◎進行胆道癌に対する標準治療は GEM＋シスプラチン(CDDP)である．
◎日本では S-1 も使用されている．

表 3　わが国で行われた切除不能胆道癌に対する主な第Ⅱ相臨床試験

	患者数	奏効率(%)	無増悪生存期間	MST(月)	1年生存率(%)	報告者	報告年
CEF(シスプラチン，エピルビシン，5-FU)	37	19	NA	5.9	24	Morizane	2003
ユーエフティー	19	5	1.0	8.8	21.1	Ikeda	2005
ユーエフティー＋ゲムシタビン塩酸塩	24	12.5	2.5	7.6	19.7	Furuse	2006
ゲムシタビン塩酸塩	40	17.5	2.6	7.6	25	Okusaka	2006
S-1(前期)	19	21.1	3.5	8.3	21.1	Ueno	2004
S-1(後期)	40	35	3.5	9.4	32.5	Furuse	2008

して発生し，遠隔転移をきたしやすいという性質から，内科治療，特に薬物療法においては胆道癌に含めることが多い．

標準治療─ GEM から GEM＋CDDP へ─●

わが国では切除不能胆道癌に対して表 3 に示すような第Ⅱ相試験が行われてきた．比較的良好な成績を示した GEM, S-1 はそれぞれ 2006 年 6 月，2007 年 8 月に胆道癌に対し保険が適用され，一般臨床で使用されてきた．わが国において切除不能，再発胆道癌患者を対象とした GEM＋S-1 療法対 S-1 単独療法の無作為化比較第Ⅱ相試験(JCOG0805)が行われており，その結果が待たれる．

2006 年に英国を中心に行われた GEM 単剤と GEM＋シスプラチン(CDDP：商品名ランダ，ブリプラチン)のランダム化比較第Ⅱ相試験(ABC-01)では，GEM 単剤群対 GEM＋CDDP 群で，奏効割合は 15.2% 対 24.3%，無増悪生存期間中央値は 4.0ヵ月対 8.0ヵ月，6ヵ月無増悪生存割合は 47.7% と 57.1% であった．

ASCO2009 において同グループの第Ⅲ相試験(ABC-02)の結果が報告され，MST は単剤群で 8.3ヵ月，併用群で 11.7ヵ月，ハザード比 0.70 と GEM＋CDDP 群で有意な生存期間の延長を認め，有害事象も許容範囲内であった[6]．同時期に日本で行われた GEM 対 GEM＋CDDP のランダム化比較第Ⅱ相試験(BT22 試験)でも，OS は単剤群で 7.7ヵ月，併用群で 11.2ヵ月とほぼ同様の結果であった．いずれも GEM は 1,000 mg/m^2 を day 1, 8, 15 に投与し 28 日を 1 コースとし，GEM＋CDDP は GEM 1,000 mg/m^2 と CDDP 25 mg/m^2 を day 1, 8 に投与し 21 日を 1 コースと設定した．BT22 試験においては，CTCAE(Common Terminology Criteria for Adverse Events)における Grade 3, 4 の有害事象は，GEM 群対 GEM＋CDDP 群で，好中球減少が(38.1% 対 56.1%)，血小板減少(7.1% 対 39.0%)，白血球減少が(19.0% 対 29.3%)，ヘモグロビン減少が(16.7% 対 36.6%)，γ-GTP 上昇が(35.7% 対 29.3%)であり，腎障害は GEM＋CDDP 群 41 名のうち 1 名に Grade 3 の急性腎不全がみられたのみであり，忍容性ありと判断された．以上から切除不能胆道癌に対する標準治療は，GEM＋CDDP 療法と考えられるようになり，2011 年 8 月に CDDP はわが国でも胆道癌において保険承認された．GEM＋CDDP 療法においては外来通院治療可能であるが，腎機能障害や嘔気などの消化器毒性が強く現れることがあるため，十分な補液と制吐剤の使用が必要である．表 4 に当院における GEM＋CDDP 療法のレ

◎進行胆管癌においても，ワクチンや分子標的薬を用いたレジメンでの臨床試験が行われており，結果が期待されている．

表4　当院における切除不能胆道癌に対するGEM＋CDDP療法の投与方法

Rp1	メインルート：3号維持液(ソリタT3，ソルデム3Aなど)	500 ml	3時間
	側管：生理食塩水	500 ml	
Rp2	デキサメタゾン(デカドロン，デキサートなど) グラニセトロン(カイトリルなど) 生理食塩水	6.6 mg 1 mg 50 ml	15分
Rp3	シスプラチン(ブリプラチン，ランダなど) 生理食塩水	25 mg/m^2 10 ml	1時間
Rp4	ゲムシタビン塩酸塩(ジェムザール)＋ 生理食塩水	1,000 mg/m^2 100 ml	30分
Rp5	生理食塩水	50 ml	15分

ジメンを示す．

今後の展望●

進行胆道癌に対してはGEM＋CDDPが標準治療だが，現在，至適血漿内濃度を保ちやすい速度(1,000 mg/m^2/100分)で静注する定速静注GEMにオキサリプラチンを併用する試験(GEMOX)が行われ，その結果が待たれる．

また，胆管癌においては約8割で過剰発現をしているといわれているWT-1蛋白を抗原として投与し，これに対する抗原特異的な細胞傷害性T細胞を誘導する，というWT-1ワクチン療法についても治療効果が期待され，現在臨床試験が行われている．

分子標的薬に関しても研究が進められている．ASCO2009では，GEMOXにcetuximabを併用する群と併用しない群の比較試験(BINGO)が行われ，中間解析では主要評価項目であった4ヵ月無増悪生存割合が，併用群で61％(95％信頼区間20～70％)，非併用群で44％(同36～83％)であり最終解析結果が待たれる．また，ABC-02試験を行ったグループで，GEM＋CDDPにVEGFRチロシンキナーゼ阻害薬のcediranibを併用する群と併用しない群を比較するABC-03試験が行われている．

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Phase I/II Study of Hepatic Arterial Infusion Chemotherapy With Gemcitabine in Patients With Unresectable Intrahepatic Cholangiocarcinoma (JIVROSG-0301)

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Objectives: No established therapy exists for unresectable intrahepatic cholangiocarcinoma (ICC). We conducted a phase I/II study to ascertain the recommended dose (RD) of hepatic arterial infusion using gemcitabine (GEM) for ICC and to assess the efficacy and safety.

Methods: For patients with unresectable ICC, GEM was administered through the hepatic artery via the port system as a 30-minute infusion on days 1, 8, and 15 every 4 weeks for 5 cycles. In phase I, dosage for levels 1, 2, and 3 was set at 600, 800, and 1000 mg/m^2, respectively, and was increased in 3 to 6 patients at a time. Maximum tolerated dose was defined as a dosage resulting in dose-limiting toxicity in 2 of 3 patients or 3 of 6 patients, and RD was estimated during the first cycle. In the phase II, more RD patients were added to assess tumor response and toxicity.

Results: During the phase I, 16 patients were enrolled. Maximum tolerated dose was not reached. Assuming RD at 1000 mg/m^2, the phase II enrolled a total of 13 patients. The following Grade 3 toxicities were observed: neutropenia 20%, increased gamma-glutamyl transpeptidase 8%, increased aspartate aminotransferase 4%, increased alanine aminotransferase 4%, increased bilirubin 4%, nausea 4%, and fatigue 4%. The tumor response rate was 7.7% (complete response 0, partial response 1, stable disease 8, and progressive disease 4).

Conclusion: Whereas the toxicity of hepatic arterial infusion with 1000 mg/m^2 GEM for ICC was tolerable, expected efficacy could not be obtained, thus suggesting only minimal activity.

Key Words: intrahepatic cholangiocarcinoma, hepatic arterial infusion, gemcitabine, phase I/II study, clinical trial

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Intrahepatic cholangiocarcinoma (ICC) constitutes 5% to 15% of cases of the primary hepatic cancer in Japan. It is a cancer with a relatively low incidence, but is characterized by spread from the biliary epithelium to Glisson capsule. ICC has a high incidence of lymph node metastasis and vascular invasion and also tends to invade adjacent organs, so that in a fair number of cases it is already advanced and unresectable at the time of detection.[1–3] Chemotherapy is the treatment option for unresectable ICC, but no standard therapy has been established.[4,5] Typically, drug regimens centered on 5-fluorouracil (5-FU) have been used, but recently, gemcitabine hydrochloride (GEM) has appeared promising.[6]

Hepatic arterial infusion (HAI) chemotherapy is one local therapy for unresectable malignant hepatic tumors and its anticancer effect is obtained by raising the local concentration of the anticancer agent. Local therapy also reduces systemic adverse response and can increase the effect on the hepatic lesions by infusing the active medicinal agent into a hepatic artery.[7] In Japan, HAI with percutaneous placement of a catheter-port system is highly feasible,[8–10] and HAI of GEM can be continued systematically. If a local effect for ICC supplying from the hepatic artery can be obtained with HAI of GEM, this treatment may contribute to prolonging patient survival.

With this as background, we designed a phase I and II clinical trial to evaluate HAI chemotherapy with GEM for unresectable ICC, and a multicenter study was carried out by the Japan Interventional Radiology in Oncology Study Group.

MATERIALS AND METHODS

Study Design and Patient Eligibility

A phase I and II clinical trial at multiple institutions was designed to determine the dose-limiting toxicity (DLT) and recommended dose (RD) for HAI chemotherapy with GEM to treat unresectable ICC, as well as to evaluate its safety and tumor response effect. Dose-limiting toxicity and recommended dose of hepatic arterial infusion of GEM were determined as the primary end point, and the frequency and severity of adverse events, tumor response effect in the liver only, and tumor response effect in the whole body were the secondary end points. In phase I portion, DLT was assessed and RD was estimated, and in phase II portion, cases were added at the estimated RD, and the tumor response effect was evaluated. Toxicity assessment was conducted in all patients with HAI chemotherapy.

The inclusion criteria were the following conditions for cases of unresectable ICC:

1. Cases of histologically confirmed ICC (initial tumor or recurrence after resection), which was determined to be unresectable by a hepatic surgeon at each institution, or it was judged to be the prognosis-determining factor, even when metastasis was found as extrahepatic lesions.
2. Cases that were previously untreated with GEM or that were previously treated with agents other than GEM in the past, but had received no chemotherapy for at least 4 weeks from the last session, and were not responded by the chemotherapy.
3. Cases in which measurable lesions that corresponded to the target lesions on response evaluation criteria in solid tumors were located in the liver and had maximum tumor diameters of 20 mm or more

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on computed tomography (CT) images with 10-mm slices or 10 mm or more on CT images with slices of 5 mm or less.

4. Cases in which a port-catheter system for HAI was placed percutaneously, and arterially infused contrast medium was distributed through the entire liver or at least the entire hepatic lesions and in whom it was confirmed that there was no distribution of the arterially infused contrast medium in the surrounding extrahepatic organs based on CT angiography or MR angiography from the implanted port.
5. Cases aged 20 years or more with an Eastern Cooperative Oncology Group performance status classification of 2 or less.
6. Cases in which major organ function was maintained (white blood cell count $\geq$3000/mm^3 and $\leq$12,000/mm^3, platelets $\geq$100,000/mm^3, transaminase $\leq$5 times the institution's upper limit of normal, serum total bilirubin $\leq$3.0 mg/dL, serum creatinine $\leq$1.5 mg/dL, electrocardiogram not indicating the need for treatment) and in whom hepatic function was Grade 2 or less on National Cancer Institute-Common Toxicity Criteria (NCI-CTC) (version 2.0) with consideration of the influence of the hepatic lesion.
7. Cases of life expectancy of more than 8 weeks.
8. Cases in which written informed consent was obtained.

Patients excluded from the trial were the patients who scheduled for radiation therapy for the hepatic portal region because of hepatic portal region invasion or lymph node metastasis, or who had previously undergone radiation therapy; patients with concurrent infection excluding viral hepatitis, fever of 38°C or above, or who required antibiotics; patients with serious complications (intestinal paralysis, intestinal obstruction, interstitial pneumonia, pulmonary fibrosis, intractable diabetes mellitus, cardiac failure, renal failure, hepatic failure, etc); patients with other concurrent cancer; patients who could not undergo angiography because of allergy to iodinated contrast material; patients with serious mental disabilities; patients who were pregnant or may have been pregnant, and nursing mothers; and patients whose catheters for HAI chemotherapy were placed via laparotomy.

This study protocol was approved by the ethics committee of the Japanese Society of Interventional Radiology and the institutional review boards of the participating hospitals.

Treatment Protocol and Evaluation Methods

Using a percutaneously placed HAI catheter-port system, 1 course was defined as HAI of GEM on days 1, 8, and 15; a course was performed every 4 weeks for a total of 5 courses.

In phase I portion, the GEM dosage was set at Level −1, 400 mg/m^2; Level 1, 600 mg/m^2; Level 2, 800 mg/m^2; and Level 3, 1000 mg/m^2. Because the approval dosage of GEM is 1000 mg/m^2 in Japan, we defined it as the upper limit in this study. The design called for increase at each level in 3 to 6 patients from Level 1. Three patients were enrolled at each level. The study on the next dose level was not conducted until all 3 patients had completed the first cycle without any problems regarding safety and tolerance. If a DLT of any type was detected in 1 of 3 patients during the first cycle, an additional 3 patients were enrolled. If DLT was detected in more than 2 patients, the dose was defined as the maximum tolerated dose (MTD). RD was estimated to be one level below that judged to be MTD. DLT was defined as follows and judged during the first course: Grade 4 leukopenia or neutropenia; Grade 4 thrombocytopenia; nonhematologic toxicities of Grade 3 or more (excluding that from PD, nausea/vomiting, and alopecia; for patients whose pre-enrollment level of transaminase or serum total bilirubin was Grade 2, DLT was taken to be more than twice the pre-enrollment level); not meeting the criteria to start administration (same as the enrollment criteria) for the next course on day 29 because of toxicity.

In phase II portion, up to 13 patients were added at the dose found to be RD in phase I portion and the tumor response effect was judged using response evaluation criteria in solid tumors. Because HAI was being used, the target lesion was limited to hepatic lesions. Tumor size was measured on intravenous contrast-enhanced CT within 2 weeks before enrollment, and the tumor response effect was judged after the completion of courses 1, 3, and 5, and as needed.

Toxicity assessment was done in all cases using NCI-CTC (version 2.0) and the frequency of the worst grade was obtained during all courses. Physical examination and blood tests were done immediately before the start of each treatment and recorded.

Statistical Analysis

In phase I portion, the number of enrolled patients per level from Level −1 to Level 1 was minimum 6. The maximum number of patients up to Level 3, in case that MTD was reached, was 18 patients in the dose finding stage. In phase II portion, when the threshold tumor response rate was taken to be 20% and the expected efficacy rate was set at 50%, 13 patients would be needed to judge the tumor response effect under conditions of $\alpha = 0.1$ and $\beta = 0.2$, and 7 to 10 cases would need to be added at the estimated RD. For the entire study, a maximum of 25 patients was needed.

RESULTS

Patient Backgrounds

A total of 16 patients were enrolled in the phase I portion (May 2004–November 2005), and 9 patients were added for the phase II portion (February 2006–November 2006). All patients met the eligibility requirements. A summary of all 25 patients is shown in Table 1.

Phase I Portion

In phase I portion, 6 patients were registered at Level 1, 6 at Level 2, and 4 at Level 3. DLT appeared in 2 of the 6 patients at Level 1, and 2 of the 6 patients at Level 2, but DLT did not appear at Level 3. The third and fourth patients at Level 3 were registered at almost the same time. Four patients did not meet the criteria to start administration for the second course on day 29. In these 4 patients, the administration of drugs had been delayed because of Grade 1 and 2 leukopenia (n = 3) or thrombocytopenia (n = 4) in the first course. No Grade 4 hematologic toxicity or nonhematologic toxicity of Grade 3 or more was seen in the first course (Tables 2, 3). MTD was not reached up to Level 3. Accordingly, the RD was assumed to be the Level 3 dose of 1000 mg/m^2.

Phase II Portion

Nine patients were added at GEM 1000 mg/m^2. In these patients, together with the patients at Level 3 in phase I portion (total: 13 patients), the tumor response effect was complete response 0/partial response 1/stable disease 8/progressive disease 3/not evaluated 0 in the liver only, and complete response 0/partial response 1/stable disease 8/progressive disease 4/not evaluated 0 in the whole body. The response rate was 7.7% (95% confidence interval [CI], 0.2%–36.0%). Although disease control was not one of the assessment items, the disease control rate with SD added was 69% (95% CI, 38.6%–90.9%). The tumor response effect and survival in all 25 treated patients are shown in Table 4 and Figure 1.

Toxicity

The incidence of adverse events (NCI-CTC version 2.0) of Grade 3 or more in all treated cases was 20% neutropenia, 8% elevated gamma-glutamyl transpeptidase (GGT), 4% elevated aspartate aminotransferase (AST), 4% elevated alanine aminotransferase (ALT), 4% elevated bilirubin, 4% nausea, and 4% fatigue. The only

TABLE 1. Patients' Characteristics

Phase Level of GEM Dose	Phase I Level 1	 Level 2	 Level 3	Phase II Estimated RD	All Patients
GEM dose	600 mg/m^2	800 mg/m^2	1000 mg/m^2	1000 mg/m^2	600, 800, 1000 mg/m^2
No. patients	6	6	4	9	25
Age (yr)					
Median (range)		64 (34–76)		56 (46–74)	58 (34–76)
Gender					
Male	3	5	3	7	18
Female	3	1	1	2	7
ECOG PS					
0	4	5	3	7	19
1	1	1	1	2	5
2	1	0	0	0	1
Previous therapy					
None	4	2	3	4	13
Resection	1	3	1	5	10
Chemotherapy	1	0	1	2	4
Embolization or ablation	0	2	0	1	3
Extrahepatic lesions					
None	3	3	2	8	16
Lymph node	3	3	2	0	8
Peritoneum	1	0	0	0	1
Lung	0	1	2	1	4
Median no. courses administered	5	4.5	4		5
Median no. administrations	15	14	12		15
Relative dose intensity	81.9%	87.3%	84.8%		84.7%

ECOG indicates Eastern Cooperative Oncology Group performance status.

TABLE 2. No. Patients With Hematologic Toxicities (Cycle 1, Phase I Portion, n = 16)

Level Dose n Grade	Level 1 600 mg/m^2 6 1	 2	 3	 4	Levele 2 800 mg/m^2 6 1	 2	 3	 4	Level 3 1000 mg/m^2 4 1	 2	 3	 4
Leucocytes	1	2	0	0	1	3	0	0	2	1	0	0
Neutrophils	0	2	1	0	1	1	2	0	1	1	0	0
Hemoglobin	0	1	0	0	0	0	0	0	0	0	0	0
Platelets	2	2	0	0	2	1	0	0	1	1	0	0

Grade 4 event was elevated bilirubin in 1 patient in the second course, but this was accompanied by portal vein tumor thrombosis (Tables 5, 6).

Events related to the HAI procedure included difficulties with the placed catheter-port system in 5 patients (catheter obstruction in 3 patients, port damage in 2 patients), and hepatic artery occlusion in 1 patient. In 2 of the patients with catheter obstruction and the 2 patients with port damage the catheter or port was exchanged and the treatment continued. The remaining patient with catheter obstruction showed an antitumor effect of PD, so the catheter was not replaced and the treatment was stopped. In the patient with hepatic artery occlusion, a left hepatic artery occlusion occurred in the second course, which meant that the drug was not reaching the left lobe of the liver, and the treatment was discontinued.

TABLE 3. No. Patients With Adverse Events (Cycle 1, Phase I Portion, n = 16)

Level Dose n Grade	Level 1 600 mg/m^2 6 1	 2	 3	 4	Level 2 800 mg/m^2 6 1	 2	 3	 4	Level 3 1000 mg/m^2 6 1	 2	 3	 4
Nausea	0	2	0	0	2	0	0	0	3	0	0	0
Vomiting	0	1	0	0	0	0	0	0	2	0	0	0
Fatigue	1	1	0	0	3	0	0	0	0	0	0	0
Stomatitis	0	0	0	0	1	0	0	0	0	0	0	0
Headache	0	0	0	0	1	0	0	0	0	0	0	0
Diarrhea	0	0	0	0	0	0	0	0	0	0	0	0
Fever without neutropenia	0	0	0	0	0	0	0	0	1	0	0	0
Anorexia	0	0	0	0	0	0	0	0	0	0	0	0
Alopecia	0	0	0	0	1	0	0	0	0	0	0	0
Alkaline phosphatase	2	0	0	0	1	0	0	0	1	0	0	0
Bilirubin	1	0	0	0	0	0	0	0	0	0	0	0
GGT	1	0	0	0	0	1	0	0	0	0	0	0
Hypoalbuminemia	0	0	0	0	0	0	0	0	1	0	0	0
SGOT (AST)	1	0	0	0	0	0	0	0	1	0	0	0
SGPT (ALT)	0	0	0	0	0	1	0	0	1	0	0	0
Hyperkalemia	0	0	0	0	1	0	0	0	0	0	0	0
Hyponatremia	0	0	0	0	0	0	0	0	1	0	0	0

TABLE 4. Objective Response and Clinical Outcome

GEM Dose	600 mg/m²		800 mg/m²		1000 mg/m² (Phase II)		All Patients	
No. Patients	6		6		13		25	
Evaluation Site	Liver	Whole Body	Liver	Whole Body	Liver	Whole Body	Liver	Whole Body
Best response								
CR	0	0	0	0	0	0	0	0
PR	0	0	2	2	1	1	3	3
SD	4	4	3	3	9	8	16	15
PD	2	2	0	0	3	4	5	6
NE	0	0	1	1	0	0	1	1
Response rate	0%	0%	33.3%	33.3%	7.7%	7.7%	12.0%	12.0%
95% CI	0%–45.9%	0%–45.9%	4.3%–77.7%	4.3%–77.7%	0.2%–36.0%	0.2%–36.0%	2.5%–31.2%	2.5%–31.2%
Disease control rate	66.7%	66.7%	83.3%	83.3%	76.9%	69.2%	76.0%	72.0%
95% CI	22.3%–95.7%	22.3%–95.7%	35.9%–99.6%	35.9%–99.6%	46.2%–95.0%	38.6%–90.9%	54.9%–90.6%	50.6%–87.9%
Median survival time	297 d		298 d		389 d		340 d	
95% CI	140–454 d		0–747 d		158–620 d		198–482 d	

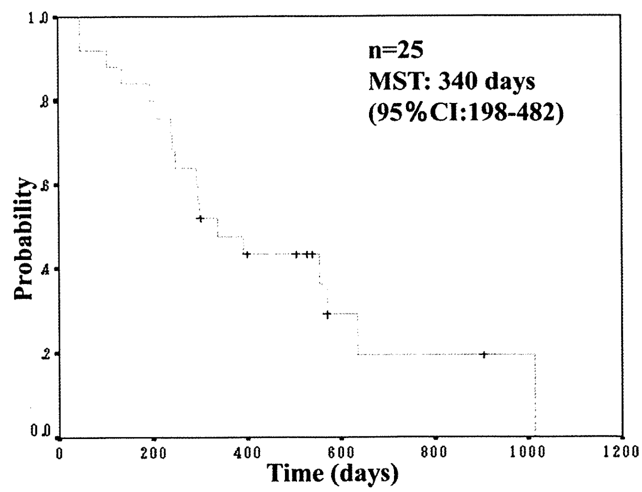

FIGURE 1. Survival time in all 25 patients received hepatic arterial infusion with gemcitabine.

TABLE 5. No. Patients With Hematologic Toxicities (Cycle 1–5, Phase I–II Portion, n = 25)

Dose n	600 mg/m² 6				800 mg/m² 6				1000 mg/m² 13			
Grade	1	2	3	4	1	2	3	4	1	2	3	4
Leucocytes	1	3	0	0	0	4	0	0	4	6	0	0
Neutrophils	0	2	1	0	1	1	2	0	1	7	2	0
Hemoglobin	0	1	0	0	0	1	0	0	2	1	0	0
Platelets	2	2	0	0	2	1	0	0	6	3	0	0

TABLE 6. No. Patients With Adverse Events (Cycle 1–5, Phase I–II Portion, n = 25)

	600 mg/m² 6				800 mg/m² 6				1000 mg/m² 13			
Dose n Grade	1	2	3	4	1	2	3	4	1	2	3	4
Nausea	0	2	0	0	3	0	1	0	7	1	0	0
Vomiting	0	0	0	0	1	1	0	0	3	0	0	0
Fatigue	1	1	0	0	3	0	1	0	3	2	0	0
Stomatitis	0	0	0	0	1	0	0	0	0	0	0	0
Headache	0	0	0	0	1	0	0	0	1	0	0	0
Diarrhea	1	0	0	0	0	0	0	0	0	0	0	0
Fever without neutropenia	0	0	0	0	1	0	0	0	4	1	0	0
Anorexia	0	0	0	0	0	0	0	0	4	1	0	0
Alopecia	0	0	0	0	1	0	0	0	1	0	0	0
Alkaline phosphatase	3	0	0	0	1	0	0	0	2	4	0	0
Bilirubin	1	0	0	0	3	0	0	0	1	1	0	1
GGT	1	0	0	0	0	1	0	0	1	0	2	0
Hypoalbuminemia	0	0	0	0	0	0	0	0	3	2	0	0
SGOT (AST)	1	0	0	0	1	0	0	0	4	2	1	0
SGPT (ALT)	0	0	0	0	1	1	0	0	3	2	1	0
Hyperkalemia	0	0	0	0	1	0	0	0	1	0	0	0
Hyponatremia	0	0	0	0	1	0	0	0	1	0	0	0

DISCUSSION

ICC originates in the biliary epithelium and is almost always adenocarcinoma. In Japan, it has been reported to account for 5% to 15% of primary hepatic cancers. The only curative treatment is surgical resection. However, at the time of detection, the cancer is often judged to be unresectable because of liver metastasis, vascular invasion, lymph node metastasis, or other distant metastasis.[1–3]

Chemotherapy is the treatment option for unresectable ICC but no standard therapy has been established.[4,5] Multiagent treatment has been reported with drugs such as 5-FU, mitomycin C (MMC), adriamycin, and epirubicin hydrochloride similar to biliary tract cancer (extrahepatic bile duct cancer, gallbladder cancer). Combined use of cisplatin and 5-FU is reportedly effective but all of these reports are from case studies only.[11,12] HAI chemotherapy has also been attempted for unresectable intrahepatic bile duct cancer and regimens such as FAM (5-FU + adriamycin + MMC), FEM (5-FU + epirubicin hydrochloride + MMC), high-dose 5-FU, and low-dose FP (5-FU + cisplatin) have been reported to be effective.[13] Again, however, all of these reports are from case studies only.

A new anticancer agent of GEM has been introduced for pancreatic cancer and biliary tract cancer, which has no standard therapy like ICC.[6] For pancreatic cancer chemotherapy, it is the drug of choice.[14,15] In treating ICC with GEM, good results were reported in 2001 from a phase II trial in Germany in which the tumor response effect was reported to be 30% and the median survival time (MST) was 9.3 months.[16] Because ICC is classified as a primary hepatic cancer in Japan, HAI of GEM has also been attempted. Tsujino et al performed HAI of GEM at the recommended dose of 1000 mg/m^2 with intravenous infusion, and they observed tumor size and tumor marker reductions.[17]

Whereas no consensus has been reached with regard to the contribution of HAI to extending survival in cases of hepatic metastasis of colorectal cancer, the local tumor response effect is considered to be superior to that with systemic chemotherapy.[18–20] Moreover, in hepatocellular carcinoma which is a primary hepatic cancer like ICC, the intra-arterial local therapy for hepatic arterial chemoembolization is thought to significantly prolong survival in unresectable cases compared with the results of symptomatic treatment.[21,22] It is possible that local therapy can also prolong survival in cases of ICC.

This study was designed with consideration of the above to establish the DLT for HAI of GEM and estimate the RD; the tumor response effect with the estimated RD was then determined and safety was evaluated. In phase I portion, GEM was increased from 600 mg/m^2 to 800 mg/m^2 and 1000 mg/m^2. A delay in the start of the second course because of Grade 1 and 2 leukopenia or thrombocytopenia as DLT was seen in 4 cases (25%). MTD was not reached up to dosage Level 3. Thus, RD was estimated to be 1000 mg/m^2, and more patients were added in phase II portion.

The incidence of adverse events of Grade 3 or more in all courses was 20% neutropenia, 8% elevated GGT, 4% elevated AST, 4% elevated ALT, 4% elevated bilirubin, 4% nausea, and 4% fatigue. The only Grade 4 event was elevated bilirubin in 1 case during the second course. However, this was a case of portal vein tumor thrombosis, which was thought to have caused the elevated bilirubin. Toxicity with HAI of GEM was generally tolerable throughout all courses and it was milder than in reports of systemic administration.[23]

Events related to the HAI itself or the implanted catheter-port system occurred in 6 cases (24%). Most were dealt with by replacing the port in order that HAI could be continued. Hepatic artery occlusion occurred in only 1 case. Compared with other reports,[8–10] more of the present cases were within the tolerable range. No catheter or port infection or induced thrombosis was observed.

The response rate of HAI of GEM at the estimated RD of 1000 mg/m^2 in 13 cases of unresectable ICC was 7.7% (CR, n = 0; PR, n = 1), which was below the established threshold efficacy rate of 20%. Although disease control was not one of the items investigated in this study, the disease control rate including SD (n = 8) was 69% and MST in all 25 patients was 340 days (95% CI: 198–482 days).

In conclusion, DLT was the delay in the start of the second course because of Grade 1 and 2 leukopenia or thrombocytopenia and RD was estimated to be 1000 mg/m^2 in HAI of GEM for unresectable ICC. Toxicity was within the tolerable range. However, the tumor response effect of HAI of GEM at 1000 mg/m^2 was low, and it was judged that no improvement in treatment results can be expected with HAI. The disease control rate and MST were acceptable, but, considering that the subjects in this study were patients whose hepatic lesions were predominant and that the implanted catheter-port system was required for HAI as a painful procedure, it cannot be claimed that this protocol has an advantage over systemic treatment.

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Outcomes and Tolerability of Systemic Chemotherapy for Pancreatic or Biliary Cancer Patients Aged 75 Years or Older

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Background: The incidence of pancreatic or biliary tract cancer is increasing in our aging population, but little is known of treatment outcomes in elderly patients with pancreatic or biliary tract cancer.
Patients and methods: Patients with pancreatic or biliary tract cancer who received chemotherapy in our institute between September 2007 and August 2009 were retrospectively reviewed to compare treatment outcomes between the elderly (aged 75 years or older) and the younger patients. Data were collected of patient backgrounds, adverse events and dose intensity within the first two cycles and overall survival time.
Results: Of the 102 who met the inclusion criteria, 19 were elderly who were introduced to full dose chemotherapy. Medication for their comorbidities was required in 15 (79%) of the 19 elderly patients and in 27 (33%) of 83 younger patients. The frequencies of haematological adverse events of grades 3 or 4 were 42% and 39%, and those of non-haematological adverse events were 21% and 16%, for the elderly and younger, respectively. Similar dose intensities were delivered to the elderly and younger. Also, similar proportions of elderly and younger received dose reductions. There was no difference in overall survival between the elderly and the younger.
Conclusion: No clear difference in treatment outcomes was seen between the elderly and the younger patients who received gemcitabine alone. Gemcitabine chemotherapy appears to be safe and the same treatment effect was seen even in older patients with pancreatic or biliary tract cancer.

Key words: elderly patients – pancreatic cancer – biliary cancer – chemotherapy

INTRODUCTION

Pancreatic or biliary tract cancer (PBCa) is known to have poor outcomes and advancing age has been associated with an increased incidence of this disease. Changing demographics in developed countries are characterized with the elderly comprising an increasing proportion of the population. This will result in a growing number of elderly patients with PBCa. In 1990, newly diagnosed pancreatic and biliary tract cancer patients aged 75 years or older showed incidences of 37% of 14 583 and 43% of 13 770 patients in Japan. However, in 2003, those numbers increased to 46% of 24 442 pancreatic cancer patients, and 58% of 11 401 biliary tract cancer patients (1). Despite the increased incidence of PBCa with age, elderly patients tend to be under-represented in clinical trials (2,3). Most clinical trials have excluded elderly patients because of the progressive reduction of organ function and co-morbidities related to age. Accordingly, only a small fraction of elderly patients have been entered into clinical trials. Hutchins reported that there was a substantial under-representation of patients 65 years of age or older in studies of treatment for cancer (4). As for lung cancer, some prospective trials showed the benefit of chemotherapy for elderly patients (5–7). However, only scant data are available among elderly patients with PBCa. Therefore, it is not known whether elderly patients with PBCa can tolerate standard full-dose chemotherapy regimens and result in outcomes similar to those seen in younger patients. Because of this lack of evidence, chemotherapy has generally been excluded from the treatment options for elderly patients with advanced PBCa probably for the reasons that chemotherapy is never curative and has toxic effects.

To determine the safety and effectiveness of chemotherapy for elderly PBCa patients, we reviewed the data of patients who were treated at our institution.

PATIENTS AND METHODS

PATIENTS

Patients were selected from our database with the following criteria: (i) radiologically confirmed pancreatic or biliary tract carcinoma (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder carcinoma, or ampullary carcinoma), (ii) histologically or cytologically proven adenocarcinoma, (iii) no prior anti-cancer chemotherapy for PBCa, (iv) chemotherapy with gemcitabine (Gem) alone initiated between September 2007 and August 2009 at the Cancer Institute Hospital. Elderly patients were defined as 75 years of age or older, and treatment outcomes were compared between the elderly and the other patients.

CHEMOTHERAPY

In clinical practice, we generally employed Gem alone as the front line chemotherapy for PBCa. Gem was delivered at a dose of 1000 mg/m^2 by intravenous infusion on days 1, 8 and 15 of a 4-week cycle. Indicators of consensus criteria of chemotherapy in our team included good performance status, adequate organ function and historical absence of serious cardiac or cerebral vascular disease or mental disorder. For elderly patients, no geriatric assessment scoring system was used but Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1 was regarded as essential for chemotherapy. However, details of indicators or treatment management depended on each physician. In general, Gem was suspended to allow recovery from the following toxicities: neutrocyte count $<1000/mm^3$, platelet count $<70\,000/mm^3$ or grade 3/4 non-haematologic toxicity.

ANALYSIS

Individual data were collected from all medical records of the study patients. This included the past medical history, present illness, documents of imaging diagnosis, laboratory data and adverse events within the first two cycles of chemotherapy, and status at the last visit. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 3.0. Dose intensity was surveyed within the first two cycles for Gem monotherapy. Overall survival data was fixed on June 2010.

In the current study, the responses between the elderly (75 years or older) and the younger were subjected to statistical comparisons. This study protocol was approved by the institutional review board in Cancer Institute Hospital.

STATISTICAL ANALYSIS

Differences between the elderly and the younger were compared using the exact Wilcoxon test for numeric or ordinal variables, Fisher's exact test for binary variables and likelihood ratio test for multi-category discrete variables. Two-sided P values <0.05 were considered to be statistically significant. Overall survival was measured from the date of the start of chemotherapy to the date of death or last follow-up. Survival curves were generated using the Kaplan–Meier method, and median survival times were reported with 95% confidence intervals.

All statistical analyses were performed using the SPSS statistical software program package (SPSS version 11.0 for Windows).

RESULTS

PATIENT AND TUMOUR CHARACTERISTICS

There were 102 PBCa patients who met the selection criteria (Table 1). Of the 102, 19 (19%) were elderly patients.

The median ages were 78.0 years (range 75–85) and 65.3 years (range 41–74)) for the elderly and younger patients, respectively. The ECOG PS at the baseline was either 0 or 1 in all of the patients. The median follow-up duration was 9.1 months. There were no significant differences for background data between the elderly and the younger patients.

COMORBIDITIES OF THE PATIENTS

The comorbidities of the patients are listed in Table 2. Of the 19 elderly patients, 15 (79%) had at least one

Table 1. Patient characteristics for the elderly (aged 75 years or older) and the younger (under 75 years)

	≥75	<75	Total	p
No. of patients	19	83	102	
Male	12	45	77	
Female	7	38	45	0.61
Median age, years (range)	78.0 (75–85)	65.3 (41–74)		
Primary tumour site				
Pancreas	13	60	73	
Biliary	6	23	29	0.78
Status				
Locally advanced	10	35	45	
Metastatic	9	48	57	0.53

Table 2. Summary of comorbidities of the patients

Comorbidities (medication)	≥75	<75	
Cerebral disease			
Old cerebral infarction	1[a]	0	
Anticoagulant use	1		
Cardiovascular			
Hypertension	9[b]	20[c]	
Angina pectoris	1	5	
Arrhythmia	0	2	
Rheumatic aoritis	0	1	
Antihypertensive drugs	9	20	
Anticoagulant use	2	5	
Respiratory disease			
Asthma	1[d]	1	
Inhaler use	1	1	
Diabetes mellitus	6	13	
Insulin use	1	4	
Oral administration	5	9	
Renal failure	0	0	
Total cases (%)	15 (79%)	27 (33%)	$P < 0.001$

The numbers refer to patients who had one or more comorbidities.
Of 19 elderly patients, 8 patients had one, 6 had two and 1 had three kinds of comorbidities.
[a]The patient also used antihypertensive drug.
[b]Five patients also used diabetes drugs.
[c]Nine patients also used diabetes drugs.
[d]The patient also used antihypertensive drug and diabetes drugs.
Of 83 younger patients, 15 patients had one and 12 had two kinds of comorbidities.

Table 3. Summary of grades 3–4 toxicity in the elderly (aged 75 years or older) and the younger (under 75 years)

	No. of events		*p*
	≥75	<75	
Anaemia	0	0	
Leucopoenia	1	4	
Neutropenia	6	49	
Thrombocytopenia	2	5	
Total (*Haematological AE*) cases (%)	**8 (42%)**	**32 (39%)**	0.61
Lethargy	2	6	
Infection (non-neutropenic)	1 cholangitis	5 cholangitis 1 pneumoniae 1 liver abscess	
Infection (neutropenic)	0	2	
Bilirubin	0	2	
Transaminases	3	10	
Gastrointestinal	0	1 ascites	
1 ileus			
Diarrhoea	0	1	
Renal	0	0	
Pulmonary	0	1 interstitial pneumoniae	
Others	0	1 hypocalcaemia	
Total (*non-haematologic AE*) cases (%)	**4 (21%)**	**13 (16%)**	0.77
Total (all AE) cases (%)	**8 (42%)**	**37 (45%)**	1.00

Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria version 3.0.

comorbidity which needed some degree of medication. In contrast, comorbidities were seen in 27 of 83 (33%) younger patients. The proportion of the elderly with comorbidities was significantly higher than in the younger patients. Cardiovascular disease and diabetes mellitus were most frequently observed. Serum creatinine levels at the initiation of chemotherapy were under 1.5 mg/dl for all patients and severe renal dysfunction was not seen in the current study. Of the 19 elderly patients, there were 5 patients with medical history of cancer surgery: 3 with gastric cancer, 1 with breast cancer, and the remaining 1 with thyroid cancer. Of the 83 younger patients, there were 9 patients with history of cancer surgery: 1 with oesophageal cancer, 4 with gastric cancer, 3 with colorectal cancer, 2 with uterus cancer, and the remaining 1 with prostate cancer (1 with both gastric cancer and colorectal cancer).

Toxicities

Adverse events, for which grading resulted in the worst values were encountered within the first two cycles of treatment, and are reported in Table 3. Haematological toxicities of grades 3–4 were seen in 8 (42%) of the 19 elderly and in 32 (39%) of the 83 younger patients. Non-haematological toxicities occurred in 4 (21%) of the elderly, and in 13 (16%) of the younger patients. The number of any grade 3–4 toxicities were 8 (42%) in the elderly and 37 (45%) in the younger patients. Severe adverse events occurred in 1 (5%) of the elderly and in 9 (11%) of the younger patients.

Severe adverse event in the elderly patient was cholangitis due to progression of the original lesion and recovery was observed within a few days by biliary drainage. Most of the adverse events were also related to progression of PBCa.

The number of patients who could not continue chemotherapy by two cycles due to adverse events was two (11%) in the elderly and eight (10%) in the younger patients. The frequencies of any of the grade 3–4 toxicities and severe adverse events were not significantly different between the elderly and the younger patients.

Dose Intensity

Similar dose intensities (538 mg/m^2 per week to the elderly and 596 mg/m^2 per week to the younger) were delivered within the first two cycles of GEM chemotherapy. The dose of Gem within the first two cycles was reduced in five (26%) of the elderly and in 20 (24%) of the younger patients.

Overall Survivals

Regarding the 102 patients with unresectable tumours who received Gem alone, 11 patients survived, 70 died and the remaining 21 were censored mainly because they changed hospitals at the time when we fixed the data in June 2010. The median overall survival days were 308 (95%CI: 130–486) and 315 (95% CI: 232–398) days in the elderly and younger patients, respectively (Fig. 1). There was no statistical difference between the two groups ($P = 0.340$).

DISCUSSION

With the increasing life expectancy of the overall population in Japan, there has also been a rise in the number of elderly cancer patients. Because of comorbidities or age itself, the deterioration in organ function is seen more frequently in the elderly, compared with the younger patients. Therefore, consideration of treatment feasibility needs special attention for the elderly cancer patients. A less toxic regimen has been tried, in particular, for advanced-staged lung cancer or haematological malignancies (5–7). The current study was conducted to examine the feasibility and effectiveness of chemotherapy for elderly PBCa patients because of lack of knowledge on this issue.

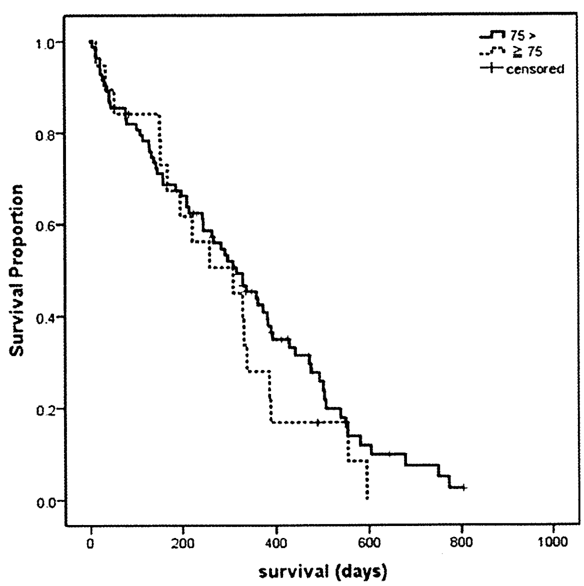

Figure 1. Overall survival in the elderly and in the younger who received gemcitabine alone for unresectable PBCa. The median overall survival days in the elderly and in the younger patients were 308 and 315 days, respectively ($P = 0.340$).

To date, either Gem or fluoropyrimidine has been a key drug for PBCa. Gem has been widely used as a standard chemotherapeutic agent for advanced PBCa. Especially in pancreatic cancer, Gem alone still remains as the standard regimen both in the adjuvant setting after surgery and in treatment of advanced disease.

Gem is thought to be less toxic than other cytotoxic agents, such as platinum or taxens (8), which showed grades 3–4 haematological and non-haematological adverse events of 10–24% and 20–50% (9–11), respectively. Therefore, special attention may not be necessary to perform Gem chemotherapy for the elderly. In fact, the current study demonstrated that full-dose chemotherapy with Gem for PBCa was feasible in the younger as well as the elderly patients. The favourable results seen for the elderly in the current study may be attributed to good patient selection. Special emphasis was placed on performance status rather than comorbidities. Marechal et al. (12) also pointed out the importance of performance status when considering chemotherapy for elderly patients with pancreatic cancer.

Recently, a consensus has been achieved for Gem in combination with cisplatin as the standard regimen for biliary tract cancer based on results of ABC-02 (11) and BT22 trials (10). For chemotherapy with cisplatin, hydration is commonly recommended to reduce renal toxicity. Cisplatin is thought to be difficult to adapt elderly patients with cardiac and/or renal disease at baseline. Accordingly, another platinum agent such as carboplatin or nedaplatin is often employed for lung or oesophageal cancer chemotherapy regimen as an alternative to cisplatin for the treatment of elderly patients. In both ABC-02 and BT22 trials, cisplatin was delivered at low (25 mg/m^2) and fractional (days 1 and 8 of a 3-week cycle) doses. This might lead to low-frequency renal toxicity (1.5%, with grades 3–4 renal adverse events) (11). Despite low toxicity, whether the combination of Gem and cisplatin is an appropriate option for the elderly patients needs to be validated because cisplatin will be approved by the Japanese government in the near future.

The toxicities of chemotherapy were evaluated only for two cycles. Late-onset adverse effects might occur especially in elderly patients due to deterioration of organ function. Unquestionably, adverse effects for the elderly need to be monitored carefully during all courses of chemotherapy. However, in view of the lack of a consensus of dose setting, our data support the use of first-line Gem for PBCa by the full-dose setting.

In conclusion, our data shows that old age is not a contraindication to full-dose chemotherapy with Gem for PBCa. Gem monotherapy appears to be safe and delivers the same treatment effect even in older patients with PBCa. Chemotherapy using Gem can be applied to elderly patients as well as younger patients, if those patients with wellpreserved physical status and organ functions are appropriately selected.

Conflict of interest statement

None declared.

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EXPERT REVIEWS

Inhibitor of MEK1/2, selumetinib, for biliary tract cancer

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It is necessary to establish effective chemotherapy to improve the survival of patients with biliary tract cancer. Although the useful of some molecular-targeted agents as first-line therapies has been investigated, none have been found to exert satisfactory efficacy. In this article, we report the results of a Phase II study of selumetinib in patients with metastatic biliary cancer. Selumetinib is an inhibitor of MEK1/2 targeting the RAS/RAF/MEK/extracellular signal-related kinase pathway. Three out of 28 patients showed a confirmed partial response, representing a response rate of 12%. The median progression-free survival was 3.7 months and the median overall survival was 9.8 months. The most common toxicities were rash, xerostomia and nausea. Most toxicities were grade 1 or 2, and the most common grade 3/4 toxicities were diarrhea and nausea. All toxicities were manageable and reversible. The results warrant further evaluation of the use of selumetinib in patients with metastatic biliary cancer.

Keywords: biliary tract cancer • mitogen-activated protein kinase kinase • molecular targeted therapy • Phase II study • selumetinib

Bile duct cancer is subdivided according to the anatomic location of origin into intrahepatic cholangiocarcinoma, gallbladder cancer, extrahepatic cholangiocarcinoma or cancer of the ampulla of Vater. Although surgery currently remains the only potentially curative treatment for each of the aforementioned diseases, many patients are diagnosed at an unresectable advanced stage of the disease. Chemotherapy has been recognized as a recommended therapy for unresectable biliary tract cancer based on the results of comparative studies between chemotherapy and best supportive care.

Despite the numerous Phase II studies conducted on treatments for advanced biliary tract cancer, no accepted standard treatment for this tumor type has been established as yet owing to the low incidence of this cancer, the small number of patients studied and the lack of adequately powered randomized controlled trials. Recently, randomized controlled trials comparing the combination of cisplatin plus gemcitabine with gemcitabine alone have shown the survival benefit of the former regimen [1,2]. Thus, the combination of gemcitabine plus a platinum agent (cisplatin or oxaliplatin) has come to be recognized as standard therapy for unresectable biliary tract cancer.

One of the next issues that needs to be addressed is whether molecular-targeted agents might also be effective against biliary tract cancer. To date, although clinical trials of molecular-targeted therapies as monotherapy or in combination with gemcitabine-based regimens have been conducted, no molecular-targeted agent has been confirmed to be of clinical benefit for biliary tract cancer.

Methods & results

This study was a Phase II study of selumetinib monotherapy in patients with unresectable biliary tract cancer, including intra- or extra-hepatic cholangiocarcinoma and gallbladder cancer [3]. Selumetinib is an inhibitor of MEK1/2 targeting the RAS/RAF/MEK/extracellular signal-related kinase (ERK) pathway, which plays a central role in the regulation of cellular processes, including proliferation, apoptosis and metabolism.

The primary objective of this study was to determine the overall response rate, as defined by the Response Evaluation Criteria In Solid

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Tumors, and the secondary objectives included evaluation of toxicity, overall survival, progression-free survival, assessment of *BRAF* and *KRAS* mutations, and measurement of phosphorylated (p) ERK and pAKT as indicators of activation of the relevant pathways.

With regard to the starting dose and dosing schedule of selumetinib, the drug was administered orally at 100 mg twice daily in 28-day cycles without interruption. Two levels of dose reductions were planned (50 mg twice daily and 50 mg once daily), with patients taken off the study in the case of a need for any additional dose reductions.

A total of 29 patients were enrolled between December 2007 and January 2009. Three patients showed a confirmed partial response, representing a response rate of 12%. In total, 17 patients (68%) showed stable disease. The majority of patients (52%) showed a decrease in the size of the target lesion. The median progression-free survival was 3.7 months (95% CI: 3.5–4.9) and the median overall survival was 9.8 months (95% CI: 5.97–not available).

The most common toxicities were rash (90%), xerostomia (54%) and nausea (51%). Although most toxicities were grade 1 or 2, the most common grade 3/4 toxicities were diarrhea, nausea and fatigue; in particular, grade 4 fatigue was observed in 4% of the patients. All toxicities were manageable and reversible.

Analyses of biologic markers revealed no *BRAF* V600E mutations. Two patients with short-lived stable disease had *KRAS* mutations. Absence of pERK staining was associated with lack of response and positive immunostaining for pERK was associated with improved overall survival.

Expert commentary

Some growth factors, including EGF receptor (EGFR) and VEGF receptor (VEGFR), and various signal transduction pathways that play important roles in the progression, proliferation and metastasis of various cancers, have been identified. Some studies have demonstrated overexpression of EGFR and VEGFR or mutations of their signaling pathways in biliary tract cancer [4]. Furthermore, biliary tract cancer includes various types of cancers, each with different molecular biological characteristics. For example, overexpression of EGFR has been reported to be observed in 10.7, 5.1, 12.4 and 0% of cases of intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer and cancer of the ampulla of Vater, respectively [5]. Relationships between the presence/absence of various genetic mutations and the efficacy of molecular-targeted agents have been identified in various cancers; for example, the efficacy of anti-EGFR antibodies was limited to colorectal cancer patients with wild-type KRAS expression in the tumor. MEK inhibitors, including selumetinib, may be expected to exhibit activity, even against tumors with KRAS mutation. There is as yet, however, no consensus on the molecular–biologic characteristics of biliary tract cancer.

Recently, combined gemcitabine plus cisplatin or oxaliplatin therapy has been established as the standard first-line treatment for biliary tract cancer. Usage of molecular-targeted agents has been focused on as the next step. There are two directions in which molecular-targeted agents can be expected to be applied: one is in combination with standard chemotherapy regimens as first-line therapy, and the other is as monotherapy in second-line chemotherapy. In many patients with progressive disease receiving first-line chemotherapy with the relatively toxic regimen of cisplatin plus gemcitabine or gemcitabine plus oxaliplatin, the general condition is poor and serious cholangitis can easily develop. Less toxic therapy, such as monotherapy with a targeted agent, may be useful in such patients.

In this study, although 11 patients (39%) had a previous history of exposure to prior chemotherapy, there were three objective responses, representing a response rate of 12%, and another 14 patients (68%) showed stable disease [3]. In addition, both the progression-free survival and overall survival compare favorably with published historical controls. These results of selumetinib seem to suggest the promising activity of the drug against biliary tract cancer. Validation is required to confirm the efficacy of MEK inhibitors against biliary tract cancer according to the tumor site or the biological characteristics of the tumor.

Few preclinical studies of molecular-targeted agents for biliary tract cancer have been reported. In an examination conducted using human cholangiocarcinoma cell lines, ZD6474, an inhibitor of VEGFR and EGFR signaling, showed promising anticancer activity [6]. This study revealed that the absence of KRAS mutation and presence of EGFR amplification may be potentially predictive molecular markers of the sensitivity of cholangiocarcinoma to EGFR-targeted therapy [6]. Thus, therapeutically beneficial effects of molecular-targeted agents, including MEK inhibitors, may be expected against tumors with KRAS mutations and further investigations are warranted to confirm the efficacy.

Five-year view

Molecular-targeted therapy should be established based on the biologic features, and it is important to identify the characteristic biologic features of each of the aforementioned types of cancer of the biliary tract. Furthermore, efficient development of targeted therapy should be advanced based on the identification of appropriate biological markers.

Biliary tract cancer is still a difficult disease to treat. Development of new molecular-targeted agents will hopefully allow for improvement of the survival rates in patients with biliary tract cancer, and individualized therapy using targeted agents can be established according to the tumor's biological features.

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Key issues

- Selumitinib is an inhibitor of MEK1/2, and a Phase II study of selumetinib showed promising activity against biliary tract cancer.
- The most common toxicities were rash, xerostomia and nausea, and all toxicities were manageable and reversible.
- Analyses of biologic markers suggested the existence of a relationship between the KRAS and BRAF status, and the efficacy of selumitinib.
- The results warrant further evaluation of the use of selumetinib in patients with metastatic biliary cancer.

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胆道癌化学療法の最新情報

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要約：2007年の胆道癌診療ガイドラインでは，化学療法について，十分なエビデンスは確立していないものの，全身状態が良好な場合には十分効果が期待されると記載され，胆道癌に対し，有用性の期待される薬剤として，Gemcitabine（GEM）とS-1が推奨されていた。最近，切除不能胆道癌において，GEMとGEM＋cisplatin併用療法（GC療法）の大規模な比較試験が行われ，GC療法の有意な生存期間の延長効果が示された。わが国でも同じレジメンでのGC療法の有用性が確認され，GC療法が切除不能胆道癌の標準治療として認識されている。また，小規模ではあるが，支持療法と化学療法の比較試験により，GEM＋oxalplatin併用療法（Gemox療法）の延命効果が報告されている。胆道癌の術後補助療法はこれまでほとんど臨床試験が行われていなかったが，わが国や英国において大規模な比較試験など，積極的に実施されている。胆道癌においても，エビデンスに基づく標準化学療法が確立してきている。

Key words：胆道癌，標準化学療法，Gemcitabine，Cisplatin

はじめに

胆道癌における化学療法は切除不能の進行癌や切除後の再発例に適応されているが，多数例によるランダム化比較試験はほとんど行われておらず，標準的化学療法は確立しているとはいえなかった。2007年，胆道癌診療ガイドラインが作成され，胆道癌に対する治療指針が示されたが，化学療法に関する推奨も多くは第Ⅱ相試験相当の小規模な前向き試験か後ろ向き研究に基づくものであった[1)]。

ガイドラインの作成から3年が経過し，大規模な比較試験の結果が報告され，また新規薬剤の開発も行われてきている。同ガイドラインでは，①切除不能胆道癌に化学療法は有効か，②切除不能胆道癌に有効な化学療法は何か，③術後補助化学療法を行うことは推奨されるか，の三つの点についてまとめられている[1)]。本稿ではそれらに関するこれまでのエビデンスと最近の動向を含め，胆道癌化学療法の現状について概説する。

Update of Chemotherapy for Biliary Tract Cancer
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Ⅰ．切除不能胆道癌に化学療法は有効か

一般に固形癌の化学療法の意義は延命と症状緩和にある。胆道癌では閉塞性黄疸や胆管炎などの合併により化学療法の実施が難しい例も少なくないことから，化学療法を行う意義について議論のあるところであり，いくつかのランダム化比較試験が実施されている（表1）。スウェーデンで行われた試験では，膵・胆道癌患者を対象にfluorouracil（5-FU）/leucovorin（LV）あるいは5-FU/LV/etoposideによる化学療法と支持療法が比較された。胆道癌では症例数が少なく，両群に有意差は認められなかったが，化学療法群で生存期間の延長が認められ，高いQOLの改善率が報告されている[2)]。わが国では，切除不能の膵癌，胆嚢癌，胆管癌患者に対し5-FU/doxorubicin/mitomycin C（FAM）を用いた化学療法とバイパス術などの姑息手術との比較試験が行われた。症例数が少なく，有意差は得られていないものの，胆嚢癌では対照群に比べ化学療法群で良好な予後が得られている[3)]。最近，胆嚢癌患者を対象とした支持療法と5-FU/LVあるいはGemcitabine/oxaliplatin（Gemox）の化学療法の比較試験が報告された。それによると，支持療法と5-FU/

表 1 切除不能胆道癌における化学療法と支持療法との比較試験

Treatment arm	n	Median OS	p-value	Improvement of QOL	Author (year)
BSC	19	2.5 mo	0.1	5%	Glimelius (1996)[2]
5-FU/LV or 5-FU/LV/etoposide	18	6.5 mo		33%	
Gallbladder cancer	18				Takada (1998)[3]
Control	8	2.4 mo	0.302	—	
5-FU/DXR/MMC	10	5.16 mo		—	
Biliary tract cancer	13				
Control	9	7.56 mo	0.619	—	
5-FU/DXR/MMC	4	4.01 mo		—	
BSC	27	4.5 mo	0.039	—	Sharma (2010)[4]
5-FU/LV	28	4.6 mo		—	
GEMOX	26	9.5 mo		—	

BSC : best supportive care, 5-FU : fluorouracil, LV : leucovorin, DXR : doxorubicin, MMC : mitomycin C, GEMOX : gemcitabine＋oxaliplatin, OS : overall survival, QOL : quality of life

LV では生存期間に差は認めなかったが，Gemox 療法では有意に生存期間の改善が得られている[4]。

これらの結果から，切除不能胆道癌に対する化学療法の臨床的な意義は十分あるものと考えられる。2007 年のガイドラインでは，統計学的有意差を示したエビデンスはなかったことから，推奨度 C1 とされたが，Gemox 療法での有意な生存期間の延長効果から，もっと高い推奨としてもよいかもしれない。

Ⅱ．切除不能胆道癌に有効な化学療法は何か

1．GEM，S-1 を中心とした臨床試験

2000 年以降，わが国ではゲムシタビン（GEM）あるいはテガフール・ギメラシル・オテラシルカリウム配合剤（S-1）の単アームの第Ⅱ相試験が行われ，GEM 単剤では奏効率 17.5%，全生存期間（OS）中央値 7.6ヵ月，S-1 単剤では奏効率 35%，OS 中央値 9.4ヵ月と単剤としては良好な成績が得られた[5,6]。これらの結果に基づき，GEM と S-1 がそれぞれ胆道癌に保険適応に承認され，胆道癌診療ガイドラインでは，切除不能進行胆道癌に対する化学療法として GEM または S-1 が推奨されている。しかし，これらは大規模な比較試験に基づくものではなく，推奨度は C1 にとどまっていた。

切除不能胆道癌における化学療法では，主に GEM を基本薬剤としてフッ化ピリミジン剤，プラチナ系薬剤などの薬剤との併用療法が試みられてきた。その中で，英国で行われた GEM 単独と GEM/cisplatin 併用（GC 療法）のランダム化第Ⅱ相試験（ABC-01 試験）では GEM 単独群の奏効率 15%，無増悪生存期間（PFS）中央値 4ヵ月に対し，GC 療法群では奏効率 24%，PFS 中央値 8ヵ月と GC 療法の有用性が示唆され[7]，引き続いて大規模な第Ⅲ相試験（ABC-02 試験）が行われた。その結果，GEM 単独群に比べ，GC 療法群で有意な生存期間の延長が確認された（表 2)[8]。わが国でも ABC-02 試験と同様のレジメンでランダム化比較試験（BT-22 試験）が行われ，ほぼ同じ結果が得られている（表 2)[9]。これらの試験では GEM は通常の用法用量の 1,000 mg/m^2，30 分点滴静注が用いられたが，cisplatin は 1 回 25 mg/m^{2}と低用量で投与された。いずれの薬剤も週 1 回，2 週連続投与後，1 週休薬の 3 週を 1 サイクルとするレジメンである。Cisplatin の投与量を少なくしたことが毒性をマイルドにし，良い結果につながったと推察されている。

GEM とその他のプラチナ製剤やフッ化ピリミジン薬との併用療法も多くの第Ⅱ相試験が行われている。Gemox 療法では奏効率 15～35%，OS 中央値 8～15ヵ月と GC 療法と同等の治療成績が得られている（表 2)[10～14]。新しいフッ化ピリミジン薬である capceitabine や S-1 を用いた臨床試験では，GEM＋capecitabine 併用療法は，奏効率 25%～32%，OS 中央値 12～14ヵ月[15～18]，GEM＋S-1 併用療法（GS 療法）は，奏効率 30%，OS 中央値 11ヵ月の成績が得られている（表 2)[19]。わが国では，S-1 単独と GS 療法あるいは GC 療法の位置づけが臨床上の課題となっている。日本臨床腫瘍研究グループ（JCOG）では S-1 と GEM＋S-1 併用によるランダム化比較第Ⅱ相試験が実施され[20]，すでに 100 例を超す登録が終了している。この結果に基づいて第Ⅲ相試験に進む計画が進められている。さらに，GEM＋プラチナ＋5-FU による 3 剤併用治療も試みられている[21～23]。

2．分子標的薬の開発

最近の化学療法として，分子標的薬が大きな注目を

表 2　切除不能胆道癌に対する Gemcitabine-based 化学療法の治療成績

Regimen	n	Response rate	Median PFS/TTP	Median OS	Author (year)
Gemcitabine	206	15.5%	5.0 mo	8.3 mo	Valle (2010)[8]
Gemcitabine/cisplatin	204	26.1%	8.0 mo	11.7 mo	
Gemcitabine	42	11.9%	3.7 mo	7.7 mo	Okusaka (2010)[9]
Gemcitabine/cisplatin	41	19.5%	5.8 mo	11.2 mo	
Gemcitabine/oxaliplatin	33	35.5%	5.7 mo	15.4 mo	Andre' (2004)[10]
Gemcitabine/oxaliplatin	31	26.0%	6.4 mo	11 mo	Harder (2006)[11]
Gemcitabine/oxaliplatin	67	14.9%	3.4 mo	8.8 mo	Andre' (2008)[12]
Gemcitabine/oxaliplatin	40	15.0%	4.2 mo	8.5 mo	Kim (2009)[13]
Gemcitabine/oxaliplatin	43	18.9%	4.8 mo	8.3 mo	Jang (2009)[14]
Gemcitabine/capecitabine	45	31%	7.0 mo	14.0 mo	Knox (2005)[15]
Gemcitabine/capecitabine	45	32%	6.0 mo	14.0 mo	Cho (2005)[16]
Gemcitabine/capecitabine	75	29%	6.2 mo	12.7 mo	Riechelmann (2007)[17]
Gemcitabine/capecitabine	44	25%	7.2 mo	13.2 mo	Koeberle (2008)[18]
Gemcitabine/S-1	35	34.3%	5.9 mo	11.6 mo	Sasaki (2010)[19]
Gemcitabine/oxaliplatin/5-FU	72	21%	6.2*, 5.7**mo	10*, 9.9**mo	Wagner (2009)[21]
Gemcitabine/cisplatin/5-FU	21	33%	13.4 mo	18.8 mo	Yamashita (2010)[22]
Gemcitabine/cisplatin/5-FU/EPI	37	43%	7.9 mo	12.1 mo	Cereda (2010)[23]

*胆管癌，**胆嚢癌，PFS：progression-free survival，TTP：time-to progression，OS：overall survival，
5-FU：fluorouracil，EPI：epirubicin

集め，すでに多くの癌で実際の臨床の場で使用されている。胆道癌でも上皮成長因子受容体（EGFR）の阻害薬として erlotinib や lapatinib あるいはマルチキナーゼ阻害剤 sorafenib が単剤で用いられ，また抗 EGFR 抗体薬 cetuximab や抗血管内皮成長因子（VEGF）抗体薬 bevacizumab は Gemox 療法との併用で臨床試験が行われている（表 3）[24~29]。

これまでの単アームの第Ⅱ相試験では，単剤の治療成績は十分とはいえず，1 次治療としての開発は進められていない。Gemox 療法との併用では，cetuximab あるいは bevacizumab の上乗せ効果の可能性が示され，cetuximab ではランダム化第Ⅱ相試験が実施されている。

最近，わが国ではペプチドワクチンを用いたがん免疫療法の開発が注目されている。VEGFR-2 に対するペプチドワクチンは血管新生を阻害することによる抗腫瘍効果が期待され，胆道癌でも GEM との併用療法の第Ⅱ相試験が実施されている。また，ウイルムス腫瘍の原因遺伝子として単離されたウイルムス腫瘍遺伝子（WT1）はさまざまな癌に過剰発現していることが明らかとなり，がんワクチン療法の標的として注目されている。胆道癌においても過剰発現が認められ，GC 療法との併用で臨床試験が開始されている。これらのペプチドワクチンは注射部位の局所反応が主な副作用であり，一般的に重篤な有害反応は少ない。ただ，効果が発現するのに数ヵ月を要するとのこともあり，適切な対象の設定など有用性の確立が期待される。

Ⅲ．術後補助化学療法を行うことは推奨されるか

これまで，術後補助療法の大規模な臨床試験はほとんど行われておらず，ガイドラインでは，現状では推奨すべきレジメンがなく，臨床試験として行われることが望まれる，とされている。

国内外を含め，これまで報告された胆道癌に対する術後補助療法の比較試験は，わが国で行われた Mytomycin C＋5-FU 併用療法と手術単独によるものだけである。この試験では，膵癌 158 例，胆管癌 118 例，胆嚢癌 112 例，乳頭部癌 48 例の適格例について疾患ごとに解析され，胆嚢癌では化学療法群で 5 年生存率が有意に良好であったと報告されている[30]。しかし，胆嚢癌の治癒切除例では有意差を認めていないこと，intention-to-treat（ITT）解析では胆嚢癌においても有意差はみられなかったことなどから胆道癌術後補助療法の標準治療としては位置付けられるに至っていない。

わが国では現在，GEM 単独あるいは GEM-based による臨床試験がいくつか行われている[31]。特に NPO

表 3　切除不能胆道癌に対する分子標的治療の治療成績

Regimen	n	Response rate	Median PFS/TTP	Median OS	Author (year)
Erlotinib	42	7%	2.6 mo	7.5 mo	Philip (2006)[24]
Lapatinib	17	0%	1.8 mo	5.2 mo	Ramananthan (2009)[25]
Sorafenib	46	2%	2.3 mo	4.4 mo	Bengala (2010)[26]
Bevacizumab/erlotinib	53	12%	4.4 mo	9.9 mo	Lubner (2010)[27]
Gem/oxaliplatin/bevacizumab	35	40%	7.0 mo	12.7 mo	Zhu (2010)[28]
Gem/oxaliplatin/cetuximab	30	63%	8.8 mo	15.2 mo	Gruenberger (2010)[29]

PFS：progression-free survival, TTP：time-to progression, OS：overall survival

表 4　切除不能胆道癌に対する 2 次化学療法の治療成績

Regimen	n	Response rate	Median PFS/TTP	Median OS	Author (year)
Gem	32	6.9%	1.6 mo	4.1 mo	Oh (2010)[33]
Gem/cisplatin	20	0	3.6 mo	5.9 mo	Sasaki (2010)[34]
S-1	40	7.5%	2.5 mo	7.3 mo	Suzuki (2010)[35]
S-1	22	22.7%	5.4 mo	13.5 mo	Sasaki (2010)[36]

法人名古屋外科支援機構による第Ⅲ相試験（BCAT）は，胆管癌切除例に対する GEM の術後補助療法と手術単独との比較試験であり，300 例を目標として，症例集積も終了するようである。一方，英国では capecitabine と observation による第Ⅲ相試験（n＝360 例）が行われている。しかし，大規模な第Ⅲ相試験はいずれも 300 例以上の症例が必要としており，症例数の比較的少ない胆道癌では完遂が容易ではない。また胆道癌の手術では胆道再建や消化管バイパスなどがほぼ全例で行われることから，胆管炎や消化管障害などのリスクもある。現在，国立がん研究センター東病院を中心とした研究班により S-1 を用いた feasible study が進んでいる。切除不能胆道癌に続き，術後補助療法についてもエビデンスに基づいた標準治療が確立されるものと期待される。

Ⅳ．2 次化学療法

切除不能胆道癌に対する 2 次化学療法については，現在のガイドラインでは言及されていないが，GEM，S-1，GC 療法，GS 療法など有効な治療法も確立してきており，1 次治療後も治療継続が可能な症例も少なくない。GEM と GC 療法の比較試験での 2 次治療をみると，英国の ABC-02 試験では 2 次治療の実施は GEM 群 17.5%，GC 群 17.6% とあまり行われていない。一方，BT-22 試験では GEM 群 78.6%，GC 群 73.1% と高率である[32]。この差は使える薬剤や医療制度の違いが関係しているものと考えられる。また，2 次治療に大きな差があるにもかかわらず，両試験での全生存期間には差がなかったなど，2 次治療の意義について検討が必要である。これまで胆道癌の 2 次化学療法の臨床試験は行われていなかったが，最近 5-FU-based 化学療法後の GEM や GEM 後の GC 療法，S-1 など，いくつか第Ⅱ相試験の結果が報告されている（表 4）[33~36]。今後，1 次治療での標準治療の確立とともに，重要な課題となっていくものと考えられる。

おわりに

わが国では胆道癌による罹患数，死亡数はともに年間 16,000 人を超え，予後不良の疾患である。切除不能例はもちろん術後補助療法としての化学療法など有効な治療法の確立が胆道癌全体の治療成績の向上に必要である。2007 年のガイドライン作成後，胆道癌においても多くの臨床試験が実施され，エビデンスに基づく標準治療も確立してきた。次のガイドラインでは，さらに推奨度の高い治療法が増えるものと考えられる。

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