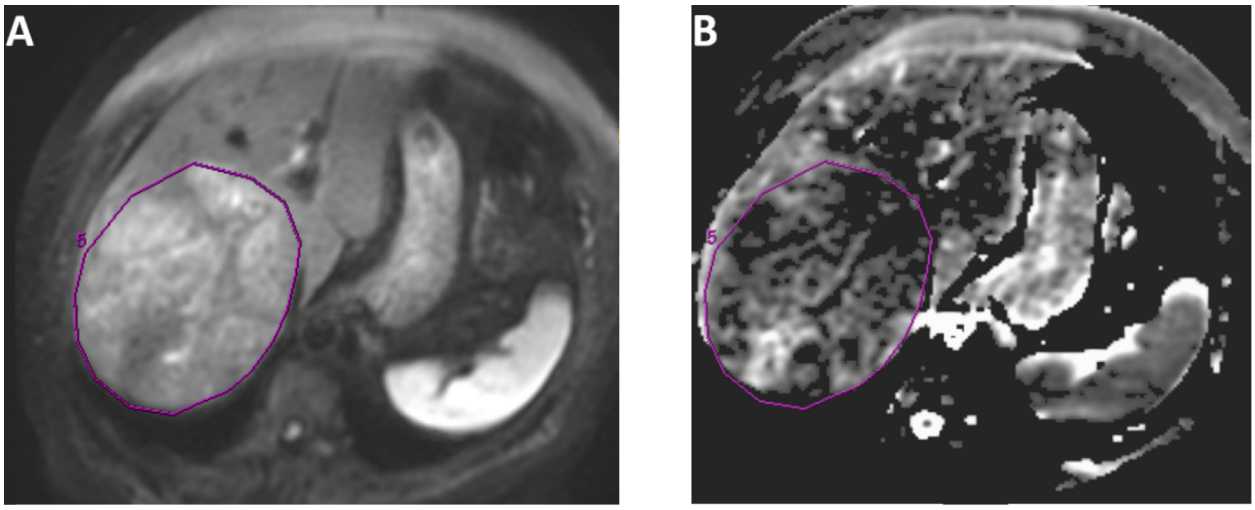

Figure 2. Regions of interest before sorafenib treatment are shown by DWI **(A)** and ADC **(B)** images.

MR imaging

Baseline MR imaging was performed before treatment. After sorafenib started, clinical and radiological response were evaluated at approximately 3 months later (median 3; min.-max: 2-4). MR imaging was obtained using a 1.5 T device (Signa HDxt Excite II; GE Medical Systems, Waukesha, U.S.A) and an 8-channel body coil. T2WI was taken on axial and coronal planes as fast spin echo (TR/TE: 3440/87 ms; slice thickness: 10 mm; FOV: 430 mm, matrix: 256x256, NEX:2). For DWI, axial single-shot spin-echo echo planar imaging sequences were performed (TR/TE: 4000/83 ms; slice thickness: 5 mm; FOV: 430 mm; matrix: 256x256, NEX: 4, b value: 200 s/mm^2). The DWI was set up in accordance with the previous T2WI, angled to be perpendicular to the tumor. The ADC map was generated automatically. T2WI and DWI images before and after treatment were analyzed to determine the tumor (More hyper intense than normal liver parenchyma; Figure 1). Due to the higher resolution of the DWI images relative to the ADC maps, the regions of interest (ROIs) were manually placed in the DWI images and copied to the ADC maps. Post-treatment measurements were made by placing the primary tumor in the ROI measurement area at the beginning of treatment (Figure 2). ADC measurements were performed by a 12-year experienced radiologist in the post-radiological evaluation of MR imaging before and after sorafenib therapy. The ADC measurement was made by surrounding the outline of the single section, which was the largest of the tumors. ADC measurements were performed before and after sorafenib treatment. The ROI area ranged from 80 mm^2 to 14522 mm^2 (median, 952).

Table 1. Patient and disease characteristics

Characteristics	*n (%)*
Age, years	
Median (Interquartile range)	60 (51-66)
Gender	
Male/Female	13/4
Risk factors	
Chronic liver disease	6 (35.2)
HBV	9 (52.9)
HCV	1 (5.8)
Alcohol abuse	5 (29.4)
Diabetes mellitus	4 (23.5)
Obesity	2 (11.7)
Clinical outcome	
Responders	11 (64.7)
Non-responders	6 (35.3)
Histological classification	
Well-differentiated	13 (76.6)
Undifferentiated	3 (17.6)
Spindle cell variant	1 (5.8)
Tumor type	
Nodular	15 (88.3)
Infiltrative	2 (11.7)
Tumor size, cm	
Multiple, ≤ 5	13 (76.6)
>5	4 (23.4)
Tumor localization	
Liver only	10 (58.8)
Extrahepatic involvement	7 (41.2)
Eastern Cooperative Oncology Group status	
0	7 (41.2)
1	6 (35.4)
2	4 (23.4)

Statistics

Statistical analyses were performed using SPSS software, version 22 (Chicago, IL, USA). Data were presented as mean±standard deviation or median and interquartile ranges, as appropriate. Categorical variables were reported as frequencies and group percentages. Differences in ADC values between responders and non-responders were evaluated by Mann– Whitney U-test. The Wilcoxon signed-rank test was used to compare changes in ADC values between baseline and 3 months after sorafenib. A p value less than 0.05 was considered as statistically significant.

Results

Patient demographics and baseline clinical characteristics

Table 1 shows the baseline clinical characteristics of the patients with advanced HCC. The median age was 60 years (51-66) and men were more affected than women (3.25:1). Hepatitis B virus as positive in about half of the patients with HCC. All diagnoses were confirmed with biopsy and 76.6% of them showed well-differentiated disease. Nodular tumor type prevailed compared to infiltrative disease (88.3 vs 11.7%, respectively), and size was multiple and less than 5 cm. ECOG performance status of all patients ranged between 0 and 2 and 10 patients had only liver localized disease.

Change in baseline tumor diameter and ADC scores during the study period

Baseline ADC values were similar in both groups. A significant increase in ADC levels in responders was observed 3 months after sorafenib therapy, whereas ADC values of nonresponders did not change significantly (p=0.003 and p=0.91, respectively; Figure 3). Table 2 shows that change (Δ ADC) in ADC values between baseline and the third month comparison of the follow-up was significant only in patients with the favourable response (p=0.03).

Table 3 shows that the change in mean diameter of the lesion between baseline and after 3

months of sorafenib therapy were similar between both groups (p>0.05, for all).

Median overall survival (OS) was 8.0 months (95% CI=6.4-9.6) in all patients. Median OS was 10.0 months (95% CI=2.7-17.2) in responders and 4.0 months (95% CI=0.4-7.6) in nonresponders (p=0.04). Moreover, median OS was 8 months (95% CI=4.5-11.5) in patients with increased ADC value and 4 (95% CI=0.9-7.9) in patients with non-increased ADC value (p=0.39). In univariate analysis, baseline and after sorafenib treatment ADC values were not significantly associated with mortality (HR baseline ADC=1.003, p=0.98 and HR after sorafenib=0.480, p=0.48, respectively).

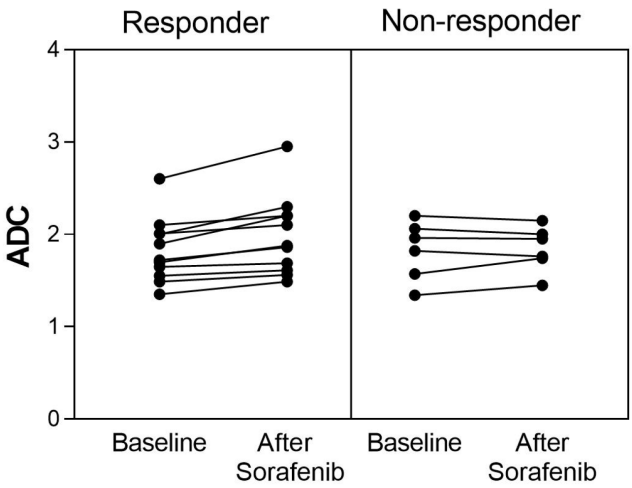

Figure 3. ADC change in responder and non-responder groups. ADC values increased in the responder's group after sorafenib treatment, but ADC values mostly remained unchanged in non-responder's group.

Discussion

New treatment modalities with molecularly targeted drugs do not always cause a decrease in tumor volume. ADC measurement with DW-MRI is sensitive to changes occurring at the molecular level. Our study revealed that advanced HCC patients with a favorable response to sorafenib had a significant increase in ADC value at the first radiological evaluation. Second, change in the lesions' diameter was not significant between baseline and after 3 months of sorafenib therapy. In addition, baseline ADC value had no any predictive outcome for both prognosis and response to sorafenib.

HCC constitutes 85-90% of all primary liver cancers [5]. Viral hepatitis and cirrhosis are the major causes of the disease. On the other hand, HCC has high molecular heterogeneity associated with multiple drug resistance. So, conventional chemotherapy is less effective than molecularly targeted drugs. More than 100 randomized clinical trials showed that conventional chemotherapy and other systemic treatments failed, whereas only sorafenib emerged as standard therapy with survival advantage in advanced HCC treatment [6-8].

Sorafenib is a multi-tyrosine kinase inhibitor (up to 40, VEGFR, PDGFR, BRAF etc.) and targets angiogenesis and proliferation [9,10]. The SHARP trial demonstrated that sorafenib is effective in prolonging median OS from 7.9 to 10.7 months with easily manageable side effect profile [6]. We showed that overall survival was significantly higher (10.0 months, 95% CI=2.7-17.2) in the responders' group rather than in nonrespond-

Table 2. Change in ADC values between baseline and after sorafenib therapy (mean±SD)

	Responders	*Non-responders*	*p value*
Baseline ADC, mm²/sec	1.83±0.36	1.82±0.32	0.98
ADC after sorafenib, mm²/sec	1.98±0.42	1.84±0.24	0.46
Percentage of ADC change , %	8.50±4.80	1.67±6.20	0.04
p value	0.003	0.91	

Table 3. Change in diameter of lesions between baseline and after sorafenib therapy (mean±SD)

	Responders	*Non-responders*	*p value*
Baseline mean diameter, cm	7.4±4.5	7.9±3.2	0.85
Diameter after sorafenib, cm	7.2±4.3	8.2±3.3	0.76
Change in mean diameter			
Δ diameter value, cm	-0.2±0.5	0.2±0.3	0.16
p value	0.22	0.16	

ers' group (4.0 months, 95% CI=0.4 - 7.6; p=0.04). Moreover, grade 3 or 4 toxicity was not observed in any study subjects.

Dimensional tumor response measurements can be falacious when applied to molecular targeting therapies in advanced HCC. Due to its cytostatic effect, sorafenib therapy may not result in a dimensional reduction in target lesions [11]. Therefore, modified RECIST criteria for measuring treatment response based on the viable tumor load provides more accurate information rather than the standard RECIST based on the dimensional change and tumor shrinkage of the target lesion in patients with HCC [11]. In our study, the dimensional change of the target lesions in the responders' group was similar to those in the nonresponders' group. We believe that sorafenib efficacy in HCC lesions should be considered by measuring tumor viability rather than imaging using conventional response criteria.

DWI is based on the measurement of water diffusion and can provide tumor viability on tissue microstructure [11]. The increased ADC response to conventional chemotherapy or radiation has been linked to increased tissue necrosis. ADC changes after conventional therapy were shown in different malignancies. First, Hao et al. showed that post-treatment ADC increase was significantly associated with favorable response to neoadjuvant chemoradiotherapy in esophageal squamous cell cancer [12]. In addition, Blazic et al. reported that post-treatment ADC measurements and increased ADC change showed excellent performance in rectal cancer response to neoadjuvant combined chemotherapy and radiation therapy [13]. Recently, a meta-analysis has demonstrated that correlation between ADC and cellularity is different in several tumors [14]. It was weak in lymphomas, weak-to-moderate in breast cancer and meningiomas, moderate in most investigated epithelial tumors, and strong in gliomas, ovarian cancer, and lung cancer. Presumably, not only cell count, but also other histopathological features, such as extracellular matrix, nucleic areas, ratio stroma/parenchyma, and/or microvessel density may play a role here [14]. However, there was no sufficient data about the association between ADC and HCC.

Previous studies about tumor ADC changes after sorafenib therapy in patients with HCC showed a decrease in ADC in the early phase of therapy. Firstly, Schraml et al. revealed that baseline ADC values were decreased after 2-4 weeks of sorafenib treatment [15]. The reduction in ADC values is thought to be the result of the ischemic environment caused by the effect of the angiogenesis inhibitor drug. Then after 3 months, it was shown that patients with re-increased ADC values had treatment-responsive groups. Especially, it is also noteworthy that patients with long-term (> 3 months) ADC values continued to decline in the nonresponder group. Zhao et al. showed that histological changes (necrotic areas) as response to sorafenib presented with ADC increment in a mice model [16]. Moreover, Lewin et al. revealed that lesion sizes and ADC values did not significantly alter during treatment [17]. Recently, Chen et al. suggested that multiparametric DWI can serve as imaging biomarker for ultra-early evaluation of treatment response to sorafenib in HCC as early as 1 hr in HCC xenografts [18]. Kim et al. reported that ADC changes in response to sorafenib only were found to be increased in a small (5 patients) HCC group [19]. On the other hand, Vouche et al. did not find significant ADC change in 7 HCC patients treated together with sorafenib and radioembolization [20]. We thought that the cytostatic effect of sorafenib on tissue may cause intratumoral histological changes by inhibition of angiogenesis resulting ischemia/hypoxia and later necrotic area and these histopathological changes are presented as ADC increase in DW imaging. It is a fact that there is not any accepted clinical and/or radiological predictive marker of sorafenib response. We suggest that intratumoral ADC changes adding to conventional MRI measurement to assess the tumor viability by using DW imaging technique can be a potentially valuable marker to evaluate the clinical efficacy of angiogenesis-targeting agents. Especially, unchanged or constant decrease in ADC values may be a potential marker to show tumor progression in long-term follow-up (> 2-3 months).

Data on the prognostic value of ADC is controversial. Giganti et al. reported ADC as a sole biomarker for staging and prognosis of gastric cancer [21] and Lambrecht et al. demonstrated that baseline ADC value is a prognostic factor in head and neck squamous cell carcinoma [22]. However, no sufficient data exists about the predictive and prognostic value of ADC in patients with HCC. We found that pre- and post-treatment ADC is not a predictive marker for mortality.

There are several limitations in our study. A major limitation is ADC increase, detected after 3 months of sorafenib, was not pathologically confirmed. Histopathological changes after sorafenib may enlighten the degree of correlation between ADC change and HCC in response to sorafenib. ADC is strongly subjected to measurement error and could be measured by more than one radiologist with different methods. Other limitations include the small number of patients and the retrospective nature of data collection.

Conclusion

The potential clinical use of ADC change may be a valuable and early predictive radiological marker to monitor sorafenib response in patients with advanced HCC. The predictive and prognostic role of ADC for overall survival is still unknown and further research is needed to investigate any possible association.

Conflict of interests

The authors declare no conflict of interests.

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