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Case Report

Tumor Shrinkage in Response to Vitamin K2 in Hepatocellular Carcinoma with Multiple Lung Metastases: A Case Report

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Abstract

Introduction: Advanced or metastatic hepatocellular carcinoma (HCC) can be lethal because of the limited therapeutic approach such as sorafenib. Recently, Vitamin K2 (VK2) has been increasingly recognized to have anti-cancer effects for HCC in *vitro* and *vivo*. However, the direct anti-cancer effect of VK2 to HCC has not been established yet in human.

Presentation of Case: We presented here a 88-year-HCC patient displayed a tumor shrinkage in response to VK2 in multiple lung metastases, indicating the possibility of VK2 as an anti-cancer agent in human. Menatetrenone, a VK2 analogue, was introduced for multiple lung metastases as a palliative treatment, and thereafter multiple lung metastases, except one lung lesion, displayed tumor shrinkage and disappeared within five months after VK2 intake. The residual one lesion continued to grow up during the intake of VK2, suggesting that the residual tumor was insensitive to VK2 represented by tumor heterogeneity. Consequently, after a radiation therapy for the residual lesion, the elevated tumor markers of all were finally decreased into normal levels, and he is still alive for 18 months after VK2 intake without elevated tumor marker levels and toxic adverse effects.

Conclusion:VK2 may be a therapeutic option for advanced and metastatic HCCs without any toxic adverse.

Keywords: hepatocellular carcinoma; vitamin K;menatetrenone

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Consent: We confirm that family members of the patients have given their informed consents for the case report to be published.

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Introduction

Advanced or metastatic hepatocellular carcinoma (HCC) can be lethal cause of the limited therapeutic approach such as sorafenib. Sorafenib is an oral multikinase inhibitor with anti-proliferative and anti-angiogenic effects and is worldwidely used for the treatment of advanced or metastatic HCC. While two phase-3 randomized double-blind controlled trials (SHARP and Asia-Pacific studies) demonstrated statistically significant improvement in overall survival and in time to disease progression in patients with advanced HCC, the overall incidence of treatment-emergent (drug- or non-drug related) adverse events of any grade has been reported to be up to 81.9%~97.2%[1, 2].Although the most of sorafenib-associated adverse effects are mild to moderate, and tolerable[2, 3], overall incidence of drug-related severe adverse events was up to 8.7%[1, 2]. Therefore, an induction of sorafenib in elderly patients more than 80 year-old is unlikely to be feasible. These adverse effects often disturbthe induction of sorafenib, which leads in a palliative treatment especially in elderly patients. Recently, Vitamin K2 (VK2) has been increasingly recognized to have anti-cancer effects for HCC without any toxic effect.VK2 or menatetrenone, a VK2 analogue, have been reported to suppress cell growth in HCC in vitro and in vivo[4-7]. Furthermore, VK2 has also been reported to synergically enhance the 5-fluorouracil- or sorafenib-induced growth inhibition for HCC in *vitro* and in vivo[8, 9].Thus, accumulating evidence has pointed towards anti-cancer agent for VK2 in HCC, which suggests that VK2 may be non-toxic and alterative therapeutic approach beyond the ineffective in sorafenib. However, its anti-cancer effect in human HCC is still unclear. For examples, the preventable effect by VK2 intake in HCC patients after curative hepatectomy is still controversial[10]. The Five randomized control trials evaluated the preventive efficacy of menatetrenone on HCC recurrence after hepatic resection or local ablative therapy, and the meta-analysis of all five studies failed to confirm thebeneficial effect on the overall survival, suggesting a large, higher quality randomized controlled trials are still required[11]. Thus, the direct anti-cancer effect of VK2 to HCC has not been established yet in human, we presented here a 88-year-elderly HCC patient displayed a dramatic anti-cancer effect by intake of VK2 for extrahepatic multiple lung metastases.

Case presentation

A 88-year-old man, with hepatitis C viral (HCV),was diagnosed as a primary HCC(27mm in size) on segment 6/7 with elevated tumor markers [50 mAU/ml in des-gamma carboxyprothrombin,7045 ng/ml in alpha-fetoprotein (AFP), and 3.6% in lectin-reactive alpha-fetoprotein (L3%)],and then was treated with transchemo-embolization twice in October 2011 and June 2012 in our institute (**Figure 1**). Three months later, a radiation therapy with total 45Gy was introduced for a residual viable lesion with invasion into right hepatic vein until October 2012, and then thereafter there was no viable lesion in the liver. Four months later post-radiation, multiple lung metastases appeared. Thereafter, multiple lung metastases increased in number and size, and the AFP (L3%) level was elevated from 401 (2.8%)ng/ml into 615 (2.5%) ng/ml during one month, suggesting those lung lesions were malignant. Although his liver reserved function was Child-Pugh Class A, he and his

family were not desired to treat with sorafenib due to his advanced age, and then he started to take a menatetrenone(45mg/day)as a palliative therapy. Thereafter, tumor markers including des-gamma carboxyprothrombinand AFP (L3%)showed considerable decrease from 198 mAU/ml and 615 (2.5%) ng/ml into 16 mAU/ml and 36.3 (1.8%) ng/ml within five months after the intake, respectively. Multiple lung metastases also displayed tumor shrinkage day by day, and they disappeared within five months after VK2 intake, except one lung lesion insensitive to VK2 (**Figure 2**). The residual lung lesion revealed a growth up even after VK2 intake, and AFP (L3%) levels eventually turned into an elevation up to 198(5.1%) ng/ml. We introduced a radiation therapy for the residual lung tumor, and the elevated AFP (L3%) finally decreased into within normal level of 2.2 (< 0.5) ng/ml. He is still alive for 18 months after VK2 intake without elevated tumor marker levels and toxic adverse effects.

Figure 1.

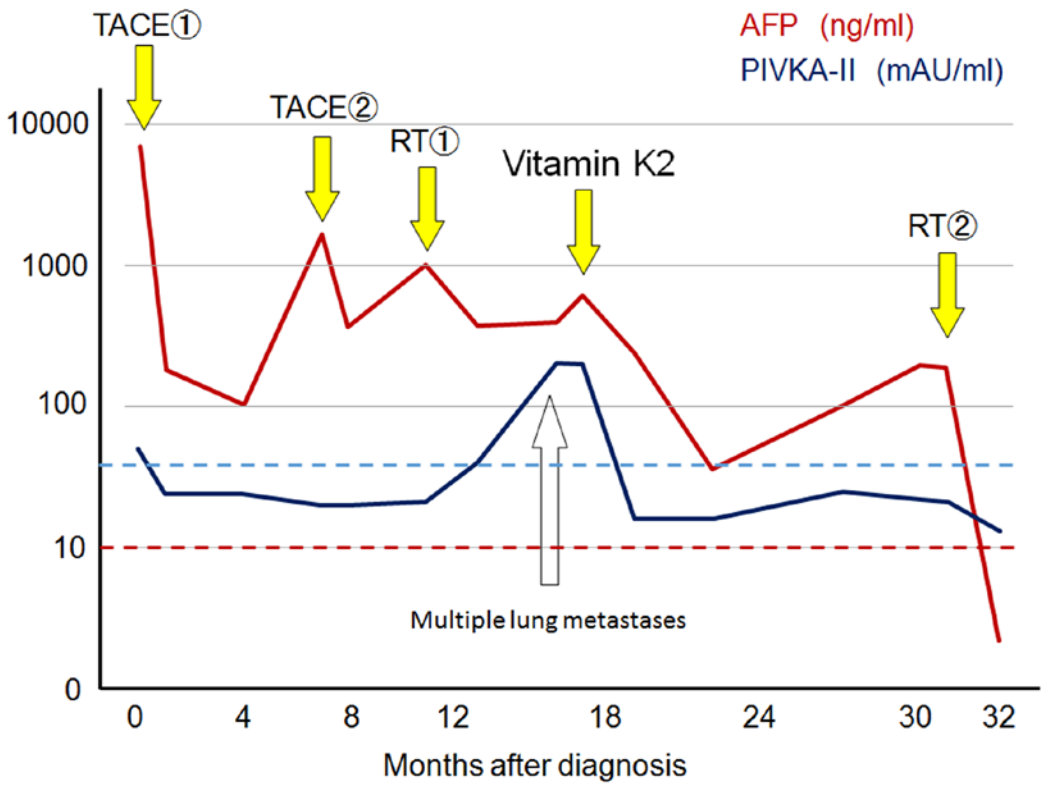

Figure 1 Changes in tumor markers (AFP and PIVKA-II) in response to various treatments.

TACE①, first transchemo-embolization for S6/7 HCC; TACE②, second transchemo-embolization for residual viable HCC in S6/7 tumor; RT①, radiation therapy for residual viable HCC in S6/7 tumor with hepatic venous invasion; RT②, radiation therapy for the residual one lung lesion, which was insensitive for vitamin K2.Dot lines reveals upper limit each of tumor markers.

Figure 2.

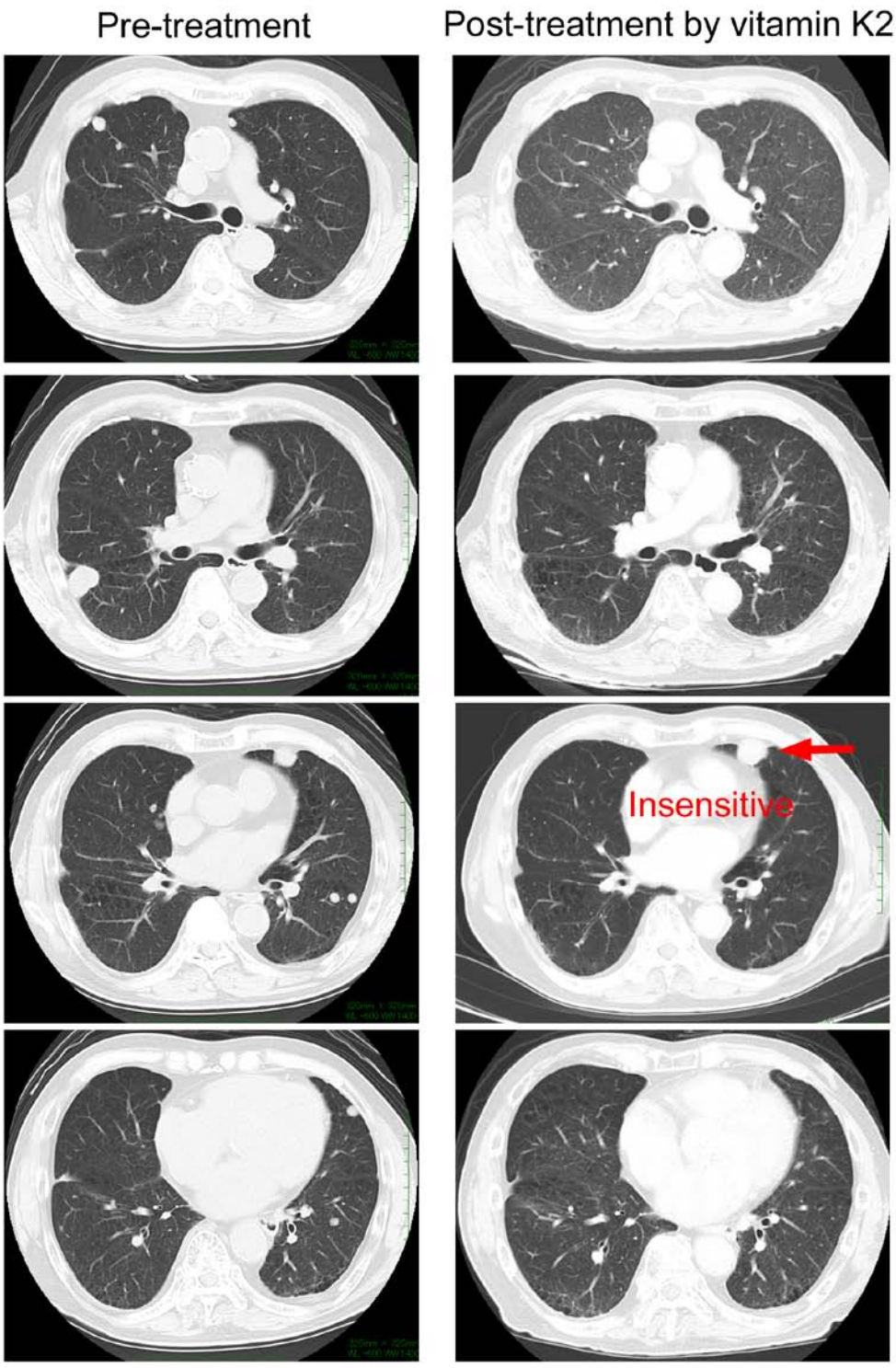

Figure 2 Multiple lung metastases before and after treatment with vitamin K2.

Discussion

Here, we experienced an oldest-old patient with complete tumor shrinkage in response to VK2 in multiple lung metastatic HCCs except one lung lesion, which was finally well controlled by radiation therapy. In this case, VK2successfully not only inhibited the tumor growth, but also abolished the multiple lung metastases (more than twenty lesions). During five months after the intake of VK2, the lung metastatic lesions disappeared except one lesion. The decreased tumor marker level of AFP confirmed anti-cancer effect by the intake of VK2. Indeed, VK2 has been reported to induce the cell cycle arrest at the G1 phase and involvement of apoptosis in *vitro* because the sub-G1 fraction appeared in flow cytometric analysis and nuclear condensation and fragmentation appeared after VK2 treatment [5]. On the other hand, VK2-induced growth inhibitory effect has been suggested to be elective as VK2 inhibited growth of Hep3B, but not of HepG2, HLF, and Huh6 in *vitro*[5]. Also in this case, the residual one lesion continued to grow up during the intake of VK2, suggesting that the residual tumor was insensitive to VK2represented by tumor heterogeneity. Consequently, after a radiation therapy for the residual lung metastatic lesion, the elevated tumor markers of all were finally decreased into normal levels. Fortunately, although a majority of metastatic lesions was sensitive for VK2 in this case, it was still unknown which type of HCC was sensitive for VK2 in human. To elucidate the sensitive cases for VK2 treatment, a further experimental and clinical studies are required.

The limitation of the present report was that it was difficult to totally eliminate the possibility of natural tumor shrinkage in multiple lung metastatic lesions. In this case, multiple lung metastatic lesions displayed the increased number and size with the increasing AFP level during one month between the initial diagnosis of lung metastases and the intake of VK2. These findings strongly suggested the tumor shrinkage in response to VK2 rather than natural tumor shrinkage.

Conclusion

We experienced a case with the direct anti-cancer effect of VK2 to HCC.VK2may be a therapeutic option for advanced and metastatic HCCs without any toxic adverse effect especially in elderly patients or patients who were in-effective for sorafenib.

Abbreviations

HCC, hepatocellular carcinoma; VK2; vitamin K2, HCV, hepatitis C viral, AFP; alpha-fetoprotein

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