ANTICANCER RESEARCH *36*: 4965-4970 (2016)
doi:10.21873/anticanres.11065

No Survival Benefit from the Inhibition of Renin–Angiotensin System in Biliary Tract Cancer

YOUSUKE NAKAI, HIROYUKI ISAYAMA, TAKASHI SASAKI, NAMINATSU TAKAHARA, KEI SAITO, TSUYOSHI TAKEDA, GYOTANE UMEFUNE, TOMOTAKA SAITO, KAORU TAKAGI, TAKEO WATANABE, TSUYOSHI HAMADA, RIE UCHINO, SUGURU MIZUNO, KEISUKE YAMAMOTO, HIROFUMI KOGURE, SABURO MATSUBARA, NATSUYO YAMAMOTO, HIDEAKI IJICHI, KEISUKE TATEISHI, MINORU TADA and KAZUHIKO KOIKE

Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Abstract. *Aim: The renin–angiotensin system (RAS) was investigated as a target for cancer treatment. Patients and Methods: A total of 287 patients with biliary tract cancer (BTC) receiving chemotherapy were retrospectively studied to evaluate the role of inhibition of RAS by angiotensin system inhibitors (ASIs). Progression-free survival (PFS) and overall survival (OS) were compared between 74 patients with hypertension, on ASIs (ASI group), 50 patients with hypertension not on ASIs (non-ASI with HT group) and 163 patients without hypertension (non-HT group). Interactions between the use of ASIs and various subgroups were explored. Results: The median PFS was 3.6, 3.9 and 4.6 months (p=0.495) and the median OS was 11.6, 10.9 and 13.1 months (p=0.668), respectively. The use of ASIs was not associated with OS (hazard ratio 1.00, p=0.975) and no subgroups with better survival were identified. Conclusion: No survival benefit from ASIs was observed in BTC.*

The local renin–angiotensin system (RAS) in association with angiogenesis, cell proliferation, or fibrosis has been intensively investigated as a potential target for cancer treatment (1, 2). Increasing evidence has been reported regarding better clinical outcomes in various cancer types from the use of angiotensin system inhibitors (ASIs) (3-7). We previously reported the use of ASIs was associated with better survival in patients with advanced pancreatic cancer (8).

Correspondence to: Hiroyuki Isayama, Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo Bunkyo-ku, Tokyo 113-8655, Japan. Tel: +81 338155411, Fax: +81 358009801, e-mail: isayama-tky@umin.ac.jp

Key Words: Angiotensin system inhibitor, biliary tract cancer, chemotherapy, renin-angiotensin system.

Although in biliary tract cancer (BTC) limited evidence is available on the role of RAS, it is reportedly associated with fibrosis, cancer incidence and survival in chronic liver disease and hepatocellular carcinoma (9-11). The association of RAS and intra- or extra-hepatic BTC was also suggested (12-14). Therefore, we conducted this retrospective analysis of 287 patients with advanced or recurrent BTC receiving systemic chemotherapy in order to evaluate the role of inhibition of RAS in BTC.

Patients and Methods

Patients. Consecutive patients receiving first-line systemic chemotherapy for advanced or recurrent BTC between February 2002 and May 2015 at the University of Tokyo Hospital were retrospectively studied. Data on the use of ASIs, including angiotensin I-converting enzyme inhibitors (ACEIs) or angiotensin II type-1 receptor blockers (ARBs), and other medications were retrospectively retrieved from the medical records. This study was approved by the local Ethics Committee (no.1804).

Treatment outcomes. Tumor response was assessed by computed tomography (CT) using Response Evaluation Criteria In Solid Tumors (RECIST) criteria (15). The evaluation was repeated every two courses (every 6 to 12 weeks depending on the regimens), or more frequently in patients with clinically suspected progression. Tumor response, progression-free survival (PFS) and overall survival (OS) were compared among patients with hypertension on ASIs (the ASI group), patients with hypertension not on ASIs (the non-ASI with HT group), and patients without hypertension (the non-HT group).

Statistical methods. PFS and OS were estimated using the Kaplan–Meier method and compared using the log-rank test. The Chi-square test or Fisher's exact test was used to compare categorical variables. The independent *t*-test or Mann–Whitney *U*-test was used to compare continuous variables as appropriate.

The univariate and multivariate Cox proportional hazard model was performed to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) of prognostic factors for OS. In addition, interactions

Table I. *Patient characteristics*.

	ASI group (n=74)	Non-ASI with HT group (n=50)	Non-HT group (n=163)	*p*-Value
Age	74 (21-88)	75 (55-92)	67 (25-89)	<0.001
Male/female	46 (62%)/28 (38%)	32 (64%)/18 (36%)	95 (58%)/68 (42%)	0.718
PS 0/1/2	33 (51%)/38 (51%)/3 (4%)	27 (54%)/20 (40%)/3 (6%)	74 (45%)/81 (50%)/8 (5%)	0.742
Tumor status				0.864
Locally advanced	14 (19%)	11 (22%)	26 (16%)	
Metastatic	40 (54%)	25 (50%)	87 (53%)	
Recurrent	20 (27%)	14 (28%)	50 (31%)	
Tumor location				0.947
Intrahepatic	29 (39%)	17 (34%)	54 (33%)	
Extrahepatic	19 (26%)	15 (30%)	52 (32%)	
Gallbladder	21 (28%)	16 (32%)	48 (29%)	
Ampulla	5 (7%)	2 (4%)	9 (6%)	
Site of metastasis				
Liver	29 (39%)	14 (28%)	58 (36%)	0.428
Lung	13 (18%)	7 (14%)	19 (12%)	0.429
Peritoneum	17 (23%)	8 (16%)	36 (22%)	0.612
Lymph nodes	29 (39%)	23 (46%)	85 (52%)	0.177
Smoking	37 (50%)	19 (38%)	83 (51%)	0.276
Alcohol (>50 g/day)	13 (18%)	4 (8%)	17 (10%)	0.203
Diabetes	24 (32%)	9 (18%)	21 (13%)	0.002
Hyperlipidemia	21 (28%)	12 (24%)	5 (3%)	<0.001
Chronic liver disease	10 (14%)	9 (18%)	16 (10%)	0.275
CEA, ng/dl	6.6 (1-1921)	5.5 (1-460)	5.6 (0.8-7453)	0.671
CA19-9, IU/l	258 (1-100800)	243 (1-106900)	160 (1-196400)	0.808

Numbers are shown either as absolute numbers (%) or median (range). ASI, Angiotensin system inhibitor; HT, hypertension; PS, performance status.

between the use of ASIs for each subgroup were tested with $p<0.10$ suggesting heterogeneity across subgroups for each factor. Potential prognostic factors and subgroups for interaction included age (<69 or ≥69 years old); gender (male or female); performance status (PS, 0 or ≥1); tumor status (locally advanced, metastatic or recurrent disease), tumor location (intrahepatic or non-intrahepatic); the presence of metastasis in the liver, lung, peritoneum and lymph nodes (yes or no); smoking (ever or never smokers); alcohol intake (<50 g/day or ≥50 g/day); carcinoembryonic antigen (CEA) (<5.8 or ≥5.8 ng/dl); carbohydrate antigen 19-9 (CA19-9) (<205 or ≥205 IU/l); the use of calcium channel blockers (yes or no) and beta blockers (yes or no); diabetes (yes or no), hyperlipidemia (yes or no); chronic liver disease (yes or no); the use of statins (yes or no) and aspirin (yes or no); and treatment protocol (monotherapy or combination therapy). Age, CEA and CA19-9 were dichotomized by the median value of each parameter. All reported *p*-values, other than p for interaction described below, were the results of two-sided tests, with $p<0.05$ considered statistically significant. JMP software version 11.0 (SAS Institute, Inc, Cary, NC, USA) was used for all statistical analyses.

Results

Patients. In total, 287 patients received first-line chemotherapy for advanced or recurrent BTC between March 2002 and May 2015 at The University of Tokyo Hospital, with a median follow-up time of 9.3 months. Administered regimens were gemcitabine monotherapy (n=74), S-1 monotherapy (n=59), gemcitabine and cisplatin (n=57), gemcitabine and S-1 (n=78) and gemcitabine, S-1 and leucovorin (n=19). Among 124 patients with hypertension, 74 patients took ASIs: 61 ARBs and 13 ACEIs. The other antihypertensive medications used in our study population were calcium channel blockers (n=84) and beta blockers (n=17).

Patient characteristics of three groups are shown in Table I. There were significant differences only in age and the prevalence of diabetes and hyperlipidemia between the three groups.

Treatment outcomes. In the total cohort of 287 patients with advanced or recurrent BTC, the response rate was 13.6% (95% CI=10.1-18.0%), and the median PFS and OS were 4.0 (95% CI=3.6-5.0) and 12.3 (95% CI=10.9-14.7) months, respectively.

When three groups categorized by hypertension and the use of ASIs were compared, there were no significant differences in clinical outcomes. Response rates were 10.8% (95% CI=5.6-19.9%), 14.0% (95% CI=7.0-26.2%) and 14.7% (95% CI=10.1-21.0%) in the ASI, non-ASI with HT and non-HT groups ($p=0.727$), respectively. The median PFS was 3.6 (95% CI=2.8-5.5) months, 3.9 (95% CI=1.9-6.7)

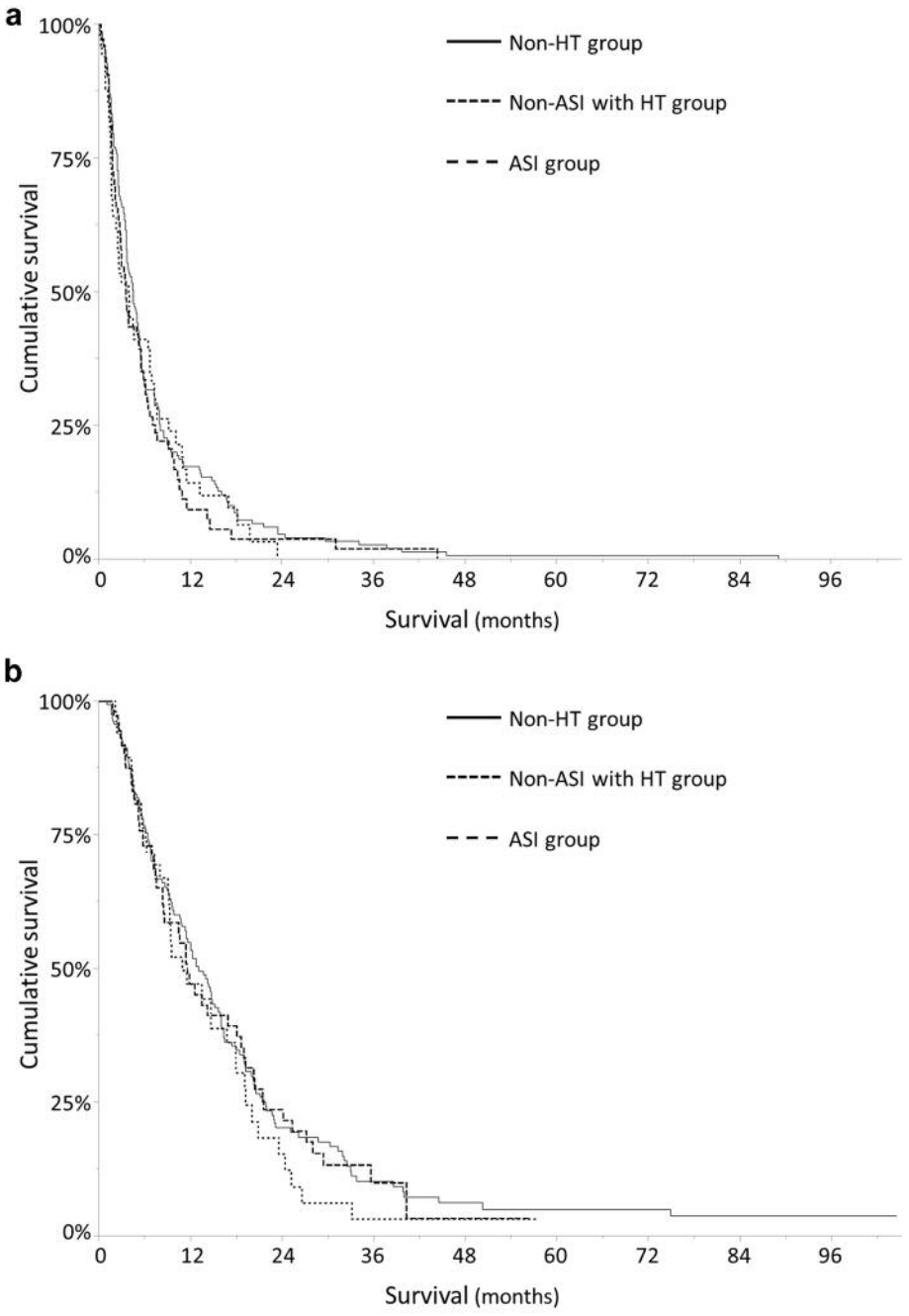

Figure 1. *a: Progression-free survival. The median progression-free survival was 3.6 months, 3.9 months and 4.6 months in the angiotensin system inhibitor (ASI), non-ASI with hypertension (HT) and non-HT groups (p=0.495). b: Overall survival. The median overall survival was 11.6 months, 10.9 months and 13.1 months in the ASI, non-ASI with HT and non-HT groups (p=0.668).*

months and 4.6 (95% CI=3.6-5.2) months and the median OS was 11.6 (95% CI=8.4-18.0) months, 10.9 (95% CI=9.0-17.9) months and 13.1 (95% CI=10.9-15.6) months in the ASI, non-ASI with HT, and non-HT groups (p=0.668), respectively. Kaplan–Meier curves of PFS and OS are shown in Figure 1.

The univariate and multivariate analyses of prognostic factors for OS are shown in Table II. The use of ASIs was not associated with OS (HR=1.00, p=0.975) in univariate analysis. PS, lung metastasis and peritoneal dissemination were found to be significant prognostic factors in the multivariate analysis. The association of ASI use with OS

Table II. *Univariate and multivariate analyses of prognostic factors for overall survival.*

		Univariate			Multivariate		
		HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age	≥69 Years	1.39	1.06-1.82	0.016	1.22	0.92-1.60	0.166
Gender	Male	0.83	0.63-1.08	0.161			
PS	0	0.54	0.41-0.70	<0.001	0.51	0.38-0.68	<0.001
Tumor status	Locally advanced	1			1		
	Metastatic	1.62	1.15-2.32	0.005	1.22	0.80-1.86	0.358
	Recurrent	1.10	0.74-1.63	0.649	0.98	0.62-1.54	0.921
Tumor location	Gallbladder	1			1		
	non-gallbladder	0.70	0.53-0.93	0.015	0.78	0.57-1.06	0.111
Metastasis	Liver	1.37	1.03-1.82	0.031	1.26	0.92-1.72	0.142
	Lung	1.48	1.00-2.12	0.048	1.56	1.04-2.28	0.032
	Peritoneum	1.43	1.02-1.96	0.040	1.47	1.01-2.08	0.043
	Lymph nodes	1.34	1.03-1.75	0.030	1.09	0.80-1.47	0.586
Smoking	Yes	0.90	0.69-1.18	0.453			
Alcohol (>50 g/day)		0.98	0.62-1.46	0.920			
Hypertension		1.09	0.83-1.43	0.510			
ASIs		1.00	0.73-1.36	0.975			
Ca channel blockers		1.04	0.77-1.39	0.791			
Beta blockers		0.94	0.48-1.64	0.835			
Diabetes		1.10	0.78-1.53	0.572			
Hyperlipidemia		1.01	0.67-1.46	0.970			
Chronic liver disease		1.30	0.84-1.93	0.225			
CEA	≥5.8 ng/dl	1.59	1.21-2.07	0.001	1.27	0.94-1.70	0.107
CA19-9	≥205 IU/l	1.45	1.11-1.90	0.007	1.28	0.97-1.69	0.083
Monotherapy		1.19	0.92-1.55	0.190			

ASI, Angiotensin system inhibitor; CEA, carcinoembryonic antigen; CA19-9: carbohydrate antigen19-9; CI: confidence interval; HR, hazard ratio; PS, performance status.

was not significant even after matching with those patient characteristics related to ASI use (age, diabetes and hyperlipidemia), with an HR of 1.08 (p=0.647).

Cox proportional hazard analyses were then performed to explore subgroups with better survival according to the use of ASIs, but no subgroups associated with better survival were identified (Table III).

Discussion

There have been increasing reports on the association of RAS with prognosis of patients with cancer, including pancreatic cancer (8). In hepatocellular carcinoma, the inhibition of RAS was also reported to be associated with longer OS and recurrence-free survival after radiofrequency ablation (11). Although the association of RAS with BTC development and progression was suggested, especially in intrahepatic BTC (12, 14), there have been no clinical studies investigating the association of prognosis with the inhibition of RAS. In this retrospective analysis of 287 patients receiving chemotherapy for BTC, the inhibition of RAS was not associated with better tumor response, PFS or OS.

In our previous analysis of patients with advanced pancreatic cancer (16), never-smokers, and those receiving gemcitabine monotherapy were likely to show better outcomes by use of ASIs. However, this exploratory analyses in BTC failed to identify any subgroup which would benefit from the inhibition of RAS. In addition, *ex vivo* experiments suggested medications such as aspirin (17) and statins (18) might have inhibitive effects on cancer development or progression, but no interaction of aspirin or statins with ASIs was identified. In advanced pancreatic cancer, prospective studies (19, 20) failed to demonstrate additional effects of ARB despite positive results in our retrospective study (8), and it is possible that cancer developing in patients who have been on ASIs might behave differently from cancer in patients who start ASIs after cancer development. Subtyping by gene-expression analysis (21), rather than by clinical factors in our study, might be useful to identify any subgroup which would benefit from the inhibition of RAS.

This study has certain limitations. Firstly, this was a single-center, retrospective analysis. Secondly, our study population was heterogeneous, including patients with various sites of BTC with different disease stages, compared

Table III. *Subgroup analyses for overall survival*.

		n	HR	95%CI	*p*-Value	P for interaction
All		287	1.00	0.73-1.36	0.975	-
Age	<69 Years	143	1.00	0.60-1.60	0.989	0.683
	≥69Years	144	0.84	0.55-1.26	0.409	
Gender	Male	173	0.93	0.61-1.39	0.728	0.518
	Female	114	1.15	0.71-1.79	0.565	
PS	0	134	0.84	0.53-1.31	0.453	0.127
	≥1	153	1.32	0.85-2.00	0.210	
Tumor status	Locally advanced	51	1.26	0.60-2.45	0.520	0.908
	Metastatic	152	0.98	0.63-1.46	0.906	
	Recurrent	84	0.96	0.49-1.73	0.893	
Tumor location	Intrahepatic bile duct cancer	100	0.83	0.47-1.40	0.495	0.339
	Others	187	1.12	0.76-1.62	0.545	
Metastasis						
Liver	Yes	101	0.95	0.55-1.57	0.845	0.854
	No	186	1.01	0.68-1.46	0.963	
Lung	Yes	39	1.03	0.46-2.15	0.938	0.515
	No	248	0.96	0.68-1.33	0.809	
Peritoneum	Yes	61	1.22	0.63-2.26	0.545	0.569
	No	226	0.95	0.66-1.34	0.782	
Lymph nodes	Yes	137	1.11	0.67-1.74	0.676	0.531
	No	150	0.95	0.62-1.42	0.817	
Smoking	Ever smokers	139	0.92	0.57-1.42	0.706	0.511
	Never smokers	148	1.13	0.73-1.71	0.571	
Alcohol (>50 g/day)	Yes	34	0.57	0.22-1.35	0.208	0.233
	No	253	1.09	0.78-1.50	0.618	
CEA	<5.8 ng/dl	145	1.25	0.77-1.93	0.353	0.143
	≥5.8 ng/dl	142	0.78	0.50-1.18	0.247	
CA19-9	<205 IU/l	143	1.04	0.64-1.62	0.859	0.658
	≥205 IU/l	144	0.91	0.59-1.37	0.669	
Ca channel blockers	Yes	84	0.83	0.50-1.37	0.462	0.417
	No	203	1.13	0.71-1.71	0.588	
Beta blockers	Yes	17	0.45	0.09-1.86	0.270	0.321
	No	270	1.06	0.76-1.45	0.743	
Diabetes	Yes	54	0.94	0.51-1.76	0.853	0.700
	No	233	0.95	0.64-1.36	0.778	
Hyperlipidemia	Yes	38	0.80	0.38-1.69	0.554	0.650
	No	249	1.04	0.72-1.47	0.810	
Chronic liver disease	Yes	35	0.95	0.39-2.15	0.907	0.788
	No	252	1.00	0.71-1.39	0.979	
Statins	Yes	35	0.90	0.41-2.02	0.787	0.918
	No	252	1.03	0.72-1.45	0.863	
Aspirin	Yes	23	0.92	0.23-2.42	0.866	0.720
	No	264	1.00	0.72-1.38	0.979	
Monotherapy	Yes	133	0.87	0.54-1.37	0.567	0.376
	No	154	1.14	0.74-1.70	0.542	

CEA, Carcinoembryonic antigen; CA19-9: carbohydrate antigen19-9; CI: confidence interval; HR, hazard ratio; PS, performance status.

with our previous report on advanced pancreatic cancer (8). Therefore, the number of patients in subgroup analyses was too small, and a large-scale study might identify some subgroups which would benefit from ASIs.

In conclusion, no survival benefits from the use of ASIs were observed in patients receiving chemotherapy for advanced or recurrent BTC in our retrospective analysis.

References

1 Ager EI, Neo J and Christophi C: The renin-angiotensin system and malignancy. Carcinogenesis *29*: 1675-1684, 2008.

2 Khakoo AY, Sidman RL, Pasqualini R and Arap W: Does the renin–angiotensin system participate in regulation of human vasculogenesis and angiogenesis? Cancer Res *68*: 9112-9115, 2008.

3 Wilop S, von Hobe S, Crysandt M, Esser A, Osieka R and Jost E: Impact of angiotensin I converting enzyme inhibitors and angiotensin II type 1 receptor blockers on survival in patients with advanced non-small-cell lung cancer undergoing first-line platinum-based chemotherapy. J Cancer Res Clin Oncol *135*: 1429-1435, 2009.

4 Keizman D, Huang P, Eisenberger MA, Pili R, Kim JJ, Antonarakis ES, Hammers H and Carducci MA: Angiotensin system inhibitors and outcome of sunitinib treatment in patients with metastatic renal cell carcinoma: a retrospective examination. Eur J Cancer *47*: 1955-1961, 2011.

5 Kim ST, Park KH, Oh SC, Seo JH, Kim JS, Shin SW and Kim YH: How does inhibition of the renin-angiotensin system affect the prognosis of advanced gastric cancer patients receiving platinum-based chemotherapy? Oncology *83*: 354-360, 2012.

6 Yuge K, Miyajima A, Tanaka N, Shirotake S, Kosaka T, Kikuchi E and Oya M: Prognostic value of renin-angiotensin system blockade in non-muscle-invasive bladder cancer. Ann Surg Oncol *19*: 3987-3993, 2012.

7 Aydiner A, Ciftci R and Sen F: Renin-Angiotensin system blockers may prolong survival of metastatic non-small cell lung cancer patients receiving erlotinib. Medicine *94*: e887, 2015.

8 Nakai Y, Isayama H, Ijichi H, Sasaki T, Sasahira N, Hirano K, Kogure H, Kawakubo K, Yagioka H, Yashima Y, Mizuno S, Yamamoto K, Arizumi T, Togawa O, Matsubara S, Tsujino T, Tateishi K, Tada M, Omata M and Koike K: Inhibition of renin-angiotensin system affects prognosis of advanced pancreatic cancer receiving gemcitabine. Br J Cancer *103*: 1644-1648, 2010.

9 Jonsson JR, Clouston AD ando Y, Kelemen LI, Horn MJ, Adamson MD, Purdie DM and Powell EE: Angiotensin-converting enzyme inhibition attenuates the progression of rat hepatic fibrosis. Gastroenterology *121*: 148-155, 2001.

10 Yoshiji H, Yoshii J, Ikenaka Y, Noguchi R, Tsujinoue H, Nakatani T, Imazu H, Yanase K, Kuriyama S and Fukui H: Inhibition of renin-angiotensin system attenuates liver enzyme-altered preneoplastic lesions and fibrosis development in rats. J Hepatol *37*: 22-30, 2002.

11 Facciorusso A, Del Prete V, Crucinio N, Muscatiello N, Carr BI, Di Leo A and Barone M: Angiotensin receptor blockers improve survival outcomes after radiofrequency ablation in hepatocarcinoma patients. J Gastroenterol Hepatol *30*: 1643-1650, 2015.

12 Okamoto K, Tajima H, Ohta T, Nakanuma S, Hayashi H, Nakagawara H, Onishi I, Takamura H, Ninomiya I, Kitagawa H, Fushida S, Tani T, Fujimura T, Kayahara M, Harada S, Wakayama T and Iseki S: Angiotensin II induces tumor progression and fibrosis in intrahepatic cholangiocarcinoma through an interaction with hepatic stellate cells. Int J Oncol *37*: 1251-1259, 2010.

13 Beyazit Y, Purnak T, Suvak B, Kurt M, Sayilir A, Turhan T, Tas A, Torun S, Celik T, Ibis M and Haznedaroglu IC: Increased ACE in extrahepatic cholangiocarcinoma as a clue for activated RAS in biliary neoplasms. Clin Res Hepatol Gastroenterol *35*: 644-649, 2011.

14 Okamoto K, Tajima H, Nakanuma S, Sakai S, Makino I, Kinoshita J, Hayashi H, Nakamura K, Oyama K, Nakagawara H, Fujita H, Takamura H, Ninomiya I, Kitagawa H, Fushida S, Fujimura T, Harada S, Wakayama T, Iseki S and Ohta T: Angiotensin II enhances epithelial-to-mesenchymal transition through the interaction between activated hepatic stellate cells and the stromal cell-derived factor-1/CXCR4 axis in intrahepatic cholangiocarcinoma. Int J Oncol *41*: 573-582, 2012.

15 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC and Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst *92*: 205-216, 2000.

16 Nakai Y, Isayama H, Sasaki T, Takahara N, Saito K, Ishigaki K, Hamada T, Mizuno S, Miyabayashi K, Yamamoto K, Mohri D, Kogure H, Yamamoto N, Ijichi H, Tateishi K, Tada M and Koike K: The inhibition of renin–angiotensin system in advanced pancreatic cancer: an exploratory analysis in 349 patients. J Cancer Res Clin Oncol *141*: 933-939, 2015.

17 Fendrich V, Chen NM, Neef M, Waldmann J, Buchholz M, Feldmann G, Slater EP, Maitra A and Bartsch DK: The angiotensin-I-converting enzyme inhibitor enalapril and aspirin delay progression of pancreatic intraepithelial neoplasia and cancer formation in a genetically engineered mouse model of pancreatic cancer. Gut *59*: 630-637, 2010.

18 Chae YK, Valsecchi ME, Kim J, Bianchi AL, Khemasuwan D, Desai A and Tester W: Reduced risk of breast cancer recurrence in patients using ACE inhibitors, ARBs and/or statins. Cancer Invest *29*: 585-593, 2011.

19 Nakai Y, Isayama H, Ijichi H, Sasaki T, Kogure H, Yagioka H, Miyabayashi K, Mizuno S, Yamamoto K, Mouri D, Kawakubo K, Yamamoto N, Hirano K, Sasahira N, Tateishi K, Tada M and Koike K: Phase I trial of gemcitabine and candesartan combination therapy in normotensive patients with advanced pancreatic cancer: GECA1. Cancer Sci *103*: 1489-1492, 2012.

20 Nakai Y, Isayama H, Ijichi H, Sasaki T, Takahara N, Ito Y, Matsubara S, Uchino R, Yagioka H, Arizumi T, Hamada T, Miyabayashi K, Mizuno S, Yamamoto K, Kogure H, Yamamoto N, Hirano K, Sasahira N, Tateishi K, Tada M and Koike K: A multicenter phase II trial of gemcitabine and candesartan combination therapy in patients with advanced pancreatic cancer: GECA2. Invest New Drugs *31*: 1294-1299, 2013.

21 Andersen JB, Spee B, Blechacz BR, Avital I, Komuta M, Barbour A, Conner EA, Gillen MC, Roskams T, Roberts LR, Factor VM and Thorgeirsson SS: Genomic and genetic characterization of cholangiocarcinoma identifies therapeutic targets for tyrosine kinase inhibitors. Gastroenterology *142*: 1021-1031 e1015, 2012.

Received July 27, 2016
Revised August 9, 2016
Accepted August 18, 2016