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# KML001, an arsenic compound, as salvage chemotherapy in refractory biliary tract cancers: A prospective study ☆

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ABSTRACT

*Background:* Sodium meta-arsenite ($NaAsO_2$, KML001) is a potential oral anticancer agent acting on telomerase and telomere length. This prospective study evaluated its safety, tolerability, and effectiveness as salvage chemotherapy in patients with advanced biliary tract cancer (BTC) resistant to gemcitabine-based chemotherapy.

*Methods:* Forty-four patients (21 women and 23 men) with advanced BTC and failure history of gemcitabine-based chemotherapy, performance status (PS) 0–2, normal cardiac, hepatic, and renal function were enrolled. Daily dose of KML001 (7.5 mg. p.o.) was administered to eligible subjects for 24 weeks divided into six treatment cycles. Response was evaluated bimonthly using CT.

*Results:* After an average of 1.5 months of treatment (range: 0.5–10.0), 3 patients (6.8%) obtained progression-free status, 23 patients (52.3%) had disease progression, and 18 patients (40.9%) dropped out before evaluation. One patient (2.3%) completed six treatment cycles without progression. During the treatment, morphine dosage kept the same or decreased in 20 patients (47.6%). Nine patients (20.5%) experienced grade-3 adverse events (AEs), while no patient experienced grade-4 AEs. The most common AEs were liver enzyme elevation (11/44, 25%) and anemia (10/44, 22.7%). KML001 was discontinued in six patients (13.6%) due to AEs, including liver toxicity ($n=3$), QTc prolongation ($n=2$), and abdominal pain ($n=1$).

*Conclusions:* KML001 did not have enough anticancer effect on patients with advanced BTC resistant to gemcitabine. However, KML001 was safe and well-tolerable in terms of AEs and pain control when used as salvage therapy. Further studies are needed to establish arsenic agents as a reliable treatment option in patients with BTC.



## Introduction

Biliary tract cancer (BTC) is a relatively rare cancer that includes intrahepatic/extrahepatic cholangiocarcinoma and gallbladder cancer [1]. About 10,000 new cases of BTC are diagnosed in the United States per year, and the 5-year survival rate is lower than 20% [2]. Only surgical resection is a curable therapy. However, majority of the BTCs are diagnosed at unresectable stage. Moreover, the recurrent rate is high, even after curative resection [3]. Therefore, chemotherapy is important in the treatment of advanced or recurrent BTC. Currently recommended treatment options for patients with advanced BTC include gemcitabine and cisplatin combination therapy. A previous randomized controlled trial revealed that the combination of gemcitabine with cisplatin improved the overall survival (OS) by 3.6 months compared to gemcitabine alone [4]. Still, there is no effective second-line anticancer drug that could be used for patients who have failed to gemcitabine-based chemotherapy. Moreover, cisplatin is associated with severe toxicity, including dose-dependent nephrotoxicity and neurotoxicity, which may limit the opportunities for second-line treatment after disease progression.

Telomeres are noncoding DNA sequences at the end of chromosomes. Due to imperfect replication, about 30–100 base pairs of telomeric DNA are lost during a cell cycle [5]. Telomerase is a ribonucleoprotein reverse transcriptase that prevents immortality of human cells due to loss of telomeric DNA [6]. Approximately 85% of human cancer tissues are known to display telomerase

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activity. In contrast, normal tissues adjacent to cancerous and human somatic tissues do not show detectable telomerase activity. Telomeres and telomerase can be potential targets for chemotherapy [7].

Arsenic compounds have been used in traditional medicine as anti-tumor and anti-inflammatory agents for centuries [8]. However, their clinical use has decreased due to the adverse carcinogenic effects and toxicity [9]. Arsenic trioxide ($As_2O_3$, ATO) is known for its effects on telomerase and telomere length. ATO inhibits the transcription of reverse transcriptase subunit of human telomerase reverse transcriptase, which results in telomere shortening and chromosomal instability. ATO has been shown to be a potential treatment for acute promyelocytic leukemia [10,11]. It is also known to induce apoptosis in various human solid tumor cell lines [12–14].

Sodium meta-arsenite ($NaAsO_2$, KML001) is a water-soluble and orally bioavailable arsenical compound. KML001 has been shown to have a strong anti-tumor effect in human solid tumor cells both *in vitro* and *in vivo*. and has entered phase 1/2 clinical trials for the treatment of human prostate cancer [15,16]. It may also be a candidate for the treatment of refractory non-Hodgkin's lymphoma [17]. Sequential administration of ionizing radiation and sodium arsenite accelerated tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis of human melanoma cells [18]. Additionally, KML001 was studied as a potential agent for the treatment of pancreatic cancer. A combination of KML001 and gemcitabine significantly reduced cell proliferation, migration, and invasion in pancreatic cancer cell lines, and it also significantly reduced EGFR and MMP2 expression compared to gemcitabine alone [19].

However, the effect of KML001 has not been evaluated in BTC patients, for which second-line chemotherapeutic agents have not been established. There are some patients with advanced BTC who have failed previous gemcitabine-based chemotherapy. In these patients, salvage chemotherapy is needed, as it can reduce patient's symptoms such as cancer pain, and improve quality of life with anticancer effect. To assess the potential of KML001 as an anti-BTC agent, we investigated its safety and efficacy when used as salvage chemotherapy agent in patients with advanced BTC after failure of prior chemotherapies.

## Methods

### *Eligibility and evaluation of patients*

This prospective study was designed to evaluate the safety, tolerability, and effectiveness of KML001 as salvage chemotherapy in advanced BTC patients who were resistant to previous gemcitabine based regimens. Patients were prospectively enrolled at Severance Hospital in Seoul, Korea, between November 2011 and October 2014, based on the criteria outlined below.

The inclusion criteria were as follows: (1) advanced or metastatic cholangiocarcinoma or gallbladder cancer confirmed by histopathological examination, including recurrent cases after surgical resection; (2) failure history of gemcitabine-based chemotherapy; (3) expected survival greater than 3 months; and (4) adequate hematological, liver, and kidney functions to tolerate chemotherapy. Baseline white blood cell count $> 3.0 \times 10^3/\mu L$, neutrophil count $> 1.5 \times 10^3/\mu L$, and platelet count $> 75\,000/mL$ were required, as well as levels of hepatic enzymes ALT and AST $< 2.5 \times$ upper limit of normal (ULN), total bilirubin level $< 2.0 \times$ ULN, and normal renal function (serum creatinine $< 1.5$ mg/dL).

Exclusion criteria were (1) no history of chemotherapy; (2) Eastern Cooperative Oncology Group performance status (ECOG PS) $> 2$; (3) history of decompensated congestive heart failure, uncontrolled arrhythmia, or corrected QT interval (QTc) prolongation ($> 480$ ms); and (4) serious psychiatric or neurological disorders or uncontrolled systemic infection. The following concomitant therapies were forbidden at the time of registration for the study: drugs associated with torsades de pointes and prolongation of QT interval (indapamide, dobutamine, amiodarone, ibutilide, etc.), hormonal therapy, other chemotherapy, and systemic steroids.

**Table 1**
Baseline characteristics of patients ($n = 44$).

| Variables | Values |
|---|---|
| Age at enrollment (yr, mean ± SD) | 61.5 ± 8.9 |
| Gender | |
| Female | 21 (47.7%) |
| Male | 23 (52.3%) |
| Primary tumor site | |
| Intrahepatic CCC | 17 (38.6%) |
| Perihilar CCC | 9 (20.5%) |
| Extrahepatic CCC | 7 (15.9%) |
| Gallbladder cancer | 11 (25.0%) |
| Extent of disease | |
| Locally advanced | 3 (6.8%) |
| Metastatic | 41 (93.2%) |
| ECOG PS | |
| 0 | 6 (13.6%) |
| 1 | 24 (54.5%) |
| 2 | 14 (31.8%) |
| Number of prior anticancer treatments | |
| 1 | 18 (40.9%) |
| 2 | 16 (36.4%) |
| 3 or more | 10 (22.7%) |
| Previous gemcitabine-based treatment | |
| Gemcitabine and cisplatin | 40 (90.9%) |
| Gemcitabine alone | 1 (2.3%) |
| Gemcitabine and other agents | 3 (6.8%) |

SD: standard deviation; CCC: cholangiocarcinoma; ECOG PS: Eastern Cooperative Oncology Group performance status.

### *Treatment and assessment*

KML001 (Kominox, Komipharm International Co., Ltd., Siheung, Korea) was administered at a daily dose of 7.5 mg (2.5 mg three times a day orally before meals) to eligible subjects. KML001 dose was determined as safety-proven based on the results of previous studies, considering the salvage aim of our study [16,17]. Patients visited an outpatient clinic every two weeks for laboratory tests, including complete blood cell count and liver function test. Blood coagulation test, urine analysis, and electrocardiography were taken every four weeks. Every eight weeks, treatment response was evaluated by biliary CT. The best overall response to therapy was defined as the most favorable response after KML001 therapy according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [20]. Treatment-related toxicities were characterized using the Common Terminology Criteria for Adverse Events (CTCAE), version 4 [21]. Treatment was discontinued at 24 weeks, or due to disease progression, unacceptable toxic effects, poor general condition of the patient, loss to follow-up, and at the discretion of the patient or clinician. If disease progression was absent at 24 weeks, patients could continue the same treatment for another 24-week period. Treatment was stopped immediately if symptoms suggestive of acute arsenic toxicity, such as convulsions, muscle weakness, and confusion, were present.

### *Ethical approval and consent to participate*

The current study was approved by the institutional review board, and was conducted in accordance with the *Declaration of Helsinki* and the Good Clinical Practice Guidelines of the International Conference on Harmonisation (IRB approval number: 4-2012-0025). Patients provided their written consent before participating in the study. The human clinical study was performed

**Table 2**
Treatment outcomes ($n = 44$).

| Variables | Values |
|---|---|
| Treatment duration received (mon, median, range) | 1.5 (0.5–10.0) |
| Cause of dropping out | |
| Disease progression | 24 (54.5%) |
| AEs | 6 (13.6%) |
| Withdrawal of consent | 5 (11.4%) |
| Cancer-related death | 3 (6.8%) |
| Poor general condition | 3 (6.8%) |
| Loss to follow-up | 2 (4.5%) |
| Treatment response | |
| CR/PR | 0 |
| SD | 3 (6.8%) |
| PD | 23 (52.3%) |
| Could not be evaluated | 18 (40.9%) |
| Survival (mon, median, IQR) | |
| Progression-free survival | 1.7 (0.8–2.3) |
| Overall survival from study enrollment | 2.5 (1.4–4.9) |
| Overall survival from diagnosis | 16.7 (10.7–26.9) |
| Cases of KML001 toxicity | |
| Total | 29 (65.9%) |
| Grade 1 | 12 (27.3%) |
| Grade 2 | 18 (40.9%) |
| Grade 3 | 9 (20.5%) |
| Grade 4 | 0 |
| ECOG PS during treatment* | |
| Increased | 31 (73.8%) |
| Stable | 11 (26.2%) |
| Morphine needed during treatment* | |
| Increased | 22 (52.4%) |
| Stable | 18 (42.9%) |
| Decreased | 2 (4.8%) |

* ECOG PS and morphine need variances were evaluated in 42 patients, excluding two patients lost to follow-up. AEs: adverse events; CR: complete response; PR: partial response; SD: stable disease; PD: progressing disease; IQR: interquartile range; ECOG PS: Eastern Cooperative Oncology Group performance status.

under the emergency use of an investigational new drug (emergency IND) program approved by the Korean Ministry of Food and Drug safety (MFDS).

*Statistical analysis*

The primary endpoint of this study was disease control rate (DCR) of KML001, defined as the proportion of patients with a complete response (CR), partial response (PR), or stable disease (SD). The secondary endpoints were toxicity, OS, and progression-free survival (PFS). Data are presented as descriptive values and percentages, mean values with standard deviation (SD), or median values with range /interquartile ranges (IQR), as appropriate. OS and PFS are reported based on the Kaplan-Meier method. For data analysis, Predictive Analytics Software (Version 23, PASW, Chicago, IL, USA) was used.

## Results

*Baseline characteristics of patients*

Forty-four patients (21 women, 23 men) were enrolled between November 2011 and October 2014. Characteristics of these patients are summarized in Table 1. The mean age was $61.5 \pm 8.9$ years. There were 17 patients (38.6%) with intrahepatic cholangiocarcinoma, nine patients (20.5%) with perihilar cholangiocarcinoma, seven patients (15.9%) with extrahepatic cholangiocarcinoma, and 11 patients (25.0%) with gallbladder cancer. There were three patients (6.8%) with locally advanced disease and 41 patients (93.2%) with metastatic disease. Baseline ECOG PS scores were 0 in six patients (13.6%), 1 in 24 patients (54.5%), and 2 in 14 patients (31.8%). The median ECOG PS score was 1 (IQR, 1–2) in the entire cohort.

**Table 3**
Safety profile.

| Toxicity | CTCAE grade | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Hematological AE | | | | |
| Anemia | 3 | 4 | 3 | |
| Leucopenia | | 1 | | |
| Thrombocytopenia | | 2 | 1 | |
| Liver function | | | | |
| Liver enzyme elevation | 6 | 3 | 2 | |
| Jaundice | | 5 | 1 | |
| ALP level elevation | 1 | 1 | 1 | |
| Non-hematological AE | | | | |
| Nausea/vomiting | 1 | 2 | | |
| Anorexia | 1 | | | |
| Abdominal pain | | 1 | | |
| Abdominal distension | | 1 | | |
| Diarrhea | | | 1 | |
| Constipation | 1 | 1 | | |
| Impaired renal function | | 1 | 1 | |
| Hyponatremia | | | 1 | |
| Hypocalcemia | 2 | 1 | | |
| Hypoalbuminemia | 1 | 4 | | |
| Proteinuria | | 1 | | |
| Ascites | | 1 | 1 | |
| Herpes zoster | | 1 | | |
| Insomnia | 1 | | | |
| QTc prolongation | 1 | 1 | | |

CTCAE: common terminology criteria for adverse events; AE: adverse event; ALP: alkaline phosphatase; QTc: corrected QT interval.

The majority of patients had received two or more prior anticancer treatments (26 patients, 59.1%), and 18 patients (40.9%) had received one prior treatment. Forty patients (90.9%) had received gemcitabine and cisplatin combination therapy, three patients (6.8%) had received a different gemcitabine-based combination therapy, and one patient (2.3%) had received gemcitabine alone before enrollment.

*Treatment outcomes*

Treatment outcomes are described in Table 2. The mean treatment duration was 1.5 months (range: 0.5–10.0). At the end of the 24 weeks, only one patient remained in the study, while the other 43 patients dropped out due to disease progression detected during response evaluation (24 patients, 54.5%), AEs during treatment (six patients, 13.6%), withdrawal of consent by the patient (five patients, 11.4%), cancer-related death (three patients, 6.8%), poor general condition (three patients, 6.8%), and loss to follow-up (two patients, 4.5%).

Out of the 44 patients, 18 patients (40.9%) stopped the treatment before response evaluation. The causes of stopping the treatment were as follows: AEs (six patients, 13.6%), withdrawal of consent (five patients, 11.4%), cancer-related death (three patients, 6.8%), poor general condition (two patients, 4.5%), and loss to follow-up (two patients, 4.5%). Among the 26 patients who underwent response evaluation, three patients (6.8%) had SD, and 23 patients (52.3%) experienced disease progression. The median PFS was 1.7 months (IQR, 0.8–2.3 months), and the median OS from the time of enrollment was 2.5 months (IQR, 1.4–4.9 months).

Forty-two patients, excluding the two patients lost to follow-up, were evaluated for ECOG PS and the morphine need variance from the beginning until the end of treatment. During the treatment, 11 patients (26.2%) remained in tolerable general condition with no increase in ECOG PS, and the use of morphine as an analgesia remained the same or decreased in 20 patients (47.6%).

*Toxicity profile*

All of the 44 patients received KML001 for at least 2 weeks, and were evaluated for toxicity (Table 3). Sixty-one episodes of toxicity, mainly grade-1 or −2 AEs, were documented in 29 patients (65.9%), including 12 episodes of grade-3 AEs in nine patients (20.5%), including anemia ($n=3$), thrombocytopenia ($n=1$), liver enzyme level elevation ($n=2$), jaundice ($n=1$), alkaline phosphatase level elevation ($n=1$), diarrhea ($n=1$), impaired renal function ($n=1$), hyponatremia ($n=1$), and ascites ($n=1$). No grade-4 AEs were reported. The most common adverse event of any grade was liver enzyme elevation ($n=11$), followed by anemia ($n=10$). KML001 was discontinued in six patients (13.6%) due to AEs including liver toxicity ($n=3$), QTc prolongation ($n=2$), and abdominal pain ($n=1$). Symptoms suggestive of acute arsenic toxicity were not reported. No patient died from KML001-related toxicity.

## Discussion

This prospective study evaluated the outcomes of the use of KML001, an oral arsenic compound, as salvage treatment for advanced BTC patients after failure of gemcitabine-based chemotherapy in 44 patients. This is the first study of KML001 in BTC patients, as well as the largest clinical study of KML001 in patients with solid tumors. KML001 was found to be relatively safe and well-tolerated in terms of toxicity without grade-4 AEs. Furthermore, there were only two cases of drug-related cardio-toxicity, which had been a major concern of arsenic compound-related toxicity in a previous clinical trial [16]. In terms of safety, KML001 as single agent seemed to be a safe salvage treatment option for patients with intractable BTC.

Few studies have evaluated KML001 as a chemotherapeutic agent in patients. In a pilot preclinical study of Yoon et al., KML001 had an effect in two lymphoma patients [17]. In particular, two patients with refractory non-Hodgkin's lymphoma received 10 mg of KML001 as a single agent orally every day for 16 and 24 weeks, respectively. PR were seen in both patients without severe toxicity, except for grade-I/II anorexia and nausea. Although there were only two patients, this study produced valuable initial data on clinical effects of KML001.

Another phase-I study reported clinical effects and toxicity of KML001 and cisplatin combination therapy in 18 patients with advanced solid tumors after failure of prior chemotherapy [16]. Eleven patients with lung cancer, three with colorectal cancer, and four with other cancers received 75 mg/m$^2$ of cisplatin on day 1 and a daily dose of oral KML001 ranging from 7.5 mg to 20 mg on days 1–14, in a 21-day cycle. Among 13 patients evaluated for response, one demonstrated PR and nine had SD. The dose-limiting toxicity effect was QTc prolongation, observed in three patients who had received 20 mg/day of KML001. In addition to QTc prolongation, the most common AEs were nausea, vomiting, and cytopenia. Although results of the study provided initial valuable insights into the use of KML001 in solid tumors, the group of patients was small and heterogeneous, and whether the toxicity is from KML001 or cisplatin is not clear.

In our study, the frequency and severity of AEs of KML001 were at acceptable levels. Previous study reported overall rate of grade 3 or 4 toxic effects during treatment were 68.8% with gemcitabine alone and 70.7% with gemcitabine and cisplatin combination [4]. KML001 presented grade 3 or 4 toxicity in 20.5% of the patients, which was relatively lower than those treated with gemcitabine in the previous study. Furthermore, analysis of changes in morphine use and ECOG PS showed that KML001 administration could help pain control and general condition maintenance. Previous phase-I/II clinical trials in patients with hormone-refractory prostate cancer also reported that KML001 did not decrease the patients' feeling of well-being and improved the patients' status [16]. These characteristics can be advantageous if KML001 is used as a salvage chemotherapeutic agent for BTC, given that patients with BTC experience severe pain and are in poor general condition after administration of cisplatin as a first-line chemotherapy agent.

Previous randomized controlled study reported DCR of gemcitabine alone as first line chemotherapy was 71.8% in advanced biliary tract cancer [4]. In another previous systematic review which including 14 phase II clinical trials, 9 retrospective analyses, and 2 case reports presented that overall response rate of 2nd line chemotherapy for advanced biliary tract cancer was 7.7% and DCR was 49.5% [22]. DCR of KML001 in the present study was somewhat lower compared to that in previous studies. Furthermore, the percentage of patients who dropped out of the study was relatively high, with only one patient completing the planned 24 weeks of chemotherapy and the median duration of drug administration of just 1.5 months. However, the purpose of this study was to evaluate the salvage therapy, and a large number of patients had received multiple prior chemotherapies. Further studies in chemotherapy-naïve patients may result in better response rates and longer periods of drug administration. Furthermore, combining KML001 with a conventional chemotherapy agent could also improve response rate. A recent study in acute lymphoid leukemia cells demonstrated that a combination therapy with KML001 and doxercalciferol could become a future antileukemic treatment [23]. In another study, the combination of gemcitabine and KML001 was effective in pancreatic cancer cell lines, and KML001 enhanced the anticancer activity of gemcitabine by reducing EGFR and MMP2 expressions [19].

QTc prolongation was a frequent cause of discontinuation of KML001 in most previous studies. Although the inclusion/exclusion criteria of all above-mentioned studies included QTc prolongation, a significant number of patients experienced QTc prolongation after KML001 administration. In the present study, there were two patients with QTc prolongation among the six patients who dropped out due to AEs. Therefore, QTc prolongation may be considered the main AEs, and QTc should be continuously monitored during KML001 administration. However, torsades de pointes or drug-related deaths did not occur in our study. Close monitoring can help prevent severe AEs by managing QTc prolongation.

This study had several limitations. Since it was conducted under the emergency IND program and aimed at testing salvage chemotherapy in individuals with refractory cancer, all of the patients had already received one or more chemotherapies and were in relatively poor general condition. Although each patient had a history of receiving gemcitabine-based chemotherapy, prior chemotherapeutic profiles were heterogeneous compared to those in previous studies, with a possibility of greater resistance to chemotherapy among our patients. In addition, as mentioned above, the proportion of patients who underwent response evaluation and the rate of completion of the 24-week treatment were low, making it difficult to determine the therapeutic effect of KML001. This was also due to the fact that the patients were in need of salvage chemotherapy. To overcome such limitations, large prospective studies of KML001 alone and in combination with other agents in chemotherapy-naïve patients are needed in the future.

In conclusion, KML001 presented only limited treatment effect in terms of DCR. Although arsenic agents have been tried as a new anticancer drug, KML001 did not seem to have enough anticancer activity as single agent chemotherapy in advanced BTC patients resistant to gemcitabine. However, KML001 was safe and well-tolerated in terms of AEs, and it also showed pain control effects as palliative aim therapy. Further studies are needed to

evaluate whether arsenic agents are reliable treatment option for BTC patients.

## Contributors

SSY proposed the study. JJH and SSY performed the research and wrote the first draft. JJH collected and analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts. SSY is the guarantor.

## Funding

None.

## Ethical approval

This study was approved by the institutional review board and was conducted in accordance with the *Declaration of Helsinki* and the Good Clinical Practice Guidelines of the International Conference on Harmonisation (IRB approval number: 4-2012-0025).

## Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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