Hepatocellular Carcinoma with Peritoneal Dissemination which was Regressed during Vitamin K2 and Vitamin E Administration

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Abstract

A 65-year-old man with positive anti-hepatitis C antibody and chronic renal failure was diagnosed as having a ruptured hepatocellular carcinoma (HCC) based on computed tomography (CT). The patient underwent transcatheter arterial embolization (TAE) for the HCC. After one more session of TAE, the patient underwent surgery. But HCC seeding peritoneally was pointed out. Vitamin K2 and vitamin E were administered as a conservative treatment. Six months after starting vitamins K2 and E, the primary tumor did not increase in size and intraperitoneal dissemination disappeared on CT with a significant decrease of alpha-fetoprotein. Even though this is only one case, combination therapy of vitamin K2 and E may induce growth suppression of HCC.

Key words: hepatocellular carcinoma, vitamin K2, vitamin E

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Introduction

Hepatocellular carcinoma (HCC) is a common malignancy in Japan and the diagnosis and treatment of HCC has progressed (1). Although curative treatment is available and the survival of patients with an early stage of HCC increases, curative treatment is difficult and the prognosis is poor at advanced stage of HCC. Even in the patients with advanced stage HCC, intraperitoneal dissemination of HCC is rare (2). Ruptured HCC increases the risk of abdominal dissemination and the prognosis of patients with ruptured HCC is usually worse than that of non-ruptured HCC (3, 4). Thus, abdominal dissemination of HCC is considered in a terminal stage (2).

Vitamin K2 is known to inhibit the growth of a variety of tumor cell lines by inducing apoptosis or differentiation (5, 6). Vitamin K2 was recently used for the treatment of several human cancers including myelodysplastic syndrome (5). Vitamin E is also known to be an apoptotic agent for tumor cells and prevents hepatocarcinogenesis in animal models (7, 8). It is reported that administration of vitamin E for patients with liver cirrhosis and hepatitis C virus (HCV) infection resulted in a lower rate of development of HCC and a higher cumulative survival without development of HCC (8).

In this report, we present a case of regression of peritoneal dissemination in HCC during the administration of vitamin K2 and vitamin E.

Case Report

A 65-year-old man was referred to Tone Chuo Hospital for the diagnosis and treatment of a liver tumor in October 2004. The patient had received hemodialysis since 1995 in
Figure 1. Demonstration of hepatocellular carcinoma (HCC) by enhanced computed tomography (CT). A: CT shows a HCC measuring 3 cm in diameter at segment 4 of the liver (arrow) and high-density ascites (arrowhead). B: CT shows a HCC with lipiodol deposition (arrow) and a large amount of ascites soon after the operation. C: CT shows a HCC with lipiodol deposition (arrow) and decreased ascites 6 months after the administration of vitamins K2 and E (C). The size of the HCC did not change in 6 months.

another hospital. There was no history of alcohol abuse or smoking. The patient received blood transfusion due to a wound in 1964. Laboratory tests showed hemoglobin (Hb), 8.2 g/dL, white blood cell count (WBC), 7,500/mm³, platelet count (PLT), 143,000/mm³, total bilirubin (T-BIL) 0.41 mg/dL, albumin (ALB) 3.3 g/dL, aspartate aminotransferase (AST), 12 IU/L, alanine aminotransferase (ALT), 17 IU/L, alpha-fetoprotein (AFP), 8,997 ng/mL, protein induced by vitamin K absence or antagonist II (PIVKA-II), 41 mAU/mL. Hepatitis B surface antigen was negative and anti-hepatitis C antibody was positive. Computed tomography (CT) demonstrated a tumor, 3 cm in diameter at segment 4 of the liver and ascites of high density (Fig. 1A). Gastrointestinal endoscopy showed esophageal varices. Therefore, the patient was diagnosed with ruptured hepatocellular carcinoma (HCC) associated with liver cirrhosis caused by HCV. Hepatic arteriography showed tumor stain at segment 4 in the liver (Fig. 2). Transcatheter arterial embolization (TAE) was performed to the HCC. CT showed local recurrence of HCC at segment 4 in January 2005 and a second TAE was performed with 30 mg of epirubicin. However, after the second TAE, the AFP level was increased and the deposition of lipiodol in the tumor was decreased. The diagnosis was that the local recurrence occurred again and the patient was admitted to our hospital in June 2005.

On admission, the patient was alert and physical examination showed no abnormality. The results of routine laboratory tests on admission were as follows: Hb 10.7 g/dL, WBC 5,700/mm³, PLT 124,000/mm³, Prothrombin time 82.2%, T-BIL 0.33 mg/dL, ALB 3.5 g/dL, AST 16 IU/L, ALT 16 IU/L, ICG 15.5%, AFP 1,381 ng/mL, PIVKA-II 25 mAU/mL. Because hepatic arteriography showed no tumor stain in the liver, we could not perform TAE. We decided to perform surgical treatment for HCC in segment 4. Surgical laparotomy revealed several tumors and bloody ascites in the abdominal cavity (Fig. 3A) in July 2005. Pathologically, one of the tumors in the omentum was revealed to be moderately-poorly differentiated HCC (Fig. 3B). Surgical treatment was aborted. Soon after the operation, CT demonstrated HCC measuring 3 cm in diameter at segment 4 (Fig. 1B), disseminated tumors and ascites in the abdominal cavity (Fig. 4A, B). Because of the advanced stage of HCC and chronic renal failure, the patient declined interventional therapies. Thereafter, we prescribed oral vitamin K2 (45 mg/day) and vitamin E (150 mg/day) and the patient was discharged in August 1, 2005. Three months after the administration of vitamin K2 and vitamin E, the AFP level had decreased to 46.4 ng/mL (Fig. 5) and CT demonstrated that
the diameter of HCC at segment 4 was unchanged and dis-
seminated tumors disappeared and ascites was decreased.
Six months have passed and the AFP level was 56.5 ng/mL
(Fig. 5), and HCC in segment 4 did not increase in size
(Fig. 1C), ascites did not increase and disseminated tumors
disappeared on CT (Fig. 4C, D). During the six months, the
PIVKA-II level was within normal range.

Discussion

Although the recent improvements of the treatment for
HCC such as operation and radiofrequency ablation are re-
markable, a treatment for peritoneal dissemination of HCC
has not been established (9). In patients with extrahepatic
metastases of HCC, most patients with bone metastases died
from hepatic cause but approximately one-third of the pa-
tients with metastases other than bone died from extrahe-
patic causes (10). Therefore, it is important to treat extrahep-
tic HCC including peritoneal dissemination in order to
improve survival and provide a good quality of life even
when the patient is in the terminal stage of HCC. It is usu-
ally difficult to completely resect peritoneal dissemination
of HCC (2, 11). However, repeated resection for peritoneal dis-
semination of HCC could contribute to the long-term sur-
vival (3, 12). Radiotherapy is used either in combination
with or as an alternative to surgery (13). For example, the
patient with HCC underwent six repeated resections and two
radiotherapy for peritoneal dissemination, and the patient re-
mained alive without any evidence of recurrence for three
years (14). Hyperthermia could be considered as one of the
multimodal treatments (11). Reportedly, the combination of
transarterial chemoembolization and hyperthermia was effec-
tive against peritoneal HCC in an animal experiment (15). A
variety of systemic chemotherapy have been tested in HCC,
including combination therapies with cisplatin, doxorubicin
and tegafur and uracil (UFT), and alpha-interferon and UFT
(16-18). The case of recurrent HCC with peritoneal dissemina-
tion and splenic metastasis which disappeared after ad-
ministration of UFT was reported (19). In the present case,
TAE was repeatedly performed for primary HCC but the
peritoneal dissemination was difficult to treat because of the
poor clinical condition even though the peritoneal dissemi-
nation was detected before surgery.

Vitamin K2 is known to inhibit the growth and invasion
of HCC cell lines in vitro (20, 21). Moreover, administration
of vitamin K2 to nude mice implanted liver tumor cells in-
hibited the growth of the liver tumor (20). Although the
mechanisms associated with the antiproliferative effects of

Figure 2. Hepatic arteriography shows a tumor stain (arrow). A: Early phase. B: Late phase.

Figure 3. Pathological features of disseminated tumor in the omentum at operation. A: Macro-
scopic examination shows a dark green tumor. B: Microscopic examination shows a moderately-
poorly differentiated HCC (H&E ×40). Arrow shows bile.
Figure 4. Disseminated tumors and ascites by enhanced CT. A, B: A few disseminated tumors (arrows) and large amount of ascites are found soon after the operation. C, D: There is no disseminated tumor and only a small amount of ascites at 6 months after start of administration of vitamins K2 and E.

Figure 5. Clinical course of the patient.

Vitamin K2 against tumor cells remain unknown, it has been proposed that the effect of vitamin K2 may occur through activation of protein kinase A (PKA) pathway (20). PKA itself induces cell cycle arrest and activates downstream transcriptional factors, activating enhancer-binding protein-2 and upstream transcription factor-1, which are related to growth inhibition (20). Furthermore, Wang et al reported that vitamin K2 induced c-myc resulted in apoptosis of hepatoma cells (21). Clinically, vitamin K2 is known to be used in the treatment of myelodysplastic syndrome (22). As for HCC, administration of vitamin K2 prevents the development of HCC in women with viral cirrhosis and that suppresses the recurrence of HCC and improves survival in patients who have received curative treatment of HCC (6, 22).

Vitamin E is known to induce apoptotic cell death in various cell types in vitro and to inhibit tumorigenesis in vivo (7, 23, 24). In the mechanisms of vitamin E-induced apoptosis it has been demonstrated that vitamin E restores both transforming growth factor-β and Fas/CD95-APO-1 signaling pathway and activates extracellular signal-regulated kinase-1 and c-Jun NH2-terminal kinase-1 as well as transcriptional factors, c-Jun and activating transcriptional factor-2 (7, 24). Clinical work of administration of vitamin E to patients with viral liver cirrhosis showed that the rate of development of HCC tended to be longer and survival was higher in the vitamin E group compared with the control group (8).

Therefore, we prescribed oral vitamin K2 45 mg daily and oral vitamin E 150 mg daily. Recently, vitamin K2 was used for chemoprevention of HCC and there were no adverse effects related to administration of vitamin K2 45 mg which is the same dosage used in the treatment of osteoporosis (6). Vitamin E was also used for chemoprevention of HCC using the same dosage for the treatment of peripheral
nerve impediment and there were no adverse effects (8). As a result, intraabdominal dissemination of HCC disappeared and the primary tumor did not grow. Although the association between vitamin K2 and E in the field of antiproliferative effect on tumor cells is not known, it is suggested that administration of vitamin K2 and E inhibited the growth of HCC in the present case.

Although spontaneous regression of HCC is rare, several causes of regression of HCC have been known, such as lack of blood supply due to rapid growth of HCC, withdrawal from steroid, abstinence of alcohol consumption (5). In the present case, the speed of tumor growth was not rapid because the size of primary HCC and abdominal disseminated tumors were up to 3 cm. He did not have a history of medication with steroid and alcohol abuse. Therefore, administration of vitamin K2 and E could be reason for regression in our case. To our knowledge, this is the first case report documenting regression of HCC during the administration of vitamin K2 and E.

In conclusion, administration of vitamin K2 and vitamin E for patients with advanced stage of HCC, such as peritoneal dissemination and distant metastasis, who have no indication of interventional therapy, should be considered to prolong life and to improve quality of life. Further control study will be needed to confirm the efficacy of vitamin K2 and vitamin E for the treatment of HCC.

References