KJCO Korean Journal of Clinical Oncology
Korean Journal of Clinical Oncology 2024;20:84-87
https://doi.org/10.14216/kjco.24012
pISSN 1738-8082 · eISSN 2288-4084
Case Report

Long-term tumor suppression in cholangiocarcinoma using cytokine-induced killer cell therapy and high-dose vitamin C: a case report

Kangseok Kim[1], Hyunhye Wang[2], Jiewon Lee[3], Changhwan Yeom[3]

[1]Department of Surgery, Bangre Hospital, Incheon, Korea
[2]Department of Radiology, Bangre Hospital, Incheon, Korea
[3]Department of Family Medicine, Yeom Chang Hwan Hospital, Seoul, Korea

This case study explores the effectiveness of autologous cytokine-induced killer (CIK) cell-based immunotherapy in a 49-year-old male patient with inoperable stage IIIb cholangiocarcinoma, characterized by high levels of the sodium-dependent vitamin C transporter-2 (SVCT2) in immune cells. Despite an initial lack of tumor reduction following chemotherapy, the patient showed a significant decrease in tumor markers and stabilization of the tumor after undergoing radiation and proton therapy. Subsequently, CIK cell therapy, combined with high-dose vitamin C, was administered 52 times over 6 years. The patient's tumor size reduced, and no cancer activity was detected for 7 years and 10 months post-diagnosis, indicating a successful long-term outcome without recurrence. This study suggests that CIK cell therapy, particularly in patients with elevated SVCT2 levels, may offer a promising adjuvant treatment for cholangiocarcinoma and potentially other cancers. Further research is needed to validate SVCT2 as a biomarker for the effectiveness of CIK cell therapy.

Keywords: Cell therapy, Sodium-dependent vitamin C transporter-2, Ascorbic acid, Cholangiocarcinoma, Case reports

INTRODUCTION

Despite a relatively low incidence rate of 7.8 per 100,000, intrahepatic bile duct cancer has a 5-year survival rate of only 15.9%, reflecting a poor prognosis in Korea [1]. The main treatment for cholangiocarcinoma is surgery, but in cases where surgery is not possible, only chemotherapy and radiation therapy can be used. Unfortunately, given the limited efficacy of chemotherapy in cholangiocarcinoma, alternative therapeutic strategies are required, with cytokine-induced killer (CIK) cell therapy emerging as a potential approach to augment immune-mediated tumor control [2]. This treatment involves culturing immune cells for 2 weeks before re-administering them to the patient. However, there is no data indicating which patients would benefit most from this therapy. For immune cell therapy to be effective, vitamin C must enter the immune cells in large quantities [3]. For vitamin C to enter the immune cells, the level of sodium-dependent vitamin C transporter-2 (SVCT2), a vitamin C transporter, must be high in these cells [4]. This study reports a case of CIK cell treatment following radiotherapy in a patient with biliary tract cancer with high SVCT2 levels in immune cells, along with a literature review. Written informed consent was obtained from the patient for this publication.

Received: Nov 12, 2024 **Revised:** Dec 6, 2024 **Accepted:** Dec 9, 2024
Correspondence to: Kangseok Kim
Department of Surgery, Bangre Hospital, 472 Inju-daero, Michuhol-gu, Incheon 22228, Korea
Tel: +82-32-428-2124, **Fax:** +82-32-428-7020
E-mail: kangseok78@gmail.com

CASE REPORT

The patient, a 49-year-old man with no prior history of surgery or underlying medical conditions, presented to the hospital in October 2016 with upper abdominal pain. Initial imaging and evaluation confirmed a diagnosis of stage IIIb cholangiocarcinoma involving the portal vein. Percutaneous transhepatic biliary drainage was performed, and biopsy confirmed the diagnosis. Computed tomography (CT) and magnetic resonance imaging revealed a 3.5 cm tumor within the portal vein (Fig. 1).

From November 21, 2016, to March 3, 2017, the patient underwent five cycles of chemotherapy, comprising 1,900 mg of gemcit-

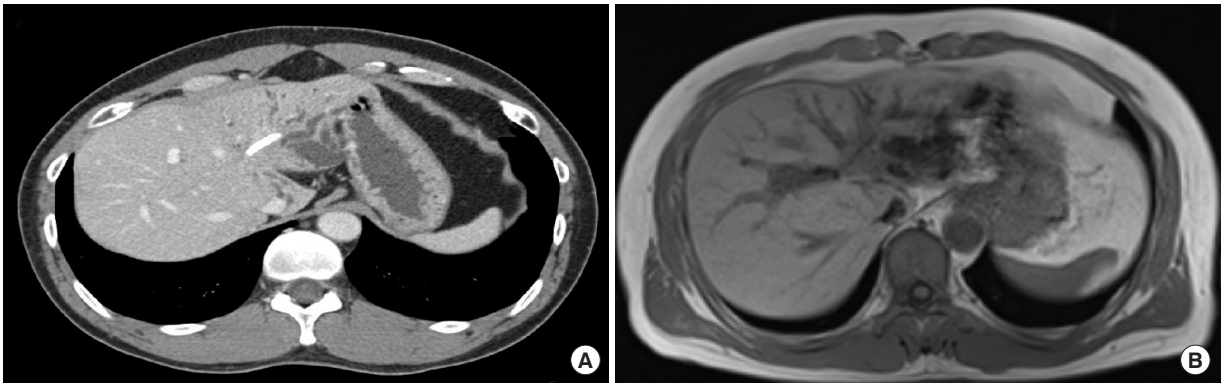

Fig. 1. Abdominal computed tomography (CT) scan and magnetic resonance imaging. (A) CT findings at the time of diagnosis in 2016. (B) Magnetic resonance, abdomen revealed a type IV Klatskin tumor at the hepatic hilum, with invasion of the left portal vein and both hepatic arteries.

Table 1. The results of tumor marker test

Date	Event	CA19-9 (U/mL)[a]
Nov 2016	Diagnosis	160.0
Mar 2017	5th Chemotherapy	55.0
May 2017	IMRT and PBT	32.0
May 2018	CIK cell therapy Vitamin C administration (70 g)	-
Jun 2018	Ongoing since May 2018	15.0
Dec 2018	Ongoing since May 2018	12.0
Aug 2019	Ongoing since May 2018	9.0
Dec 2019	Ongoing since May 2018	19.0
Jun 2020	Ongoing since May 2018	15.7
Jan 2021	Ongoing since May 2018	23.0
Mar 2022	Ongoing since May 2018	29.2
Nov 2022	Ongoing since May 2018	16.5
May 2023	Ongoing since May 2018	29.7

CA19-9, carbohydrate antigen 19-9; IMRT, intensity-modulated radiation therapy; PBT, proton beam therapy; CIK, cytokine-induced killer.
[a]Normal range (0.0–34.0 U/mL).

abine and 50 mg of cisplatin per cycle. Following treatment, the carbohydrate antigen 19-9 (CA19-9) level decreased from 160 U/mL pre-chemotherapy to 55 U/mL after the fifth cycle, although the tumor size on CT imaging remained unchanged. The patient opted to discontinue chemotherapy and proceeded with radiation and proton therapy from March 23 to April 17, 2017. Treatment included 36 Gy of intensity-modulated radiation therapy delivered in 12 sessions to address hepatic vascular invasion and 25 Gy of proton beam therapy delivered in five sessions targeting the primary bile duct site. Posttreatment evaluation revealed no change in tumor size but a further reduction in CA19-9 levels to 32 U/mL (Table 1).

From May 2018 to July 2024, the patient received a total of 52 sessions of CIK cell therapy alongside weekly intravenous administration of 70 g of vitamin C. Testing of the SVCT2 in immune cells (natural killer [NK] cells, T cells, dendritic cells) revealed elevated levels of 6.85 ng/mL. Imaging in 2023, including positron emission tomography-CT and abdominal CT, demonstrated a reduction in tumor size to 2.5 cm with no evidence of metabolic activity, suggesting an inactive tumor state (Fig. 2). Surgical options, including left hepatic lobectomy and pylorus-preserving pancreaticoduodenectomy, were considered but deferred due to high intraoperative bleeding risk and the patient's preference against surgery. The patient remains under surveillance, with surgery to be reconsidered only if stent occlusion occurs and the patient consents. The patient's cancer has remained stable and without recurrence for 7 years and 10 months since diagnosis. These findings suggest that the combined administration of CIK cell therapy and high-dose intravenous vitamin C, following radiation and proton therapy, may have contributed to long-term suppression and eradication of the patient's cancer.

DISCUSSION

Since cholangiocarcinoma is often found in an advanced stage at the time of diagnosis, surgery is often not possible, so the prognosis is very poor [5]. Recently, an immunotherapy drug called Imfinzi has been developed, which has improved treatment results compared to existing treatments. According to data published by Oh et al. [6], the 2-year survival rate increased in the group treated with durvalumab in combination with existing chemotherapy drugs (24.9% vs. 10.4%, $P < 0.001$) and the objective response rate also improved (26.7% vs. 18.7%) compared to the group treated with only existing chemotherapy drugs. Although treatment results have improved with the use of durvalumab compared to previous

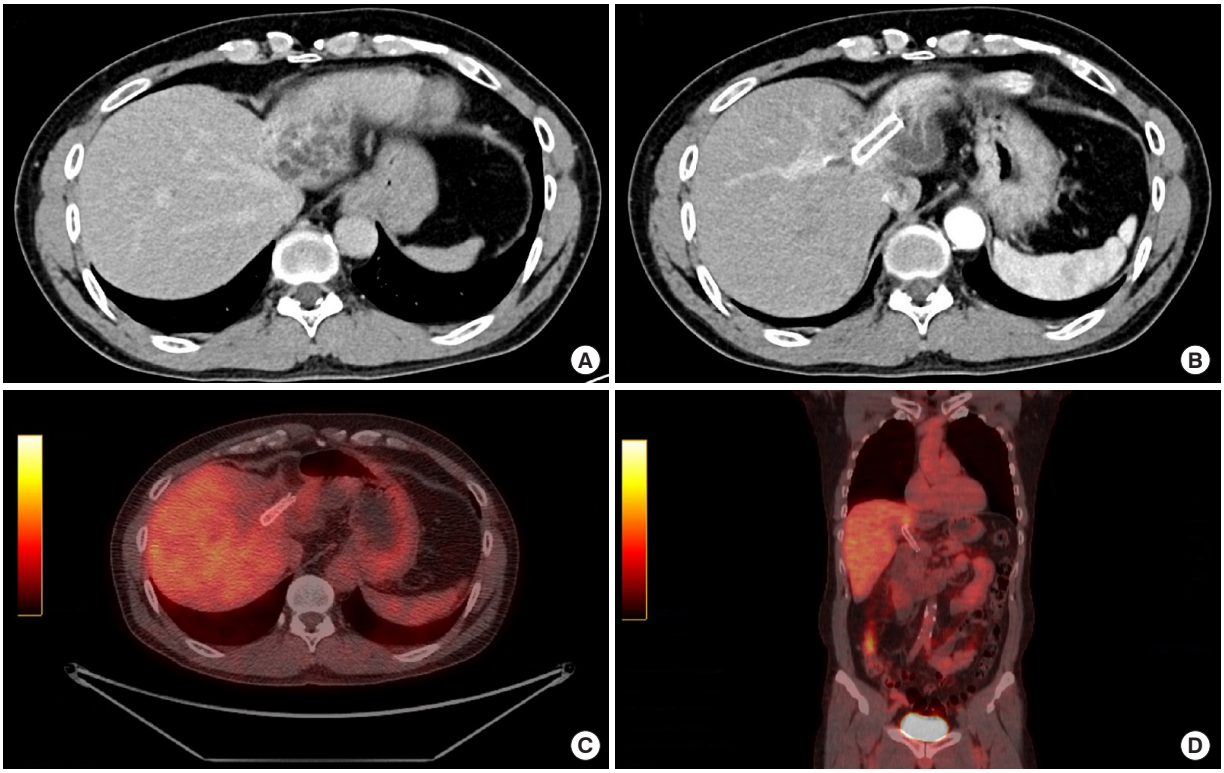

Fig. 2. Abdominal CT scan and PET-CT whole body scan. (A, B) Current CT findings in 2023, showing tumor regression posttreatment. (C, D) Follow-up PET-CT confirmed a diagnosis of inactive cancer. PET-CT, positron emission tomography-computed tomography.

therapies, they are not yet fully satisfactory. Cholangiocarcinoma is an immunogenic tumor. Compared to other solid tumors, it is characterized by a small number of tumor parenchymal cells and a large number of tumor stromal cells [7]. The tumor microenvironment in cholangiocarcinoma is predominantly regulated by inflammatory processes and a high presence of immune cells, including T and B lymphocytes, macrophages, neutrophils, and NK cells. These immune cells play a critical role in recognizing subtle differences between tumor and normal cells. Through this detection, they signal T-lymphocytes, which are key components of the immune system, to initiate and regulate the adaptive immune response, thereby contributing to immune surveillance and potential tumor control [8]. On the other hand, tumor-infiltrating lymphocytes in the adaptive immune response of cholangiocarcinoma are a very heterogeneous population, including CD8+ T cells, CD4+ T cells, B cells, and Tregs [9]. They play an important role in cholangiocarcinoma immune surveillance and tumor cell removal. These results suggest that CIK cell therapy has shown potential as a cancer treatment over the years.

Numerous studies have demonstrated the efficacy of CIK cell therapy across various cancers, including lung, kidney, breast, pancreatic, and liver cancers [10-13]. In liver cancer, CIK cell therapy has been shown to reduce recurrence rates and improve survival, particularly with 16 administrations following hepatectomy [2]. A phase 3 randomized controlled trial further reported that CIK cells enhance immune function in patients with hepatocellular carcinoma, reducing recurrence rates. Notably, in patients receiving curative treatment for hepatocellular carcinoma, adjuvant CIK cell immunotherapy led to significant improvements in recurrence-free survival and overall survival that were sustained for over 5 years, even without additional immunotherapy [14]. In gastric cancer, the combination of CIK cell therapy with chemotherapy significantly prolonged survival and reduced mortality risk, with greater therapeutic benefits observed with increased treatment frequency [15].

Furthermore, high-dose intravenous vitamin C has been found to selectively generate hydrogen peroxide, inducing oxidative stress that damages cancer cells while sparing normal tissues. This mechanism depletes nicotinamide adenine dinucleotide (NAD^+) and adenosine triphosphate, disrupting cancer cell metabolism and inducing cell death. Vitamin C also inhibits epithelial-mesenchymal transition, alters microtubule dynamics by increasing α-tubulin acetylation, and promotes collagen synthesis in the tumor stroma, collectively suppressing tumor growth and metastasis. These

multi-targeted actions, combined with its low toxicity, underscore its potential as a complementary therapy in cancer treatment.

However, there are currently limited studies identifying which patients would benefit most from CIK cell therapy, and no established biomarkers. This paper is the first to identify SVCT2, a vitamin C transporter in NK and T cells, as a potential biomarker. SVCT2 facilitates vitamin C uptake into immune cells, enhancing their activity. Culturing highly active immune cells may lead to more effective cancer eradication. While further research is needed, SVCT2 holds promise as a predictive marker for immunotherapy, offering a targeted approach to improving treatment outcomes.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

None.

ORCID

Kangseok Kim https://orcid.org/0009-0001-4756-6402
Hyunhye Wang https://orcid.org/0000-0002-7574-7016
Jiewon Lee https://orcid.org/0009-0001-0599-4951
Changhwan Yeom https://orcid.org/0000-0003-3994-3287

REFERENCES

1. Kim BW, Oh CM, Choi HY, Park JW, Cho H, Ki M. Incidence and overall survival of biliary tract cancers in South Korea from 2006 to 2015: using the National Health Information Database. Gut Liver 2019;13:104-13.
2. Lee JH, Lee JH, Lim YS, Yeon JE, Song TJ, Yu SJ, et al. Adjuvant immunotherapy with autologous cytokine-induced killer cells for hepatocellular carcinoma. Gastroenterology 2015;148:1383-91.
3. Zaher A, Stephens LM, Miller AM, Hartwig SM, Stolwijk JM, Petronek MS, et al. Pharmacological ascorbate as a novel therapeutic strategy to enhance cancer immunotherapy. Front Immunol 2022;13:989000.
4. Savini I, Rossi A, Pierro C, Avigliano L, Catani MV. SVCT1 and SVCT2: key proteins for vitamin C uptake. Amino Acids 2008;34:347-55.
5. Valle JW, Kelley RK, Nervi B, Oh DY, Zhu AX. Biliary tract cancer. Lancet 2021;397:428-44.
6. Oh DY, Ruth He A, Qin S, Chen LT, Okusaka T, Vogel A, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. NEJM Evid 2022;1:EVIDoa2200015.
7. Zhao LM, Shi AD, Yang Y, Liu ZL, Hu XQ, Shu LZ, et al. Advances in molecular and cell therapy for immunotherapy of cholangiocarcinoma. Front Oncol 2023;13:1140103.
8. Jonuleit H, Schmitt E, Schuler G, Knop J, Enk AH. Induction of interleukin 10-producing, nonproliferating CD4(+) T cells with regulatory properties by repetitive stimulation with allogeneic immature human dendritic cells. J Exp Med 2000;192:1213-22.
9. Naito Y, Saito K, Shiiba K, Ohuchi A, Saigenji K, Nagura H, et al. CD8+ T cells infiltrated within cancer cell nests as a prognostic factor in human colorectal cancer. Cancer Res 1998;58:3491-4.
10. Chung MJ, Park JY, Bang S, Park SW, Song SY. Phase II clinical trial of ex vivo-expanded cytokine-induced killer cells therapy in advanced pancreatic cancer. Cancer Immunol Immunother 2014;63:939-46.
11. Liu L, Zhang W, Qi X, Li H, Yu J, Wei S, et al. Randomized study of autologous cytokine-induced killer cell immunotherapy in metastatic renal carcinoma. Clin Cancer Res 2012;18:1751-9.
12. Zhu XP, Xu YH, Zhou J, Pan XF. A clinical study evaluating dendritic and cytokine-induced killer cells combined with concurrent radiochemotherapy for stage IIIB non-small cell lung cancer. Genet Mol Res 2015;14:10228-35.
13. Pan K, Guan XX, Li YQ, Zhao JJ, Li JJ, Qiu HJ, et al. Clinical activity of adjuvant cytokine-induced killer cell immunotherapy in patients with post-mastectomy triple-negative breast cancer. Clin Cancer Res 2014;20:3003-11.
14. Lee JH, Lee JH, Lim YS, Yeon JE, Song TJ, Yu SJ, et al. Sustained efficacy of adjuvant immunotherapy with cytokine-induced killer cells for hepatocellular carcinoma: an extended 5-year follow-up. Cancer Immunol Immunother 2019;68:23-32.
15. Jiang JT, Shen YP, Wu CP, Zhu YB, Wei WX, Chen LJ, et al. Increasing the frequency of CIK cells adoptive immunotherapy may decrease risk of death in gastric cancer patients. World J Gastroenterol 2010;16:6155-62.