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ATM Expression as a Prognostic Marker in Patients With Advanced Biliary Tract Cancer Treated With First-line Gemcitabine and Platinum Chemotherapy

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Abstract. *Background/Aim: Biliary tract cancer (BTC) has a poor prognosis due to its highly invasive and metastatic potential. Ataxia-telangiectasia mutated (ATM) is a key regulator of DNA damage response and an emerging therapeutic target; however, the association between the expression of ATM and the prognosis in advanced BTC is unknown. We aimed to identify the relationship between ATM expression, clinicopathological characteristics, and survival outcomes in patients with advanced BTC. Patients and Methods: We analyzed 113 patients with advanced BTC who received first-line gemcitabine and platinum. Results: The tumor location was intrahepatic cholangiocarcinoma (IH-CCC) in 43 patients, extrahepatic cholangiocarcinoma (EH-CCC) in 49, and gallbladder (GB) cancer in 21 patients. Fifty-four patients (47.8%) exhibited loss of ATM protein expression. The overall response rate (ORR) of ATM loss and intact ATM was 13.3% and 19.6%, respectively. In a subgroup analysis, EH-CCC patients with ATM loss tended to have improved PFS after platinum-based chemotherapy compared to those with intact ATM (7.9 vs. 6.2 months, respectively; p=0.050). Conclusion: We demonstrated that ATM loss could be a prognostic marker after platinum-based chemotherapy in patients with advanced EH-CCC.*

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Biliary tract cancer (BTC) is a rare and heterogeneous malignancy that includes intra-hepatic cholangiocarcinoma (IH-CCC), extra-hepatic cholangiocarcinoma (EH-CCC), and gallbladder (GB) cancer (1). The prognosis remains poor due to its aggressive nature with a highly invasive and metastatic potential (2). Although fewer than 30% of BTC patients in a previous study intended to undergo curative resection, it was difficult to completely resect the tumours because of their anatomical complexity (3). Furthermore, responses to palliative chemotherapy in BTC have been disappointing, with only a 5-10% 5-year survival (1). The need for predictive biomarkers and novel therapeutic targets continues to increase to overcome the current limitations.

Ataxia-telangiectasia mutated (ATM) is an important member of the phosphatidylinositol 3-kinase-related kinase (PI3K) family. ATM is a primary activator and key regulator of DNA damage response and DNA double-strand breaks repair (4). ATM activation initiates downstream pathways of DNA repair, resulting in cell cycle arrest and apoptosis (5). Also, ATM functions in cancer development through metabolic regulation, migration, and chromatin remodeling (6). Recently, ATM inhibition emerged as a novel target for cancer therapy (7) that can also improve the effect of cytotoxic chemotherapy by generating DNA double-strand breaks and causing cell death (8).

ATM expression has a different prognostic role depending on cancer type and disease stage. Kim *et al.* have demonstrated that low expression of ATM is related to lower overall 5-year survival than intact ATM in patients with curatively resected gastric cancer [5-year disease-free

survival (DFS)=62.5%, 76.4%, respectively; p=0.017; 5-year overall survival (OS)=65.9%, 78.5%, respectively; p=0.027] (9). Another study has revealed that pancreatic cancer patients with ATM loss and normal TP53 had poor overall survival after curative resection (p=0.019) (10). In colorectal cancer, loss of ATM expression had been correlated with poor survival of patients receiving adjuvant therapy at an early stage, but a recent study showed that loss of ATM expression may be associated with improved survival in patients with platinum-based first-line chemotherapy (11, 12). Despite this, whether ATM expression is associated with prognosis in patients with advanced BTC is unknown.

In this study, we sought to identify the relationship between ATM expression and clinicopathological characteristics as well as survival outcomes in patients with advanced BTC treated with first-line gemcitabine and platinum chemotherapy.

Patients and Methods

Patients. We retrospectively reviewed 113 patients with advanced BTC treated at Samsung Medical Center who received palliative first-line gemcitabine and platinum chemotherapy between January 2010 and January 2015. Patients had histopathologically confirmed BTC, based on World Health Organization (WHO) classification. BTC consisted of IH-CCC, EH-CCC, and GB cancer. Exclusion criteria were: i) Ampulla of Vater cancer and ii) duodenal cancer. Data were collected from medical records and comprised: i) age, ii) sex, iii) date of diagnosis, iv) tumor location, v) differentiation of histology, vi) disease status, vii) sites and numbers of metastases, and viii) history of palliative chemotherapy. Outcomes included treatment response and date of progression or death. Treatment response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. OS was defined as the date from the first-line palliative chemotherapy administration to death. Progression-free survival (PFS) was calculated from the date of the first-line palliative chemotherapy administration to the date of disease progression or death. Overall response rate (ORR) was defined as the percentage of patients with complete or partial response (CR or PR, respectively). This study was approved by the Institutional Review Board of Samsung Medical Center (SMC 2020-02-076-001).

ATM immunohistochemistry. All patients were evaluated for ATM expression. Tissue sections (2 mm in diameter) were prepared from formalin-fixed, paraffin-embedded biopsy samples. As previously reported (13), the tissue was arrayed into a new recipient paraffin block (tissue array block) using a trephine device (Superbiochips Laboratories, Seoul, Republic of Korea). Immunohistochemical (IHC) staining was carried out with an automatic immunostainer (DAKO, Glostrup, Denmark), according to the manufacturer's instructions. The primary antibody was anti-ATM, Y170 (Abcam, Cambridge, UK). More than 50% loss of nuclear staining was defined as loss of ATM expression.

Statistical analysis. Student's t-test or the Mann–Whitney U-test was used to compare two continuous variables, and the Chi-square test or Fisher's exact test were used for the categorical variables. OS and PFS were analyzed using the Kaplan–Meier method and were compared by the log-rank test. Cox's proportional hazard model was used to determine the hazard ratio (HR) and corresponding 95% confidence interval (CI) for evaluating the prognostic value of ATM expression in each subgroup. A p-Value<0.05 was considered significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

Table I. *Characteristics of patients with biliary tract cancer.*

Characteristics	Total (n=113)
Age (years)	
Median (range)	61.0 (39-76)
>60	61 (54.0)
≤60	52 (46.0)
Gender	
Male	67 (59.3)
Female	46 (40.7)
Tumor location	
IH-CCC	43 (38.1)
EH-CCC	49 (43.4)
GB cancer	21 (18.6)
Differentiation	
WD	10 (8.8)
MD	70 (61.9)
PD	33 (29.2)
Disease status	
Recurrence	89 (78.8)
Metastasis	24 (21.2)
Liver metastasis	
Yes	46 (40.7)
No	67 (59.3)
No. of metastatic sites	
1	92 (81.4)
>1	21 (18.6)
Lines of palliative chemotherapy	
1	70 (61.9)
>1	43 (38.1)

IH-CCC: Intrahepatic cholangiocarcinoma; EH-CCC: extrahepatic cholangiocarcinoma; GB: gallbladder; WD: well differentiated; MD: moderately differentiated; PD: poorly differentiated; No.: number.

Results

Patient characteristics. Baseline characteristics of all 113 patients are presented in Table I. The mean age was 61.0 years (range=39-76 years), and 67 patients (59.3%) were male. The tumor location was: i) IH-CCC in 43 patients (38.1%), ii) EH-CCC in 49 patients (43.4%), and iii) GB cancer in 21 patients (18.6%). Histology revealed well-differentiated (WD) tumor in 10 patients (8.8%), moderately differentiated (MD) in 70 (61.9%), and poorly differentiated (PD) in 33 (29.2%). Eighty-nine patients (78.8%) experienced recurrence, and 24 (21.2%) had metastasis at presentation. Twenty-one patients (18.6%) had more than one metastatic lesion, and liver metastasis developed in 46 patients (40.7%). Seventy patients (61.9%) received only

Table II. *Comparison of patients with biliary tract cancer according to ATM expression.*

Characteristic	ATM		
	Loss (n=54)	Intact (n=59)	*p*-Value
Age (years)			
Median (range)	63.0 (39-76)	61.0 (44-75)	0.695
>60	30 (55.6)	31 (52.5)	0.748
≤60	24 (44.4)	28 (47.5)	
Gender			
Male	35 (64.8)	32 (54.2)	0.253
Female	19 (35.2)	27 (45.8)	
Tumor location			
IH-CCC	26 (48.1)	17 (28.8)	0.105
EH-CCC	20 (37.0)	29 (49.2)	
GB cancer	8 (14.8)	13 (22.0)	
Differentiation			
WD	5 (9.3)	5 (8.5)	0.291
MD	37 (68.5)	33 (55.9)	
PD	12 (22.2)	21 (35.6)	
Disease status			
Recurrence	43 (79.6)	46 (78.0)	0.829
Metastasis	11 (20.4)	13 (22.0)	
Liver metastasis			
Yes	25 (46.3)	21 (35.6)	0.247
No	29 (53.7)	38 (64.4)	
No. of metastatic sites			
1	45 (83.3)	47 (79.7)	0.616
>1	9 (16.7)	12 (20.3)	
Lines of palliative chemotherapy			
1	30 (55.6)	40 (67.8)	0.181
>1	24 (44.4)	19 (32.2)	

ATM: Ataxia-telangiectasia mutated; IH-CCC: intrahepatic cholangiocarcinoma; EH-CCC: extrahepatic cholangiocarcinoma; GB: gallbladder; WD: well differentiated; MD: moderately differentiated; PD: poorly differentiated; No.: number.

first-line chemotherapy due to their general condition or death. Death occurred in 106 patients by the cut-off time.

Overall survival and ATM expression in patients with advanced BTC. Of the 113 patients analyzed for ATM expression, the OS was 12.7 months (95% CI=11.1-14.4). Fifty-four patients (47.8%) exhibited loss of ATM protein expression on IHC. There were no statistically significant differences in clinicopathologic features between groups. Comparisons of ATM expression are listed in Table II. Groups with ATM loss *vs*. ATM intact did not have a difference in OS [13.4 months (95% CI=10.3-16.5) *vs*. 12.4 months (95% CI=10.5-14.4), p=0.813] (Figure 1A). In a subgroup analysis of tumor location, ATM expression showed no association with OS (ATM loss *vs*. intact: $OS_{IH\text{-}CCC}$=14.3 *vs*. 20.1 months, p=0.330; $OS_{EH\text{-}CCC}$=15.6 *vs*. 12.3 months, p=0.128; $OS_{GB\ cancer}$=10.8 *vs*. 10.0 months, p=0.784) (Figure 1B-D).

Table III. *Treatment response to first-line gemcitabine and platinum in patients with biliary tract cancer.*

Best response	Total (n=96)	ATM		
		Loss (n=45)	Intact (n=51)	*p*-Value
ORR	16 (16.7)	6 (13.3)	10 (19.6)	
CR	1 (1.0)	0 (0.0)	1 (2.0)	0.666
PR	15 (15.6)	6 (13.3)	9 (17.6)	
SD	55 (57.3)	29 (64.4)	26 (51.0)	
PD	25 (26.0)	10 (22.2)	15 (29.4)	

ATM: Ataxia-telangiectasia mutated; ORR: overall response rate; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

ATM expression and treatment response to first-line gemcitabine and platinum. All analyzed patients received gemcitabine and platinum as first-line chemotherapy for advanced BTC and completed a mean of 5.2 (±3.87) cycles. Of 113 patients, 96 underwent computed tomography (CT) scan to evaluate the best response to first-line chemotherapy. Treatment response is described in Table III. The ORR of all patients was 16.7%: CR in 1 patient (1.0%), PR in 15 (15.6%), and stable disease (SD) in 55 patients (57.3%). The ORR of subjects with ATM loss and intact was 13.3% and 19.6%, respectively. The PFS of all patients was 6.2 months (95% CI=5.2-7.2). Patients with ATM loss did not have improved PFS after first-line chemotherapy compared to those with ATM intact [6.2 months (95% CI=5.2-7.3) *vs*. 6.2 months (95% CI=4.1-8.4), p=0.459] (Figure 2A). A subgroup analysis was conducted according to tumor location. EH-CCC patients with ATM loss tended to have improved PFS compared to those with ATM intact after platinum-based chemotherapy (7.9 months *vs*. 6.2 months, p=0.050) (Figure 2B). All other subgroups of tumor location showed no association between ATM expression and PFS (ATM loss *vs*. intact: $PFS_{IH\text{-}CCC}$=6.0 *vs*. 7.8 months, p=0.753; $PFS_{GB\ cancer}$=4.9 *vs*. 2.8 months, p=0.762) (Figure 2C and D).

Discussion

This study evaluated the role of ATM expression as a prognostic marker in advanced BTC treated with gemcitabine and platinum chemotherapy and demonstrated that EH-CCC patients show a meaningful association between ATM loss and improved PFS. However, ATM expression in other subgroups was not associated with survival outcomes. This may be the result of complex interactions regarding the function of ATM in carcinogenesis and progression of BTC, including multiple pathways, regulators, and effectors. This is the first study that has evaluated ATM protein expression in advanced BTC patients treated with first-line chemotherapy.

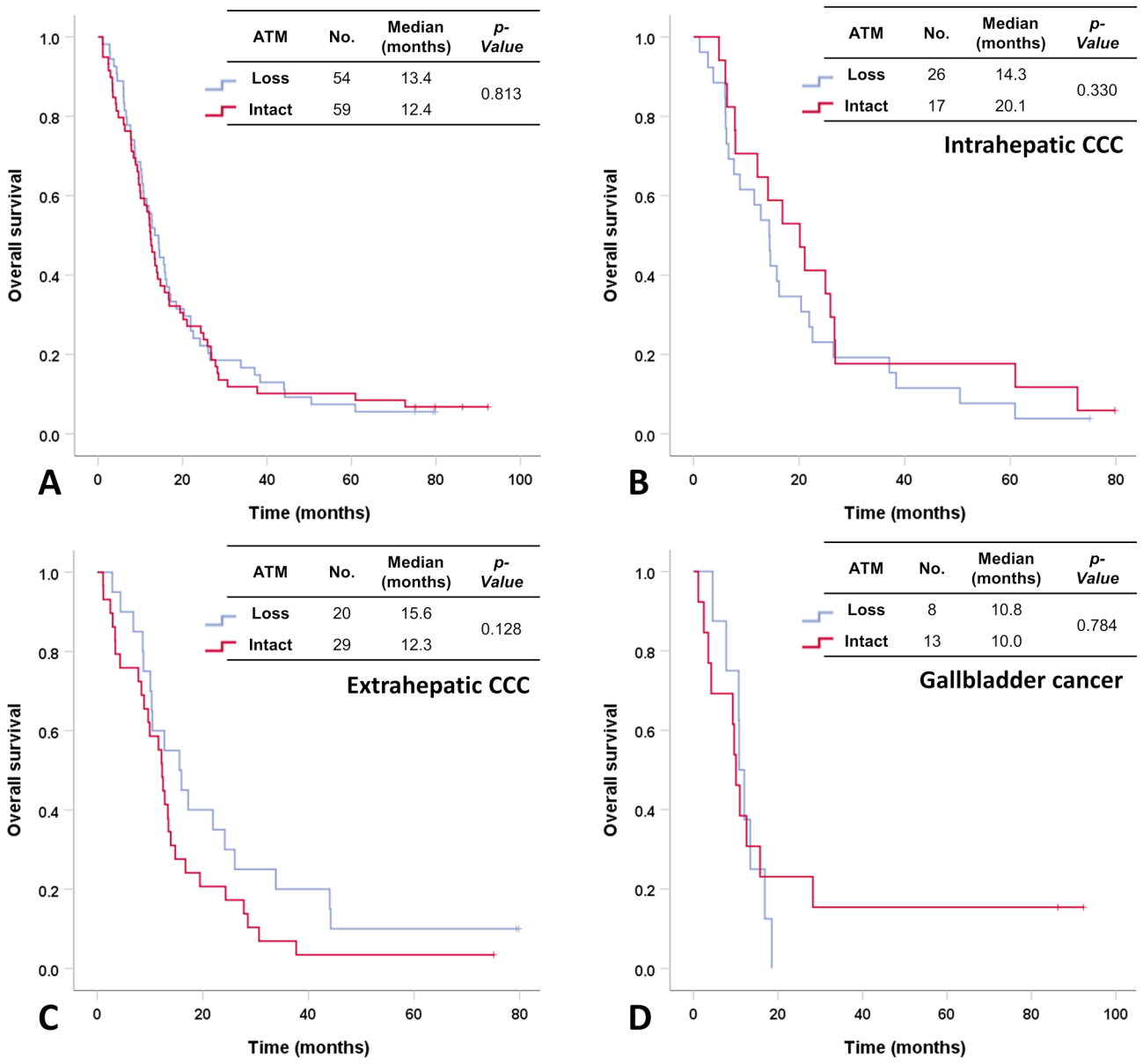

Figure 1. *Overall survival after first-line gemcitabine and platinum according to ATM expression in patients with biliary tract cancer. ATM: Ataxia-telangiectasia mutated; CCC: cholangiocarcinoma; No.: number.*

Deficient DNA mismatch repair (dMMR) is commonly found in several solid cancers and is a well-known predictive marker for patients' response to immune checkpoint inhibitors that target programmed cell death protein 1 (PD-1) (14). However, data of DNA repair mutations, including ATM in BTC, are very limited because of the considerably low incidence. Nakamura *et al*. have studied mutational spectra in 260 BTC patients and revealed that the prevalence of ATM mutation was 4% in IH-CCC, 3% in EH-CCC, and 7% in GB cancer (15, 16).

BTC patients with mutations in the DNA repair pathways are candidates for targeted therapy, such as specific DNA repair inhibitors or immune checkpoint inhibitors. ATM is required to repair DNA after PARP inhibition (17, 18). In a phase II study of paclitaxel with or without olaparib for advanced gastric cancer, subjects in the ATM-low subgroup had improved OS (19). Also, ATM influences the functions of other protein kinases related to cell-cycle arrest and survival, including ataxia telangiectasia and Rad3-related protein (ATR), ATR-checkpoint kinase (Chk), and Protein Kinase B (AKT) (4).

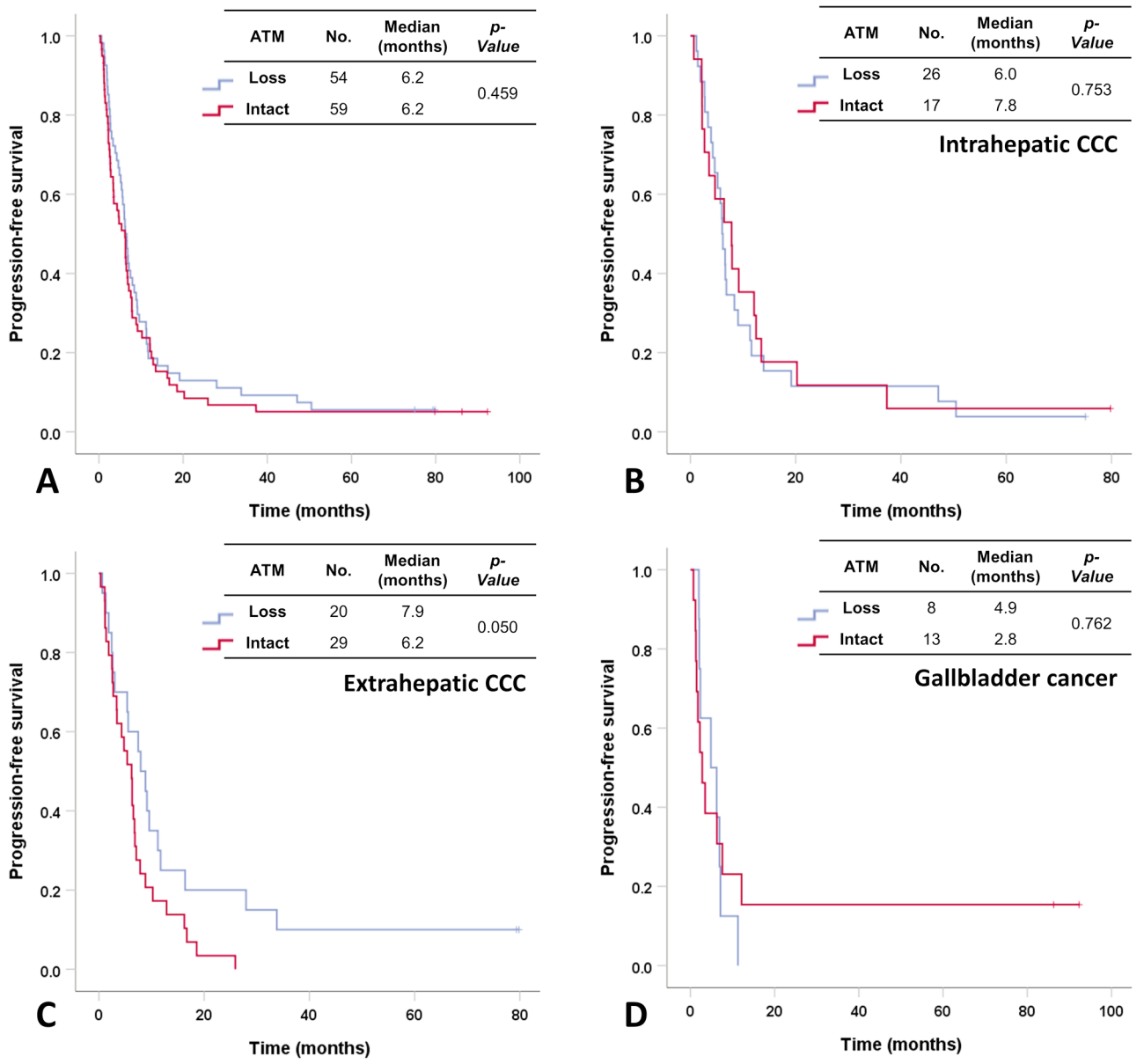

Figure 2. *Progression-free survival after first-line gemcitabine and platinum according to ATM expression in patients with biliary tract cancer. ATM: Ataxia-telangiectasia mutated; CCC: cholangiocarcinoma; No.: number.*

Inhibitors of all these protein kinases, including ATM, are potential targets in development. Further research and clinical trials are needed to develop and validate novel targeted agents.

Genetic mutations related to double-strand DNA repair pathways have a potential to enhance platinum sensitivity (20). Platinum induces double-strand DNA breaks, which lead to genomic instability and cell death. This mechanism has been demonstrated in BRCA-mutated breast and ovarian cancers. Patients with BRCA1-mutated breast cancer in both neoadjuvant and metastatic settings had a high response to platinum-based chemotherapy (21, 22). Likewise, loss of function mutations in the ATM gene are expected to generate a synergistic effect with DNA damage due to platinum. Sundar *et al*. have analyzed and demonstrated an association of ATM loss with improved OS in 223 metastatic colorectal cancer patients treated with oxaliplatin-based first-line treatment (HR=0.57; 95% CI=0.33–0.98; p=0.04) but did not show such an association with irinotecan-based treatment (12). Our study is the first report of first-line outcomes in advanced BTC patients treated with gemcitabine and

platinum that have been classified by ATM expression. In this cohort, EH-CCC patients with ATM loss tended to have improved PFS compared to patients with ATM intact after platinum-based chemotherapy.

There were several limitations to this study. First, its retrospective nature and the non-random distribution in groups could influence outcomes through selection bias. Second, we did not address the genetic mutations of ATM, which could have discordance with ATM protein expression because of non-genomic changes. Third, the heterogeneity of the cohort, such as tumor location and disease status, could result in mixed outcomes. Fourth, although we defined the cut-off for loss of ATM expression as 50%, the optimal level has not yet been established. Finally, insufficient tissue volume due to technical difficulties in biopsy can affect the laboratory result of ATM expression. Nevertheless, this study provided useful information and a direction of future research and targeted therapy in advanced BTC.

In conclusion, we demonstrated that loss of ATM expression was a prognostic marker in patients with advanced EH-CCC after platinum-based chemotherapy. A treatment strategy targeting ATM for advanced BTC patients requires more research and trials.

Conflicts of Interest

There are no relevant conflicts of interest to declare.

Authors' Contributions

Conception and design by STK, JOP; administrative support by HK, STK, KHY, JYH, YSP, HYL and JOP; provision of study materials or patients: HK, STK, KHY, JYH, YSP, HYL and JOP; collection and assembly of data by HK, STK and KHY; data analysis and interpretation by HK, STK, KHY and JOP; Manuscript writing and final approval by all authors.

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