Advanced hepatocellular carcinoma responds to MK615, a compound extract from the Japanese apricot “Prunus mume”

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Abstract

MK615, a compound extracted from the Japanese apricot “Prunus mume” has been reported to have in vitro anti-tumor activities against several cancer cell lines, including hepatocellular carcinoma (HCC). However, the clinical effects and feasibility of administering MK615 for patients with HCC were unknown. We experienced a case with advanced HCC for which MK615 was effective against both lymph node and pulmonary metastases. A 60-year-old female underwent surgical resection of a 9 cm HCC in the right lobe. The pathological diagnosis was moderately differentiated HCC with vascular invasion. The HCC recurred in the liver 8 mo after the surgery. Sorafenib was administered, but was not effective. Then, MK615 was administered as a final alternative therapy after informed consent was obtained from the patient. Three months later, her alpha-fetoprotein level decreased and both the lymph node and pulmonary metastases decreased in size. The patient has survived for more than 17 mo after the MK615 administration, and was in good condition. Although further investigations are necessary to clarify its safety and efficacy in humans, MK615 may be useful for the treatment of HCC, without serious adverse effects.

Key words: MK615; Hepatocellular carcinoma; Japanese apricot; Prunus mume

Core tip: We experienced a case with advanced hepatocellular carcinoma (HCC) for which MK615, a compound extracted from the Japanese apricot “Prunus mume” was effective against both lymph node and pulmonary metastases. MK615 was administered as a final alternative therapy. Three months later, her alpha-fetoprotein level decreased and both the lymph node and pulmonary metastases decreased in size. MK615 has been reported to have in vitro anti-tumor activities against several cancer cell lines, including HCC. Although further investigations are necessary to clarify its safety and efficacy in humans, MK615 may be useful for the treatment of HCC, without serious adverse effects.

Hoshino T, Takagi H, Naganuma A, Koitabashi E, Uehara S, Sakamoto N, Kudo T, Sato K, Kakizaki S. Advanced hepatocellular carcinoma responds to MK615, a compound extract from the Japanese apricot “Prunus mume”. World J Hepatol 2013; 5(10): 596-600 Available from: URL: http://www.wjgnet.com/1948-5182/full/v5/i10/596.htm DOI: http://dx.doi.org/10.4254/wjh.v5.i10.596
INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most intractable cancers, and the clinical outcome is still unsatisfactory despite improvements in the therapeutic strategies for HCC\cite{1-3}. For the patients with advanced HCC with poor liver function, surgical resection, radiofrequency ablation (RFA) or transarterial chemoembolization (TACE) cannot be applied because of their adverse effects, and palliative care is the only recommended treatment for such patients\cite{1-3}. Although these patients might be cured by a liver transplant, such treatment is usually not possible due to the severe donor shortage\cite{4}. For advanced stage HCC patients with preserved liver function, sorafenib is usually indicated, but its side effects, such as cytopenia and liver dysfunction, sometimes require a disruption or discontinuation of the treatment.

MK615 is a compound extracted from the Japanese apricot “Prunus mume”\cite{5} and contains several triterpenoids, such as oleanolic acid and ursolic acid\cite{5}. It has been reported that MK615 inhibits cell growth and induces the death of several tumor cell lines\cite{5-7}, including gastric cancer\cite{5}, promyelocytic leukemia\cite{5}, breast cancer\cite{8}, pancreatic cancer\cite{9}, HCC\cite{10,11}, colon cancer\cite{12}, esophageal cancer\cite{13}, malignant melanoma\cite{14,15} and lung cancer cells\cite{10}. The activities underlying the anti-tumor effects of MK615 have been reported to include the induction of apoptosis\cite{5,8}, autophagy\cite{12,16} and the suppression of aurora A kinase\cite{9,11}. Furthermore, some clinical studies have shown promising effects in some cancer patients\cite{5,12}. Recently, hepatoprotective effects of MK615 have been reported for patients with chronic liver diseases\cite{17}. However, the clinical benefit of MK615 for HCC patients has not been evaluated.

We recently experienced a case with advanced HCC in which MK615 was effective for both lymph node and pulmonary metastases. Although further investigations are necessary to clarify the safety and efficacy of the
treatment in human patients, MK615 may be useful for the treatment of HCC, without the serious adverse effects associated with the current treatments.

CASE REPORT

A 60-year-old underwent surgical resection of a primary HCC lesion in the right lobe that was 9 cm in diameter. The pathological diagnosis was moderately differentiated HCC, v1, v2, n0 and m0. The HCC recurred in the liver 8 mo later and RFA was performed, but the recurrence was not controlled. Transarterial infusion chemotherapy, including cisplatin and a 5-fluorouracil/cisplatin combination was performed for the intraparenchymal recurrence. One year after the recurrence, pulmonary and lymph metastases appeared. Sorafenib was administered, but the recurrence was not controlled. Transarterial infusion chemotherapy, including cisplatin and a 5-fluorouracil/cisplatin combination was performed for the intraparenchymal recurrence.

Then, MK615 was administered as a final alternative therapy after informed consent was obtained from the patient. MK615 (Misatol ME) was kindly provided by AdaBio Co Ltd. (Takasaki, Japan). A total of 6.5 g of Misatol ME was administered twice per day. The administration of MK615 was approved by the internal review board of Takasaki General Hospital, and adopted the protocol for clinical research entitled, “The clinical feasibility study of Misatol ME (MK615) for the patients with advanced stage-hepatocellular carcinoma”.

Three months later, the patient’s alpha-fetoprotein (AFP) levels decreased (Figure 1A) and both the lymph node (Figure 1B) and pulmonary (Figure 1C) metastases decreased in size. This patient has survived for more than 17 mo and was in good condition at her latest follow-up examination in August 2013.

DISCUSSION

MK615 contains urine-derived triterpenoids, including oleanolic acid and ursolic acid. Triterpenoids had been reported to suppress the growth of many cancer cell lines[19-22]. Although the activities underlying the anti-tumor effects have been reported to include the induction of apoptosis[15], autophagy[12,16] and the suppression of aurora A kinase[11], the exact mechanism(s) of action of MK615 are still being elucidated. A large amount of basic data regarding the effects of MK615 against cancer cells in vitro have been published[5-16]. However, there has been little clinical data with regard to the effects of MK615 against cancer. One study with a small number of clinical cases showed that MK615 was useful for malignant melanoma[18], and the clinical efficacy and safety of MK615 has been reported for patients with chronic liver disease[17]. However, the clinical benefit of MK615 for HCC patients has not been evaluated.

We experienced a case of advanced HCC in which MK615 was effective for both lymph node and pulmonary metastases. Concerning the relationship between MK615 and HCC, Sakuraoka et al[19] reported that MK615 suppresses the proliferative effects of glycolaldehyde-derived advanced glycation end-products on a
HCC cell line, HuH7, by decreasing the expression of their cellular receptor (RAGE). Another study reported that MK615 inhibited the growth of two HCC cell lines, HuH7 and Hep3B, in a dose-dependent manner\(^1\). A cell cycle analysis revealed that MK615 increased the population of cells in the G2/M phase\(^1\) and that MK615 suppressed the expression of Aurora A\(^1\). These studies demonstrated that MK615 has anti-tumor effects against HCC. Although the mechanism(s) of anti-tumor activity in the present case is unknown, MK615 appears to exert anti-tumor effects on HCC \textit{in vivo}. This case is the first case demonstrating the clinical efficacy of MK615 against HCC.

We also attempted to treat six patients with advanced stage HCC with poor liver function. Our policy is that if the patients had a chance to be treated with conventional anticancer treatments, the patients should be treated using these treatments, and alternative treatments are reserved only for those with no other options. Although the present case was the only PR, none of the subjects experienced adverse effects of the treatment. Therefore, it is considered that the effects of MK615 may be useful for patients with advanced HCC, particularly for patients with poor functional reserve, and that the treatment is not associated with the severe adverse effects associated with the conventional treatments.

Although further studies are required to demonstrate the safety and efficacy of MK615 for HCC patients, the preliminary results are promising. We are planning to conduct a clinical study of combination therapy using MK615 with other anti-cancer agents, and/or a controlled study with a large number of patients with advanced HCC.

ACKNOWLEDGMENTS

The authors thank Taro Adachi for effective discussion for the accomplishment of this study.

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